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Extended Research Article

Pramipexole in addition to mood stabilisers for treatment-resistant bipolar depression: the PAX-BD randomised double-blind placebo-controlled trial

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This article

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Abstract

Background: There are limited options currently recommended in National Institute for Health and Care Excellence guidelines for the treatment of bipolar depression. Pramipexole has been shown to improve mood symptoms in two small pilot studies in such patients.

Objectives: Primary: to evaluate the clinical effectiveness of pramipexole versus placebo alongside routine mood-stabilising medications over 12 weeks in patients with treatment-resistant bipolar depression. Secondary: evaluate the impact of pramipexole on mood and anxiety, psychosocial function, cost-effectiveness, and safety and tolerability over 48 weeks.

Design: Multicentre, randomised, placebo-controlled trial of pramipexole versus placebo in addition to standard-of-care mood stabilisers. Clinicians, researchers and participants were blinded throughout the duration of the study. Pre-randomisation stage (to adjust antipsychotics or commence mood stabilisers where required) before randomisation. Weekly online assessments of mood and anxiety from randomisation to week 52, with psychosocial function, quality of life and healthcare resource utilisation assessments conducted at regular intervals.

Setting: Twenty-one National Health Service trusts and Health Boards across England and Scotland.

Participants: Patients aged 18 years and over with a diagnosis of treatment-resistant bipolar depression currently under secondary care mental health services. Aim to randomise 290 participants.

Interventions: Pramipexole or matched placebo orally once daily, titrated from 0.25 mg to maximum of 2.5 mg (salt weight) depending on efficacy and tolerability.

Main outcome measures: Depression – Quick Inventory for Depressive Symptomology; anxiety – Generalised Anxiety Disorder-7-item scale; psychosocial functioning – Work and Social Adjustment Scale; hypomania/mania – Altman Self-rating Scale of Mania; tolerability – Treatment Satisfaction Questionnaire for Medication; well-being and quality of life – EuroQol-5 Dimensions, five-level version, ICEpop CAPability measure for Adults and Oxford CAPabilities questionnaire-Mental Health tools.

Results: Thirty-nine participants randomised (18 to pramipexole and 21 to placebo) with 36 providing data for the primary analysis. Pramipexole led to greater reductions in depressive symptoms at 12 weeks compared to placebo [4.4 (4.8) vs. 2.1 (5.1)]: a medium-sized (d = −0.72) but not statistically significant difference (95% confidence interval −0.4 to 6.3; p = 0.087). There were some statistically significant positive effects of pramipexole on secondary outcomes (reduction in depressive symptoms at 36 weeks, response and remission rates at trial exit, psychosocial function). Pramipexole was associated with an increased rate of hypomania/manic symptoms, but this appeared to be reduced by coadministration with an antipsychotic. General tolerability of pramipexole was good. There were significant annual gains in health-related quality of life and capability-well-being and tendency towards reduced health and social care costs.

Limitations: Small sample size and variable follow-up period due to recruitment during COVID-19 pandemic and the trial closing early. Participants limited to those in secondary care mental health services. All assessments only available in English.

Conclusions: No change in clinical practice can be recommended as there was not a significant difference between pramipexole and placebo on the primary efficacy outcome measure. However, there was evidence of positive effects of pramipexole on mood, psychosocial function and quality of life.

Future work: Replication in a larger population and research to investigate the impact of coadministration of antipsychotics alongside pramipexole.

Trial registration: This trial is registered as ISRCTN72151939 and EudraCT 2018-2869-18.

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Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/HBFC1953).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

List of abbreviations

AE	adverse event
ANCOVA	analysis of covariance
ARC NENC	Applied Research Collaborative, North East and North Cumbria
ASRM	Altman Self-Rating Mania Scale
BAP	British Association of Psychopharmacology
BD	bipolar depression
BDTQ	Bipolar Demographics and Treatment Questionnaire
β-hCG	beta-human chorionic gonadotropin
CEAC	cost-effectiveness acceptability curve
CI	Chief Investigator
CNTW	Cumbria, Northumberland, Tyne and Wear
CONSORT	Consolidated Standards of Reporting Trials
CRN	Clinical Research Network
CSO	Clinical Studies Officer
CTIMP	Clinical Trial of Investigational Medicinal Product
CWLY	capability-weighted life-year
DAWS	Dopamine agonist withdrawal syndrome
DMC	Data Monitoring Committee
DSM-V	*Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition
eCRF	electronic case report form
ECT	electroconvulsive therapy
EQ-5D	EuroQol-5 Dimensions
EQ-5D-5L	EuroQol-5 Dimensions, five-level version
GAD-7	Generalised Anxiety Disorder-7
GCP	Good Clinical Practice
GMC	General Medical Council
GP	general practitioner
GRIPP2	Guidance for Reporting Involvement of Patients and the Public 2
HCP	healthcare professional
HDRS	Hamilton Depression Rating Scale
HEQ	Health Economics Questionnaire
HRA	Health Research Authority
HRQoL	health-related quality of life
ICD	*International Classification of Diseases*
ICECAP-A	ICEpop CAPability measure for Adults
ICER	incremental cost-effectiveness ratio
IMP	Investigative Medicinal Product
ISF	Investigator Site File
ITT	intention to treat
MADRS	Montgomery–Åsberg Depression Rating Scale
MCID	minimal clinical important difference
MDE	major depressive episode
MHRA	Medicines and Healthcare products Regulatory Agency
MH-TRC	Mental Health Translational Research Collaboration
MINI	Mini-International Neuropsychiatric Interview
MRC	Medical Research Council
NCTU	Newcastle Clinical Trials Unit
NHB	net health benefit
NHSCII	NHS Cost Inflation Index
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NMB	net monetary benefit
OxCAP-MH	Oxford CAPabilities questionnaire-Mental Health
PET	positron emission tomography
PI	principal investigator
PIS	participant information sheet
POMH	UK Prescribing Observatory for Mental Health

PP-HE	per protocol health economic
PPI	patient and public involvement
PPIE	patient and public involvement and engagement
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	quality-adjusted life-year
QIDS-C	Quick Inventory of Depressive Symptoms, Clinician-Rated
QIDS-SR	Quick Inventory of Depressive Symptoms, Self-Rated
QUIP-RS	Questionnaire for Impulsive–Compulsive Disorders in Parkinson's Disease – Rating Scale
RA	central research assistant team
RCT	randomised controlled trial
RIS	randomisation information sheet
RSI	reference safety information
SAE	serious adverse event
SAP	statistical analysis plan
SAR	serious adverse reaction
SHAPS	Snaith–Hamilton Pleasure Scale
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TCA	tricyclic antidepressant
TMG	Trial Management Group
TRBD	treatment-resistant bipolar depression
TSC	Trial Steering Committee
TSQM	Treatment Satisfaction Questionnaire for Medication
UPDRS	Unified Parkinson's Disease Rating Scale
VAS	visual analogue scale
WSAS	Work and Social Adjustment Scale
WTP	willingness to pay
YMRS	Young Mania Self-Rating Scale

Plain language summary

Patients with bipolar disorder have symptoms (depression or elevated mood) around 50% of the time and mostly these are depressive. There are few recommended treatments for bipolar depression, they do not always work, and often come with side effects like weight gain and drowsiness. There is a suggestion that pramipexole (currently used to treat Parkinson's disease) may help treat bipolar depression. The PAX-BD trial aimed to test this, as well as seeing if it is safe and cost-effective over 48 weeks.

Those eligible for the trial were randomly allocated to receive either pramipexole or placebo. Neither the treating team nor the participants knew which treatment they were receiving.

Unfortunately, only 39 participants entered the trial due to the trial being closed early. While pramipexole did lead to a greater reduction in depressive symptoms compared to placebo at 12 weeks, the difference was not statistically significant, possibly due to there being too few participants in the trial. However, there were some statistically significant beneficial effects of pramipexole on mood, everyday functioning and quality of life later in the trial. On the downside, pramipexole appeared to increase the risk that participants experienced symptoms of elevated mood. There was evidence that pramipexole may be a cost-effective treatment. However, because of the trial being small in size, the results are not definitive and we cannot conclude that pramipexole should routinely be used for people with bipolar depression. Further research is required to give a clearer answer.

A patient and public involvement group worked on the trial and provided valuable input into its design and conduct, and we learnt more about how such input can be improved in future trials. We also learnt more about what can help and hinder people taking in part in studies like PAX-BD.

Scientific summary

Background

Patients with bipolar disorder are symptomatic around 50% of the time, the vast majority of which relates to depressive symptoms. Current National Institute for Health and Care Excellence (NICE) guidelines for the management of bipolar depression (BD) include just three medication options: lamotrigine, quetiapine and olanzapine (with or without fluoxetine). Quetiapine and olanzapine are often poorly tolerated due to weight gain and sedation. Lamotrigine has a relatively small effect size and requires slow dose titration. British Association for Psychopharmacology (BAP) guidelines include a fourth option: lurasidone. However, BD often does not respond to these options leading patients to suffer from 'treatment-resistant bipolar depression' (TRBD). Rates of TRBD are unknown, however, around 50% of patients remain depressed at 6 months, and 30% at a year, because of treatment non-response, intolerance or non-acceptance. In addition, around 70% of currently depressed bipolar disorder patients in the UK are on at least one antidepressant despite little evidence that they are effective.

Pramipexole is currently used to treat patients with Parkinson's disease and has been shown to improve depressive symptoms in these patients, with two small pilot randomised controlled trials in BD also being positive.

Objectives

Primary objective

To evaluate the clinical effectiveness of pramipexole versus placebo alongside standard mood-stabilising medication, over 12 weeks, in the management of TRBD.

Secondary objectives

- To examine the impact of pramipexole on mood and anxiety symptoms, psychosocial function (over 48 weeks), and pleasure (over 12 weeks).
- To examine the rate of known possible side effects of pramipexole (switching to mania and occurrence of impulse control disorders) as well as tolerability by reviewing rates of adverse events (AEs), serious adverse events (SAEs) and suspected unexpected serious adverse reactions (SUSARs), and overall acceptability of pramipexole.
- To examine the impact of pramipexole on quality of life, well-being, health and social care and broader societal costs of participants randomised to either pramipexole or placebo, to assess cost-effectiveness.

Methods

Randomised, double-blind, placebo-controlled trial, conducted within secondary care settings in 21 NHS Trusts and Health Boards across England and Scotland.

The trial included two stages: pre-randomisation to adjust antipsychotics and commencing mood-stabilising medication (where required) and ensuring participant engagement with study procedures, prior to randomisation.

Eligibility criteria

Inclusion criteria: pre-randomisation stage

1. Under secondary care mental health services.
2. Decision made by the patient's clinical team that a change in medication is indicated.
3. Current diagnosis of bipolar disorder (type I or II).

4. Currently meeting criteria for a major depressive episode with a Quick Inventory of Depressive Symptoms, Self-Rated (QIDS-SR) score > 10.
5. Suffering from TRBD defined as the failure (non-response, intolerance and/or refused/clinically not indicated) of ≥ 2 NICE or BAP recommended mediations for BD (quetiapine, olanzapine, lamotrigine or lurasidone) in the current episode of depression.
6. Aged 18 or over.
7. Willing and able to provide written informed consent.
8. Able to follow the trial prescription instructions and manage 8 week supplies of trial medication.
9. If female and of child-bearing potential, must have a negative pregnancy test [urine beta-human chorionic gonadotropin (β-hCG)] and required to use a highly effective contraceptive method throughout the trial.

Exclusion criteria: pre-randomisation stage

1. Severe substance use disorder.
2. Current psychotic symptoms.
3. History of retinal disease.
4. Current symptoms or significant concerns around cardiovascular disease.
5. History of significant renal disease.
6. Any known sensitivity to trial drug including its excipients.
7. Current or planned pregnancy during the trial period, or breastfeeding.
8. Starting specific psychotherapy from 4 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.
10. Confirmed diagnosis with potential confounding factors such as Parkinson's disease or restless leg syndrome.
11. Significant clinical concern regarding impulse control behaviours.

Inclusion criteria: randomisation stage

1. Been in pre-randomisation stage for a minimum of 23 calendar days.
2. Currently depressed (QIDS-SR > 10).
3. Minimum of two telephone/tele- or videoconference calls with a trial central research assistant (RA) team and two online weekly symptom ratings completed during the pre-randomisation stage.
4. On mood-stabilising medication (lithium, valproate, carbamazepine, lamotrigine).
5. Not on an antipsychotic. These criteria were amended during the trial to allow antipsychotics within specified dosing limits.
6. All regular psychotropic medication at a stable dose ≥ 4 weeks. Additionally, if taking lamotrigine, quetiapine, olanzapine or lurasidone, this must have been at the current dose or higher for ≥ 3 months.
7. If female and of child-bearing potential, a negative urine β-hCG test and using a highly effective contraceptive method.
8. Willing and able to confirm written informed consent at the point of randomisation.

Exclusion criteria: randomisation stage

As per pre-randomisation stage including.

1. Psychotic symptoms over the preceding 4 weeks.
2. Any deterioration in physical or mental health since pre-randomisation leading to a clinical concern to proceed.
3. Electroconvulsive therapy in the last 28 days.
4. Any concern regarding the patient's ability to remain engaged in the trial.

Intervention

Randomisation (1 : 1) to pramipexole or matched placebo was carried out using Sealed Envelope™, Sealed Envelope Ltd, UK (a central, secure, 24-hour web-based randomisation system with concealed allocation).

Trial medication taken orally once daily. Dose up-titrated 0.25 mg every 3 days to a maximum of 2.5 mg (salt weights) depending on acceptability and tolerability over 4 weeks. The achieved dose then fixed through to week 12 and subsequently flexibly adjusted based on response and tolerability for up to 48 weeks. Medication down-titrated 0.25 mg every 3 days at the end-of-trial involvement, unless participant switched to open-label pramipexole prescribed by their local clinical team, or they were known to have been taking placebo.

Outcome measures

Primary outcome measure

Quick Inventory of Depressive Symptoms, Self-Rated score at 12 weeks post randomisation.

Secondary outcome measures

- Weekly QIDS-SR and Generalised Anxiety Disorder-7 scores.
- Snaith–Hamilton Pleasure Scale at baseline and weeks 6 and 12.
- Work and Social Adjustment Scale at weeks 6, 12, 24, 36 and 48.
- Risk of mania (assessed weekly using the Altman Self-rating Scale of Mania), psychosis or impulse control disorders (using the Questionnaire for Impulsive–Compulsive Disorders in Parkinson's Disease – Rating Scale at baseline and weeks 6, 12 and 4 weekly thereafter).
- Gold-standard observer-rated scales (Montgomery–Åsberg Depression Rating Scale, Quick Inventory of Depressive Symptoms, Clinician-Rated and Young Mania Self-Rating Scale) at baseline and week 12 to facilitate comparison with other studies.
- Side effects and overall acceptability using the Treatment Satisfaction Questionnaire for Medication at weeks 6, 12 and then 4 weekly thereafter.
- Tolerability examined by reporting rates of AEs, SEAs and SUSARs.
- Adherence to medication examined using dose taken as reported during RA contacts.
- Quality of life, well-being, health and social care and broader societal costs of participants were examined (see health economic analysis below).

Sample size

A 30% dropout during pre-randomisation stage was predicted based on the BALANCE study (Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder), and post randomisation a 20% dropout by 12 weeks based on the CEQUEL study (Comparative economic evaluation of quetiapine plus lamotrigine combination vs quetiapine monotherapy (and folic acid vs placebo) in patients with bipolar depression). Power calculation based on a two-sample *t*-test at 12 weeks detecting a 3-point difference in QIDS-SR between drug and placebo (at $p < 0.05$) with a standard deviation (SD) of 7 (based CEQUEL study data). For 90% power, 232 (116 per arm) participants were required to complete the trial meaning a sample size of 290 at randomisation and an initial population of 414 recruited to the pre-randomisation stage.

Subsequently, a revised calculation was done based on recent data suggesting a more appropriate minimal clinical important difference of 4 QIDS-SR points, rather than 3, and early observations of dropout rates in both pre-randomisation and randomisation stages around 10%. This produced estimated required sample sizes of 126 participants to recruit, 112 to randomise and 100 to reach the 12-week primary outcome time point for 80% power.

Statistical methods

Primary outcome: QIDS-SR at week 12 used analysis of covariance (ANCOVA) to compare treatment arms covarying for baseline score. A two-sided significance level of $p < 0.05$ was used throughout. Unadjusted analysis, including the use of the *t*-test, or further related regression or ANCOVA methods were also undertaken. Secondary outcomes were analysed in a manner analogous to the primary outcome. As a result of the early closure of the trial and hence reduced sample size and not all participants followed up to 48 weeks, additional analysis was limited.

Health economic analysis

The incremental cost-effectiveness of pramipexole in comparison to placebo was assessed over 12 and 48 weeks from health and social care, and broader societal perspectives. The Health Economics Questionnaire (HEQ) captured health and social services utilisation and broader societal costs (in GBP, year 2020–1). The EuroQol-5 Dimensions, five-level version captured health-related quality of life (HRQoL) and was used to calculate quality-adjusted life-years gained as the primary outcome measure. The ICEpop CAPability measure for Adults and Oxford CAPabilities questionnaire-Mental Health (OxCAP-MH) capability well-being measures were used to calculate capability-weighted life-years gained as secondary outcome measures. Health economic data were collected at pre-randomisation, randomisation (baseline), and at weeks 12, 24, 36 and 48 for those who reached these time points. Any baseline imbalance between groups was adjusted statistically, data missingness was handled using multiple imputation, and uncertainty in the results estimated using bootstrapping and sensitivity analyses.

Qualitative study

Semistructured interviews with participants and healthcare professionals (HCPs) were conducted by central researchers via telephone to investigate barriers and facilitators to recruitment and retention of participants. Interviews were audio-recorded and outsourced to UK Transcription for transcribing. Fifteen HCPs and 11 randomised participants were interviewed. Interpretation of the transcripts was guided by an a priori framework of subthemes from a meta-analysis of studies in depression. Transcripts were independently coded by researchers using NVivo Release 1.6.1 (QSR International, Warrington, UK), reviewed by the wider qualitative team and modified on an ongoing basis. Subthemes were inductively revised, and emergent themes added per recurring discussions. Finally, 120 codes and 11 subthemes were attributed to 3 key themes: Barriers, Facilitators and Suggestions for Future Improvement.

Results

Fifty-one participants were recruited to pre-randomisation of whom 39 progressed to randomisation (dropout rate = 24%). Completion rates for self-rated online scales were around 80%. Thirty-six participants provided primary outcome data at 12 weeks and comprised the analysis population (drop-out rate = 7.7%), 16 in the pramipexole [2.18 mg/day (0.58) mean (SD)] and 20 in the placebo arms [2.25 mg/day (0.55)]. Despite the small sample size, the two arms were well matched on demographics, illness characteristics and current medication except that the pramipexole arm had a lower QIDS-SR baseline score at randomisation [pramipexole = 15.1 (5.2) vs. placebo = 17.3 (4.7): mean (SD)].

At 12 weeks, the reduction in QIDS-SR score from baseline was twice as high in the pramipexole arm compared with the placebo arm [4.4 (4.8) vs. 2.1 (5.1)]. However, ANCOVA adjusting for baseline differences in QIDS-SR was not significant [95% confidence interval (CI) −0.4 to 6.3; $p = 0.0865$]. Observation of the data suggested that the peak effect of the drug may have occurred beyond 12 weeks. ANCOVA demonstrated a significant advantage of 6.28 points lower for pramipexole at 36 weeks post randomisation. Similarly, while there was no significant difference in response (QIDS-SR reduction from baseline > 50%) and remission (QIDS-SR score ≤ 5) at 12 weeks, there was an advantage of pramipexole for response (46% vs. 6%; $p = 0.026$) and remission (31% vs. 0%; $p = 0.030$) rates at exit from the trial.

Secondary analysis indicated significant improvements in psychosocial function at 36 and 48 weeks. There were decreases in anxiety symptoms at 36 weeks ($p = 0.087$) and an increase in the ability to experience pleasure at 6 weeks ($p = 0.062$) for participants in the pramipexole arm was not significant.

Pramipexole was associated with a significant increase in manic/hypomanic symptoms at 12 weeks, but there was no significant increase in impulse control symptoms (though a higher proportion of participants in the pramipexole vs. placebo arm experienced at least one AE related to impulse control problems). There was one SAE in the pramipexole arm assessed as related to the study medication: mania that led to hospitalisation. Of 290 AEs occurring across both treatment arms, 265 (91%) required no action, 22 (8%) had treatment interrupted/dose reduced and 3 (1%) had Investigative Medicinal Product withdrawn. There were more mild and moderate AEs in the pramipexole arm, mostly of known psychiatric, nervous system and gastrointestinal side effects. Overall, tolerability and acceptability of study medication were similar between treatment arms.

Around half of the randomised participants were taking an antipsychotic. Comparing those who were and were not taking one in combination with pramipexole, it appears that the reduction in depressive symptoms was similar, but the severity of hypomanic symptoms may have been less.

Health economic analysis showed significant increase in HRQoL and capability well-being, and tendency towards reduced health and social care costs with high probability (70–90%) of cost-effectiveness for all health economic outcome measures over 48 weeks from the health and social care perspective. Sensitivity analyses confirmed the main findings.

Qualitative analysis identified barriers to recruitment and retention including the complexity of BD, difficulty accessing eligible participants, inadequate research prioritisation and the COVID-19 pandemic. Participants' concerns included receiving placebo, side effects of pramipexole, the burden of managing trial medication, using technology and/or engaging with safety monitoring for 48 weeks. Facilitators included positive relationships with care teams, central team support, responsive protocol amendments, and a strong desire for effective treatment. Lessons for future trials using semiremote methodology include using mass trial promotion strategies, reducing patient burden and fostering greater collaboration between trial staff and clinicians.

The trial was conducted during the COVID-19 pandemic and was terminated early due to funding reasons. Therefore, the sample size was much more limited, and the follow-up of some participants was shorter than planned.

Conclusions

No change in clinical practice can be recommended as there was not a significant difference between pramipexole and placebo on the primary efficacy outcome measure. This may have resulted from the early closure of the study and hence small sample size. Despite this, there were suggestions of positive effects of pramipexole on mood, psychosocial function and quality of life. However, use of the medication was complicated by the need for complex dose titration and high rates of hypomanic and impulse control symptoms, which would make implementation in routine practice challenging.

Further research is required to definitively address whether pramipexole is an effective safe and cost-effective treatment for TRBD. In addition, further studies should explore the impact of coadministration of an antipsychotic alongside pramipexole.

Trial registration

This trial is registered as ISRCTN72151939 and EudraCT 2018-2869-18.

Funding

This award was funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme (NIHR award ref: 16/154/01) and is published in full in *Health Technology Assessment*; Vol. 29, No. 21. See the NIHR Funding and Awards website for further award information.

Chapter 1 Introduction

Scientific background

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

The potential role of pramipexole as a treatment for depressive episodes in bipolar disorder is supported by a number of lines of investigation, including preclinical 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,[13] 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 BD[20] and naturalistic and open trial data,[21–27] led to two randomised controlled trials (RCTs) in BD.[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 [standard deviation (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 17-item Hamilton Depression Rating Scale (HDRS) scores at 6 weeks were 48% for pramipexole and 21% for placebo ($p = 0.05$). Zarate and colleague's RCT included 21 patients with bipolar type II,[29] who had failed at least one trial of a standard antidepressant. A mean dose of 1.7 mg/day (range 0.375–4.5 mg/day) pramipexole was given in combination with lithium or valproate. Sixty per cent of patients treated with pramipexole achieved a response [50% decrease in Montgomery–Åsberg Depression Rating Scale (MADRS)] at 6 weeks, compared with 9% taking placebo ($p = 0.02$).

Pramipexole pharmacology and issues regarding the coadministration with an antipsychotic

There is a potential pharmacodynamic interaction between pramipexole and antipsychotics. As a class, antipsychotics are dopamine receptor antagonists, while pramipexole is a dopamine agonist. There is a risk that concomitant treatment with an antipsychotic will block the effects of pramipexole.

The original trial brief from the National Institute for Health and Care Research (NIHR) Human Tissue Authority panel was that patients on antipsychotics should be excluded from the trial. However, antipsychotics are used extensively in BD. Data provided by the UK Prescribing Observatory for Mental Health (POMH) suggest that between 65% and 80% of patients with BD are prescribed at least one antipsychotic. The reason for such high rates is that they are used for many reasons. They are first-line treatment options for mania and some have an evidence base for efficacy in BD (quetiapine, olanzapine and lurasidone).[10] Some antipsychotics also have an evidence base for long-term prophylaxis.[10] However, in addition, antipsychotics are also used clinically to treat psychosis and for night-time sedation and anxiolysis. This explains why a patient with ongoing depression, despite being on an antipsychotic, might be reluctant

to withdraw it for fear of insomnia and worsening anxiety, a concern raised by our patient and public involvement (PPI) group. This concern and the impact of excluding patients taking antipsychotics led to a protocol amendment to allow for the coadministration of trial medication with an antipsychotic based on a detailed understanding of the pharmacology of pramipexole and antipsychotics. This amendment was approved by the NIHR HTA panel, ethics and the Medicines and Healthcare products Regulatory Agency (MHRA). All regulatory approvals were in place by 1 April 2021.

Antipsychotics are a broad and diverse group of medications, including both oral and depot formulations. They vary with regard to their pharmacological activity but have a common feature of blocking dopamine D2 receptors and there is evidence for a close correlation between their D2 affinity and their clinical potency as antipsychotics.[30] However, most bind to a range of additional receptors and uptake sites, including other dopamine receptors.

Pramipexole is a relatively 'clean' dopamine agonist, but it has activity at three dopamine receptors: D2, D3 and D4. The binding affinity of pramipexole is highest at the D3 receptor (Ki = 0.5 nM) – around an order of magnitude greater than at D2 (Ki = 3.9 nM) and D4 (Ki = 5.1 nM) receptors.[31–33] D3 receptors have a distinct distribution in the brain with high levels in the limbic system, nucleus accumbens and the olfactory tubercles,[34] brain areas critically involved in the regulation of motivation and reward.[35,36] An impairment of the mesolimbic dopaminergic pathway may be responsible for anhedonia, one of the major symptoms of depression. D3 receptor knockout mice have been reported to exhibit depressive and anxious features.[36] Positron emission tomography (PET) imaging data in humans suggest D3 receptor expression may be related to motivation for rewards.[37] Such findings support a hypothesis that the mechanism of action of pramipexole in BD may be mediated via D3 receptors. This is supported by additional observations. For example, pramipexole induces a dose-dependent increase of dendritic arborisation and soma size, effects antagonised by selective D3 antagonists and mediated by brain-derived neurotrophic factor.[38] This is of potential relevance given hypothesised associations between depression and impairments of neuroplasticity,[39] known to be reversed by antidepressants, exercise and electroconvulsive therapy (ECT).[40–42] Similarly, pramipexole has antidepressant effects on depression-like behaviour in mice induced by an inflammatory challenge while a D3 selective antagonist makes mice susceptible to depression-like effects.[43] Depression and BD in men are associated with raised pro-inflammatory cytokines with this hypothesised to be of aetiological significance.[44,45] In summary, the exact mechanism of pramipexole is not known. However, pramipexole binds preferentially to D3 over D2 receptors and there is evidence suggesting a key role of D3 receptors in treating depression.

Based on the receptor pharmacology of pramipexole and antipsychotics, and their hypothesised mechanism of actions, it is plausible that it may clinically be possible to capitalise on the D3 effects of pramipexole alongside the D2 antagonist effects of antipsychotics (along with their other pharmacological actions, e.g. the sedative effects of histamine receptor blockade) by combining pramipexole with an antipsychotic. Distinctly different effects of these drugs are suggested by the differential effect of the antipsychotic quetiapine and pramipexole on cerebral blood flow.[46] There is no published prospective or randomised controlled data on the combination of pramipexole with antipsychotics in patients with affective disorders. Clinical evidence can be drawn from specialist centres (such as those run by the co-applicants: Young and Stokes in London; Geddes in Oxford; Morriss in Nottingham; McAllister-Williams and Watson in Newcastle and Smith in Edinburgh) where pramipexole is prescribed for patients with difficult-to-treat BD and depression, sometimes in combination with antipsychotics. In general, expert opinion suggests that the combination is well tolerated, perhaps because some of the potential adverse effects of pramipexole are blocked by the antipsychotic. Collating clinical experience, El-Mallakh *et al.*[24] reported a retrospective naturalistic study of the effects of pramipexole in BD, finding a favourable effect on those who continued to take pramipexole for several months. Of the 16 patients in the report, 9 were prescribed antipsychotics (quetiapine n = 3, aripiprazole n = 3, risperidone n = 2, clozapine n = 1). The report does not detail whether those on antipsychotics were more or less likely to respond or experience side effects of the pramipexole. No cases of emergent mania were observed. When using pramipexole alongside an antipsychotic, clinicians tend to favour antipsychotics that have higher affinity for D2 versus D3 receptors, based on the hypothesis that pramipexole's antidepressant effects are mediated via D3 agonism. Generally, doses of antipsychotic are kept to a minimum and titrated against pramipexole to maximise antidepressant effects while retaining the sedative or anxiolytic benefits from the antipsychotic. The aim is to maximise D3 occupancy by pramipexole while allowing for D2 occupancy of the antipsychotic.

Table 23 (see *Appendix 1*) describes the affinities of the more commonly used antipsychotics in the UK. As can be seen, antipsychotics vary in the ratio of their D2 : D3 affinity. While pramipexole has an affinity for D3 receptors nearly eight times that of D2 receptors, most antipsychotics have higher affinity for D2 rather than D3 receptors. Based on these data, a protocol amendment allowed for antipsychotics to be used in addition to study mediation in PAX-BD as long as the dose of the former was within specified limits (see *Table 24* in the *Appendix 1*).

Rationale

Based on epidemiological data,[47] 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,[9] at least in part due to the limited treatment options currently available for BD.[3,10] This high prevalence and rate of treatment resistance accounts for the estimated annual UK bipolar disorder costs of £5.2B, with direct NHS costs of £342M, at 2010 prices.[48,49] Patients are eligible for this trial if their current episode of BD has not responded to two adequate trials from the three NICE-recommended medications,[3] or the additional evidence-based, though expensive, treatment with lurasidone.[50,51] A 'failed' trial, in this study, is defined as a clinically determined inadequate response to an 'adequate trial' (at least 8 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, supported by our PPI group 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 was intended to be an appropriately powered, pragmatic, RCT with economic evaluation. The primary outcome was set at 12 weeks post randomisation with a total of 52 weeks of follow-up. The trial was intended to determine efficacy and longer-term cost-effectiveness in a real-world design. The use of a validated,[52] self-reported primary outcome measure, Quick Inventory of Depressive Symptoms, Self-Rated (QIDS-SR) has successful precedents,[53–56] and allows a patient-centric assessment and experience, as well as critically facilitating the 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 was intended to further allow consideration of the utility of this treatment regime, using the NHS/Personal Social Services (PSS) perspective preferred by NICE with secondary analyses incorporating wider societal costs.

The PAX-BD trial therefore had 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 has the potential to impact on UK provision of care for patients with TRBD due to the current dearth of options available to clinicians. Additionally, any evidence of efficacy of pramipexole supports the potential role of pro-dopaminergic treatments for the management of BD.

Aims and objectives

Aim

The PAX-BD trial aimed to examine if pramipexole could be an effective treatment for patients with TRBD. To achieve this, the following objectives were set.

Primary objective

The PAX-BD trial aimed to evaluate the clinical effectiveness of pramipexole versus placebo alongside standard mood-stabilising medication, over 12 weeks, in the management of patients with TRBD. The objective was assessed with the primary outcome measure being the QIDS-SR, measured at 12 weeks and with scores in the two treatment arms compared using an analysis of covariance (ANCOVA) covarying for baseline scores.

Secondary objectives

Secondary efficacy objectives

- To examine the impact of pramipexole treatment on mood and anxiety symptoms for the duration of trial involvement, and pleasure symptoms over 12 weeks.
- To examine the impact of pramipexole on psychosocial function for the duration of trial involvement.

Secondary safety and acceptability objectives

- The trial examined known possible side effects of pramipexole: the risk of switching to mania and the occurrence of psychosis or impulse control disorders.
- Rates of impulsivity during treatment with pramipexole were examined.
- Side effects and overall acceptability of pramipexole treatment were examined.
- Tolerability of pramipexole was reviewed by reporting rates of adverse events (AEs), serious adverse events (SAEs) and suspected unexpected serious adverse reactions (SUSARs).
- Adherence to medication was also reviewed.

Health economic objectives

- To examine the quality of life, well-being, health and social care and broader societal costs of participants randomised to either pramipexole or placebo.

Comparison analysis objectives

- Content validity was increased 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.

Chapter 2 Methods

Summary of trial design

The trial is a NIHR-funded Phase III multicentre, randomised, double-blind, placebo-controlled trial. Patients with TRBD were approached to participate. The trial included two stages: pre-randomisation stage and randomisation stage. The purpose of the pre-randomisation stage was to prepare participants for recruitment to the randomisation stage by adjusting antipsychotics (where required), commencing mood-stabilising medication (where required) and ensuring participant engagement with the TrueColours database and the central research assistant (RA) team. As part of the randomisation stage, participants were randomised and commenced taking the trial medication. Participants were randomised on a 1 : 1 basis to receive either pramipexole or matched placebo alongside their existing mood-stabilising medication.

The PAX-BD trial was designed to allow flexibility regarding face-to-face versus remote completion of trial tasks. The only exception to this was the final part of the consent discussion and the physical signing of the consent form at both pre-randomisation and randomisation stages which had to be done in person.

A central pharmacy was utilised as part of PAX-BD. The sponsor pharmacy team at Cumbria, Northumberland, Tyne and Wear (CNTW) NHS Trust was used for this purpose. This meant that site team were only responsible for completion of prescription for their participants and then securely e-mailing these to the central pharmacy team in a timely manner. The central team then dispensed and posted medication to all trial participants via Royal Mail.

In addition to a central pharmacy team, a central team of RAs were also involved in PAX-BD. The central RAs carried out the majority of participant follow-up contacts via telephone and text message, supported participants with the set up and completion of questionnaires via TrueColours (prompting participants when they were due), ensuring medication was received and taken appropriately [and escalating any concerns to the Chief Investigator (CI) and local clinician/ principal investigator (PI) as applicable] and reporting any AEs reported to them via the regular telephone contacts.

The trial included a qualitative substudy and an economic evaluation.

PAX-BD included a 12-month internal pilot, as stated in the published study protocol.[57] The funder 'stop' criteria were ≤ 50 participants randomised at 12 months (from the date the first participant was recruited to pre-randomisation) and with a ≤ 70% retention of those randomised at the primary outcome time point (12 weeks). These criteria were somewhat overtaken by the internal pilot period falling coincident with the 'lockdowns' related to the COVID pandemic. Consequently, the continuation of the study was discussed periodically with the funder on an ad hoc basis.

Patient flow through the trial, and an overview of the trial stages and phases are shown in *Figure 24* [an a priori Consolidated Standards of Reporting Trials (CONSORT) diagram] and *Figure 25* in *Appendix 2*.

Sites

The trial included 21 participating Secondary and Mental Health NHS Trusts across the UK. Site set up commenced in August 2019. Details of sites, date of opening and the number of participants recruited are shown in *Table 25*, *Appendix 2*.

Participants

The trial aimed to recruit participants with TRBD. This was defined as the failure of two medications recommended for BD by NICE or the British Association of Psychopharmacology (BAP).[3,10] Eligibility criteria are described below.

Sample size calculation

PAX-BD required a pre-randomisation stage to allow for adjustment to antipsychotics and commencement of non-antipsychotic mood-stabilising medication (lithium, lamotrigine, valproate, carbamazepine), where necessary. A 30% dropout during this pre-randomisation stage was estimated based on the experience in the BALANCE study in BD run primarily in the UK.[58] This trial required participants to be switched on to lithium and valproate over a 4- to 8-week period and then be randomised to have one or other or neither.

Dropout rates during the randomised phase were estimated on the basis of the CEQUEL study,[59] which is the closest in nature to the PAX-BD trial 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.[59]

The power calculation based on a two-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 SD of 7 based on QIDS-SR data at the 12-week time point in CEQUEL.[59] Three QIDS-SR points equated to Cohen's $d = 0.4$ (which has previously been argued to represent a clinically meaningful effect size).[60] For 90% power, 232 (116 per arm) participants were required to complete the trial, meaning a sample size of 290 at randomisation, assuming a 20% dropout rate at 12 weeks as described above. It also provided an 80% power for detection of 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,[59] was representative and using the above SD estimate as the most appropriate available.

Given the estimate of a 30% dropout during the pre-randomisation stage, it was estimated that a population of 414 participants would be required. The trial closed early and recruitment to the pre-randomisation stage ceased on 5 April 2022 with a sample size of 51 recruited. Participants already in the pre-randomisation stage were allowed to progress to the randomisation stage, if confirmed as eligible, until randomisation closed on 14 June 2022 with a sample size of 39 participants randomised.

Subsequently, a revised sample size calculation was conducted based on recent data, suggesting a more appropriate minimal clinical important difference (MCID) on the QIDS-SR of 4, rather than 3, points,[61,62] and early observations that the dropout rate in the pre-randomisation stage was around 10%, and the dropout rate between randomisation and week 12 was 5%. This produced estimated required sample sizes of 155 participants to recruit to the pre-randomisation stage, 139 to randomise and 132 to reach the 12-week primary outcome time point for 90% power, or 118 recruited, 106 randomised and 100 reaching 12 weeks for an 80% power.

Recruitment

Recruitment for the trial took place in the aforementioned 21 NHS Trusts across the UK. Of the 21 sites listed, 12 of these randomised at least 1 participant into the randomisation stage. Interviews were also carried out with site staff involved in the trial as part of the qualitative element of the study.

Screening and consent

Patient identification

Suitable patients were opportunistically identified from secondary care services by clinicians at sites using patient clinic lists, databases and/or research registers. Clinicians were assisted by Clinical Studies Officers (CSOs) or other staff from the Clinical Research Networks (CRNs) where possible. The trial was also advertised to participants 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).

Screening logs were completed by recruiting sites to record reasons for participants declining to take part in the trial and reasons for ineligibility.

As part of the screening process, participants were allocated a unique participant identifier. For those who went to be consented and confirmed as eligible, this unique identifier was then used to identify them throughout their duration in the trial.

Provision of trial information for pre-randomisation stage

Potentially eligible participants were approached by a member of the clinical team at a standard clinic visit and asked for verbal consent for a member of the trial team to get in touch regarding potential participation in the trial. The participants were given a participant information sheet (PIS, see *Report Supplementary Material 1*) to consider.

Potentially eligible participants were also approached via the provision of an invitation letter and summary sent by post or e-mail. Participants then had the option to contact either the clinical or research team, if they were interested in receiving further information about the trial. This was done via completion and return of a reply slip attached to the invitation letter. A copy of the full PIS was then provided by post, e-mail or at a standard clinic visit.

All participants were given a minimum of 24 hours to consider participation. A member of the trial team then contacted the patient to ask if they did wish to proceed, and if this was the case a screening contact was arranged. Routine care continued for all participants alongside trial participation.

Patient consent to pre-randomisation stage

The initial screening/consent discussion contact was arranged at a location convenient to the participant (e.g. in clinic when attending a standard clinic appointment, at the patient's home or via telephone/teleconference or videoconference).

The need to use highly effective methods of contraception was discussed during this to ensure all women of child-bearing potential were aware of the risks of becoming pregnant while taking part in the trial.

Written informed consent was received by a General Medical Council (GMC) registered, medically trained doctor.

If the initial consent discussions (including pregnancy/contraception discussions) took place via telephone/teleconference or videoconference, written informed consent still had to be obtained in person (either at the site or at the patient's home) no later than 72 hours after the initial consent discussions.

Participants who agreed to participate in the trial were also asked if they would be willing to take part in a qualitative interview.

Eligibility assessment and confirmation for pre-randomisation stage

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After consent, eligibility for the pre-randomisation stage was confirmed via the following:

- A urine sample pregnancy test for all female participants of child-bearing potential. The sample was either collected at the site, from the patient's door by a member of the site team, delivered in person by the participant to the site, or posted back to the site team by the participant. Posting of the sample was used as a last resort as it was imperative that the samples were analysed ideally no later than 48 hours after collection to ensure validity of the results.

- Medical history and assessment of diagnosis/diagnoses according to *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-V) criteria. The assessment was completed either at a face-to-face visit or over the phone/via videoconference.
- Completion of Bipolar Demographics and Treatment Questionnaire (BDTQ) (via face-to-face visit or over the phone/via videoconference).
- QIDS-SR (paper) was self-completed by the participant using one of the following options:
    - face-to-face visit
    - a copy of the QIDS-SR posted or e-mailed, with answers then provided securely via e-mail or over the phone/via videoconference
    - made available via the trial website to allow participants access in advance of a screening telephone call/videoconference
    - questionnaire displayed via screen share during videoconference
    - completed over the phone with the questions read out to the patient by the site team as a last resort.

Eligibility was confirmed by the PI at site, or a GMC registered medically trained doctor.

For patients confirmed as eligible, a member of the site team contacted the trial RAs as soon as possible to provide them with the participant's details.

Patients who did not wish to take part in the trial, or did not meet the eligibility criteria for pre-randomisation, continued with their standard treatment pathway and were considered as 'screen failures'.

Eligibility: pre-randomisation stage

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 (type I or II), defined as in DSM-V, which is supported by the use of the Mini-International Neuropsychiatric Interview (MINI).[63]
4. Currently depressed, that is meeting DSM-V criteria for a major depressive episode (MDE) 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 refusal, of two different NICE-recommended medications (quetiapine, olanzapine + fluoxetine, lamotrigine) or lurasidone. Adequacy of treatment trial defined using a custom-designed BDTQ – see *Report Supplementary Material 5*.
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.

Exclusion criteria

1. DSM-V 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 renal disease.
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 4 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 (TMG) if in doubt].
10. Confirmed diagnosis with potential confounding factors such as Parkinson's disease, restless leg syndrome.
11. Clinical concern of previous impulse control behaviours including harmful alcohol or drug use, binge eating, gambling or sexual behaviours, or regarding significant suicidal risks.

Updates to eligibility criteria

A few minor updates were made to the eligibility criteria, mostly by way of clarification, during the course of the study. These are listed below (changes underlined and in italics):

- Inclusion criteria clarification: '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)'.
- Exclusion criteria clarification: 'History of renal disease (for example *within the last 6 months eGFR is less than 50 ml/min/1.73 m2 or there is a concern that eGFR is deteriorating and may be expected to fall below 50 during the course of the study*)'.
- Exclusion criteria clarification: '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*)'.
- Exclusion criteria relating to impulse control concerns were updated to simply read: 'Significant clinical concern regarding impulse control behaviours'.

All updates received required regulatory approvals prior to implementation at sites.

Progression to randomisation stage

Provision of trial information for randomisation stage

The RAs confirmed to the appropriate site team, once a patient was potentially eligible for randomisation. The site team then provided the participant with the randomisation information sheet (RIS, see *Report Supplementary Material 2*), at standard clinic visit, via post or e-mail, and arranged a screening and randomisation contact (again observing the 24-hour minimum time frame for the participant to read the RIS).

Patient consent to be randomised

As with the pre-randomisation stage, this contact could take place at a local clinic, at the patient's home, via telephone/teleconference or videoconference.

Again, during the informed consent discussions, female participants of child-bearing potential were reminded of the risks of becoming pregnant while taking part in the trial.

Again, as with the pre-randomisation stage, the informed consent discussion could take place via telephone/teleconference or videoconference, but written informed consent still had to be obtained in person, no later than 72 hours after the initial consent discussions.

Willingness to take part in a qualitative telephone interview was also discussed again.

Eligibility assessment and confirmation for randomisation stage

After consent to the randomisation stage the following assessments were completed in order to confirm eligibility:

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

The same options for completion were available as that for the pre-randomisation stage.

Eligibility was confirmed by the PI at site, or another GMC registered medically trained doctor.

These participants remained under the care of their usual treating team outside of the trial.

Eligibility: randomisation stage

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Inclusion criteria

1. Currently depressed, that is meeting DSM-V,[64] criteria for a MDE and with a current QIDS-SR > 10.
2. A minimum of two telephone calls with a trial RA and two online weekly symptom ratings have been completed during the pre-randomisation stage.
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 4 weeks.
5. The patient, if female and of child-bearing potential, must have a negative pregnancy test (urine β-hCG).
6. Women of child-bearing potential are required to use a highly effective contraceptive method during the post-randomisation stage of the trial.
7. Willing and able to confirm written informed consent at the point of randomisation, after the pre-randomisation period.

Exclusion criteria

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 breastfeeding.
6. Starting specific psychotherapy from 4 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 TMG if in doubt).
8. Confirmed diagnosis with potential confounding factors such as Parkinson's disease, restless leg syndrome.
9. Clinical concern of previous impulse control behaviours including harmful alcohol or drug use, binge eating, gambling or sexual behaviours or regarding significant suicidal risks.
11. Any trial team's concern regarding the patient's ability to remain engaged in the trial collecting self-ratings of their symptoms.

Updates to eligibility criteria

Changes were made to the eligibility criteria based on screening data (as this became available) and feedback received from sites. The major change made to the eligibility criteria allowed the continued use of specific antipsychotics at specific doses. Changes were as follows (changes underlined and in italics):

- A new randomisation stage inclusion criterion added: '*If on an antipsychotic this must be one listed, and at a dose of no more than the maximum stated*'. Full details of medications/doses allowed were provided in the protocol.
- An exclusion criterion was removed: 'On an antipsychotic at the point of randomisation'.
- An inclusion criterion was further clarified: 'All regular psychotropic medication, including *antipsychotics* and mood stabilisers, at a stable dose for a minimum of four weeks. *Additionally, if a participant is on lamotrigine, quetiapine, olanzapine or lurasidone then this must have been at the current dose or higher for a minimum of three months*'.

This amendment had the support of the PPI Group, Trial Steering Committee (TSC), funder and received full regulatory approvals via Substantial Amendment 11 dated 18 February 2021.

As a result of the above and the evidence outlined in *Chapter 1*, PAX-BD allowed randomisation of participants if they were taking any of the antipsychotics listed in *Table 24* in *Appendix 1* at a dose no greater than the maximum stated dose. No other concomitant treatment with antipsychotics was allowed at the time of randomisation. Participants recruited to the pre-randomisation stage of the trial who were on antipsychotics not included in *Table 24*, or at doses above those allowed, had to have these treatments adjusted to be consistent with what was allowed as defined in *Table 24*. This was managed by the participant's own local clinical team. To preclude the possibility that any change in depression severity could be attributable to ongoing, or newly initiated, treatment with an antipsychotic, antipsychotics must have been used by the participant at a stable dose for a minimum of 4 weeks. Additionally, if a participant is on lamotrigine, quetiapine, olanzapine or lurasidone, then this must have been at the current dose or higher for a minimum of 3 months. If the participant has received ECT, the last session must have been > 28 days prior.

Additional minor changes to eligibility, on top of those described above for the pre-randomisation stage and specifically related to the criteria for the randomisation stage, were:

- An inclusion criterion was added: 'Been in pre-randomisation stage for a minimum of 23 calendar days'.
- An exclusion criterion was added: 'Electroconvulsive therapy (ECT) in the last 28 days'.
- An exclusion criterion was further clarified: 'Any study team's concern regarding the patient's ability to remain engaged in the study collecting self-ratings of their symptoms *and undertake all study procedures*'.

Randomisation

Eligible participants were randomised anonymously on a 1 : 1 ratio using a central, secure, 24-hour web-based system called Sealed Envelope, to receive either pramipexole or matched placebo in addition to mood stabilisers. Randomisation was carried out by trained members of the research team at each site who had been delegated this task via the delegation log.

Randomisation took place as soon as possible and no more than 2 weeks after a participant had been confirmed as eligible. If randomisation did not take place within 4 weeks of confirmation of eligibility, eligibility had to be reconfirmed, including a repeat pregnancy test for women of child-bearing potential, before randomisation could take place.

Participant allocation

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

- bipolar I or bipolar II (based on DSM-V criteria)
- severity of depression at randomisation (QIDS-SR) – three categories: moderate 11–15, severe 16–20 and very severe > 20
- age – two categories: 18–50 and > 50
- biological sex – two categories: male and female

- site region – eight categories: North, Midlands and East, London, South East, South West, Scotland, Wales and Northern Ireland
- concurrent mood stabiliser – six categories: lithium, valproate, lamotrigine, carbamazepine and multiple mood stabilisers and no mood stabiliser.
- concurrent antidepressant (Y/*N*)
- on an antipsychotic at randomisation (Y/*N*) [This was changed from 'Withdrawn from an antipsychotic during the pre-randomisation stage (Y/N)' as part of Amendment 5 (see *Table 27*, *Appendix 1*).]
- number of mood episodes in the past year – two categories: < 4 and ≥ 4.

Blinding

PAX-BD was a double-blind trial. The Investigative Medicinal Product (IMP) and matching placebo were delivered blinded by MODEPHARMA to CNTW NHS Foundation Trust. Trial medication was dispensed at St Nicholas Hospital, then distributed directly to participants via secure post (in batches).

As the trial was double blind, neither the participants nor the local site teams were aware of which arm a participant had been allocated to.

Unblinding

While participating in the trial, participants could be unblinded if this was required due to a clinical emergency.

While it was not planned that all participants would be routinely unblinded at the point they had completed the trial, in the lead up to their final trial visit participants were asked to consider if they would want to continue taking pramipexole outside of the trial. Those that indicated they would like to continue taking pramipexole outside of the trial as part of their final visit were then unblinded after the final visit assessments had been completed. This then allowed the local site team to make provisions for ongoing open-label access to pramipexole to be put in place outside of the trial.

In both scenarios unblinding was carried out by the site PI, or another member of the team delegated this responsibility via the delegation log, by accessing the 24-hour randomisation system Sealed Envelope.

The CI and a team of delegated psychiatrists were also available via an out-of-hours on-call system called 'Out of Hours Research Mental Health'. The on-call psychiatrists had access to a trial-specific unblinding standard operating procedure (SOP) and were available as a back-up to aid sites or clinicians with emergency unblinding in the event that a delegated member of the site team was not available to perform this.

Details of trial interventions

Participants were randomised to one of two groups:

- pramipexole
- matched placebo.

For both groups, this was in addition to 'mood stabilising' medication (defined as at least on of lithium, lamotrigine, valproate or carbamazepine).

Delivery of trial interventions

Participants received trial medication for self-administration for up to 52 weeks (dependent upon when they joined the trial in relation to the early closure) – this was split into four phases:

- dose titration 0.25 mg increased every 3 days to maximum 2.5 mg depending on tolerability (weeks 1–4)
- fixed dose (weeks 5–12)
- flexible dosing 0.25–2.5 mg/day depending on response and tolerability (week 13 up to week 48/end of trial)
- tapering or continuing IMP (depending on clinical decision).

Note that these weights, and all pramipexole/placebo weights described in this report, are salt weights: 0.25 mg salt is equivalent to 0.18 mg pramipexole base and 1 mg salt equivalent to 0.7 mg pramipexole base weight.

All participants initially followed a 4-week titration schedule starting at 0.25 mg/day in a single dose usually at night for 3 days. The dose was then increased by 0.25 mg/day every 3 days. The target dose was 2.5 mg/day, but titration was based on tolerability and response.

During the fixed dose phase, the dose attained by the end of the dose titration phase was continued with mood stabilisers ideally kept stable throughout the titration and fixed dose phases (unless clinical need dictated otherwise).

During the flexible dosing stage, pramipexole was flexibly dosed between 0.25 and 2.5 mg/day (determined by response and tolerability). Decisions around dose alterations were based on weekly mood scores [QIDS-SR and Altman Self-rating Scale of Mania (ASRM)] and scores from the side-effect items of the Treatment Satisfaction Questionnaire for Medication (TSQM). Patient's mood and response, and tolerability, were categorised every 4 weeks by the RAs to allow them to provide advice to the local PI regarding the dose of trial medication to prescribe going forward. This advice was provided via a Flexible Dosing Report. It was not mandatory that this advice was followed and the clinical team, together with the patient, could agree to over-ride this if considered necessary; however, this decision had to be clearly documented within the Flexible Dosing Report which was returned to the RAs for their information.

Mood stabilisers could also be adjusted during this phase, but while the participant remained on trial medication, it was recommended that they also remain on at least one of the four recommended mood stabilisers.

At the end of participation (either end of trial or early withdrawal), medication was tapered. Dose reductions mirrored titration, in that participants decreased their dose by 0.25 mg every 3 days. This was to reduce the risk of developing dopamine withdrawal syndrome which can be caused by abrupt withdrawal of dopaminergic therapy.

Prescriptions for trial medication were written by a member of the local site team delegated to do so on the site delegation log. Prescriptions were written, signed and then a scanned copy was securely e-mailed to the central sponsor pharmacy team.

Participants were provided with 'diaries' (see *Report Supplementary Material 3* and *Report Supplementary Material 4*) that provided guidance regarding the study medication and allowed them to enter details of the medication they took and any AEs they experience, to aid discussion with the study RAs.

Outcomes

The schedule of events (see *Table 26*) and patient flow diagrams (see *Figures 24* and *25*) can be found in *Appendix 2*.

Data collection

Data were collected via a mixture of methods as part of PAX-BD including via site teams, through scheduled contacts with trained trial RAs and via participant self-reported questionnaires. All participants were allocated a unique trial identification number that was used to identify them across all documentation and databases throughout their participation.

The primary outcome and majority of secondary outcomes were collected via participant self-reported questionnaires using the online TrueColours system.

Data collected by site teams (as part of consent and eligibility checks) and by the RAs as part of their regular contacts with the participants were recorded using electronic case report forms (eCRFs) in the clinical data management system MACRO™, Ennov, Raleigh, USA. Randomisation and allocation of IMP kits were managed via the Randomisation system Sealed Envelope.

Participants could not be identified via the eCRFs as no identifiable data were held in any of these databases (participants were only identified via the unique trial identification number allocated).

Primary outcome

The primary outcome for the trial was assessed by measuring depression symptoms at 12 weeks post randomisation through participant self-completion of the Quick Inventory for Depressive Symptomology questionnaires (QIDS-SR) covarying for QIDS-SR score at baseline. Improvement in scoring was assessed through comparison of the QIDs questionnaires from baseline to 12 weeks. After 12 weeks, the original design was to follow up participants weekly up to 48 weeks; however, with the early closure of the trial, this was reduced for some participants.

Secondary outcomes

The following secondary outcomes were collected:

Secondary efficacy outcomes:

- The impact of pramipexole treatment on mood and anxiety symptoms was examined for the duration of trial involvement, and pleasure symptoms over 12 weeks. This was assessed using the QIDS-SR[65] and the Generalised Anxiety Disorder-7 (GAD-7)[66] scores, rated weekly from baseline, and the Snaith–Hamilton Pleasure Scale (SHAPS)[67] at baseline and weeks 6 and 12.
- Depression response was defined as a QIDS-SR score reduction of ≥ 50% from the baseline measure at randomisation to week 12 and similarly for remission of depressive symptoms defined as a QIDS-SR score ≤ 5 at 12 weeks.
- The impact of pramipexole on psychosocial function was examined for the duration of trial involvement. This was assessed using GAD-7 scores, rated weekly compared to baseline, and the work and social adjustment scale (WSAS),[68] at weeks 6, 12, 24, 36 and 48, compared to baseline.

Secondary safety and acceptability outcomes:

- The trial examined known possible side effects of pramipexole: the risk of switching to mania and occurrence of psychosis or impulse control disorders. This was assessed using the ASRM[69] weekly.
- Rates of impulsivity during treatment with pramipexole were examined, using the Questionnaire for Impulsive–Compulsive Disorders in Parkinson's Disease – Rating Scale (QUIP-RS)[60] at baseline and weeks 6, 12 and 4 weekly thereafter.
- Side effects and overall acceptability of pramipexole treatment were examined using the TSQM,[58] at weeks 6, 12 and then 4 weekly thereafter.
- Tolerability of pramipexole was examined by reporting rates of AEs, SAEs and SUSARs describing severity, seriousness, causality and expectedness.
- Adherence to medication to which participants are randomised was examined using dose taken as reported during RA contacts and from central trial medication accountability and reconciliation records.

Health economic outcomes:

- The quality of life, well-being, health and social care and broader societal costs of participants randomised to either pramipexole or placebo were examined. The incremental cost-effectiveness of pramipexole in comparison to placebo was established, primarily over 12 weeks with secondary analysis exploring the cost-effectiveness over longer follow-up based on available data from the trial. The Health Economics Questionnaire (HEQ) was used to capture information on health and social services utilisation and broader societal costs (e.g. lost productivity, informal care). In addition, the EuroQol-5 Dimensions, five-level version (EQ-5D-5L),[10] was used to capture health-related quality of life (HRQoL) and the ICEpop CAPability measure for Adults (ICECAP-A),[33,70] and Oxford CAPabilities questionnaire-Mental Health (OxCAP-MH),[71,72] instruments to capture broader well-being information. All questionnaires, with the exception of the HEQ, were completed at the start of pre-randomisation, baseline and at week 12, and during further follow-up at 24, 36 and 48 weeks for those who reached these time points. The HEQ was completed at baseline and during further follow-up at 24, 36 and 48 weeks for those who reached these time points.

Comparison analysis outcomes:

- Content validity was increased 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 was achieved by using the Young Mania Self-Rating Scale (YMRS),[73] to capture presence of manic symptoms, and the MADRS,[74] and Quick Inventory of Depressive Symptoms, Clinician-Rated (QIDS-C),[60] to capture severity of depressive episodes. The scales were administered at baseline and week 12.

Adverse event reporting

Adverse events for this trial were recorded by the trial RAs on the MACRO database from the date of consent to the pre-randomisation stage until completion of the final follow-up assessment.

Line listings of all AEs for a participant were sent to the site PI or delegated clinician for assessment 4 weekly during the pre-randomisation stage, then at weeks 2, 8 and 12, and then 4 weekly until the participant's final trial assessment during the randomisation stage. The PI or delegated clinician assessed each AE for seriousness, severity and also for causality if the AE occurred after the participant started taking the trial medication.

Adverse events and adverse reactions that met the definition of serious were reported as SAEs or serious adverse reactions (SARs). SAEs occurring from the date of consent to the pre-randomisation stage until the participant's final trial assessment were recorded as part of the trial. After this point, only any potential SARs that came to the attention of the site team had to continue to be reported up until the point of trial closure.

Serious adverse events occurring before the date the participant consented to the randomisation stage were recorded on the MACRO database only, whereas those occurring after randomisation/commencement of IMP also required completion of a SAE form.

All potential SARs were assessed for expectedness using the MHRA-approved reference safety information (RSI). For PAX-BD the RSI was contained in section 4.8 of the summary of product characteristics for pramipexole 0.7 mg Aurobindo Pharma – Milpharm Ltd (South Ruislip, UK), 5 September 2018.

Adverse events were coded using the Medical Dictionary for Regulatory Activities terminology (MedDRA®, MedDRA, Herndon, USA).

Compliance and withdrawal

Compliance

Participants took trial medication daily; at the highest dose, they were able to tolerate (up to a maximum of 2.5 mg daily) throughout their involvement in the trial. IMP compliance was checked via RA contacts and recorded centrally on eCRFs by the RAs in order to allow for ongoing accountability monitoring.

Unused medication and bottles were returned by the trial team (local CSO or equivalent) to the central CNTW pharmacy, or where this was not possible by the participant using the prepaid envelope provided. All returned medication was monitored by the Newcastle Clinical Trials Unit (NCTU) Trial Managers and compared against the central pharmacy accountability records. Approval for secure destruction was confirmed and documented by CNTW pharmacy. Pharmacy staff on the delegation log completed paperwork to document details of the IMP/placebo returned, documented when it had been destroyed, and retained copies of these records. The Trial Managers performed and monitored IMP accountability for all sites.

Withdrawal

Participants had the right to withdraw from the trial at any time without having to give a reason. Investigator sites tried to ascertain the reason for withdrawal and documented this on the Withdrawal Form and patient medical notes if available. Participants that withdrew were provided with an end-of-trial information sheet which reminded them how to safely taper down off the trial medication.

The Investigator could also discontinue a participant from the trial at any time if they considered it necessary for any reason.

Participants who withdrew from the trial were not replaced and were not unblinded, unless there was a clinical need.

Data collected prior to withdrawal was retained.

Definition of end of trial

The definition of end of trial was the last patient, last visit date, which took place on 29 October 2022.

Data management

Three systems were used as part of PAX-BD. MACRO was used for the trial database, Sealed Envelope for the randomisation system and TrueColours was used to collect electronic patient-reported outcomes. The MACRO database was built by the trial Data Manager with input from the TMG. Sealed Envelope was configured by the Data Manager with input from the TMG and built by Sealed Envelope. TrueColours was built by the TrueColours team with input from the central RA team.

Participants used TrueColours to complete trial questionnaires at defined time points during the trial. The central RAs supported participants with this and reminded them that these needed to be completed as part of the RA contacts that took place regularly throughout participation.

Sites used the Sealed Envelope system to randomise participants and then to subsequently allocate further IMP kits to participants as they progressed through the trial. The trial protocol provided sites with a dispensing schedule to follow so that each participant was provided with more IMP in a timely manner to prevent any gap in supply. At the appropriate time point, the site team would use Sealed Envelope to allocate more IMP kits based on the participant's current dose. Allocation of kits via Sealed Envelope had to be done by a GMC-registered clinician allocated this task via the delegation log and this was to ensure medical oversight of the number of bottles generated by Sealed Envelope as part of this process.

The central pharmacy team used the Sealed Envelope database to manage the IMP kits including moving kits between the two central storage locations and making them live for allocation. They also used the system to return unused kits that were allocated in error by site teams, so that they were available to allocate again.

Data were entered into the MACRO database by both the site team and central RA team, with site teams responsible for entering screening, consent, eligibility and end-of-trial details, while the RA was responsible for recording trial contacts, AEs and IMP compliance.

Serious adverse event data were reported by the site team via secure e-mail. This was input centrally into the MACRO database.

Essential data will be retained for a period of at least 5 years following the close of trial in line with sponsor policy and the latest Directive on good clinical practice (GCP).[75] Data were handled, digitalised and stored in accordance with the Data Protection Act 1998,[76] and the Data Protection Act 2018.[77] In line with General Data Protection Regulations, the sponsor acted as the data controller for this trial, and NCTU as data processor.

Data monitoring, quality control and assurance

Monitoring of trial conduct at sites, central RAs and central Pharmacy teams was conducted using a mixture of both onsite and remote monitoring activities to ensure a comprehensive oversight was maintained.

Primary outcome data were participant-reported through TrueColours and could not be edited after questionnaire submission. Similarly, the majority of secondary outcome data and health economics data were participant-reported through TrueColours.

Data recorded on MACRO were monitored throughout the trial by the NCTU Data Manager. Any discrepancies were queried with sites using the MACRO data clarification request function. Any changes made to the data were documented in the audit trial. This included details of who made the change, when the change was made and why the change was made. Source data verification was completed by the NCTU Trial Managers either remotely or during on-site monitoring visits. Data from MACRO were also compared with data contained within the randomisation system (Sealed Envelope) to ensure consistency. Recruitment and retention rates were reviewed regularly at TMG meetings using a data quality report.

Safety was monitored by the Data Monitoring Committee (DMC). Overall supervision of trial progress and conduct was provided by the TSC. The TSC and DMC met at the start of the trial and through the trial. Both committees met regularly throughout the trial.

Analysis

Statistical analysis

Analysis was undertaken following data lock after the closure of the trial and carried out initially on an intention-to-treat (ITT) population. Consideration was to be given to per-protocol analyses, should a population defined in this way deviate sufficiently from the ITT population. This was ultimately found not to be the case.

Analysis of the primary outcome measure of QIDS-SR at week 12 used ANCOVA or related regression methods to examine the difference between the trial arms with adjustment for baseline covariates as far as permitted by the achieved sample size. A two-sided significance level of $p < 0.05$ was used throughout. Unadjusted analysis using the *t*-test, or related regression or ANCOVA methods adjusting only for the trial arm, together with other unadjusted analyses, were also undertaken.

Sensitivity analyses were planned, as detailed in statistical analysis plan (SAP), examining the primary outcome, on a per-protocol cohort of participants who had a baseline QIDS-SR score of 10+ at the point of starting medication ($n = 33$). Based on the observations of the weekly QIDS-SR scores changing gradually over time, additional analyses were conducted of participants remaining in the trial at 24, 36 and 48 weeks – the time points when additional assessments were conducted as defined in the study protocol.

As a result of the early closure of the trial, many of those contributing 12-week data would not be able to supply data for later time points. It was decided to redefine the 48-week time point as an end-of-trial time point, using the last available data after 16 weeks for those affected by the early closure.

Secondary outcomes, other than those collected specifically for the health economic analysis, were analysed in a manner analogous to that for the primary outcome described above.

Weekly repeated measures scores for QIDS-SR were examined to ascertain patient compliance in completion. The final achieved sample size prevented using the originally planned mixed-effects linear regression model accounting for the repeated measures over time. For similar reasons, a number of other originally planned analyses were also unable to be performed.

Safety and tolerability assessments included examination of TSQM and QUIP-RS scores. Additionally, tolerability was assessed through an examination of AEs, SAEs and SUSARs.

Effect sizes (Cohen's *d*) were calculated from the difference in mean scores divided by the pooled SDs where relevant.

Full details of the planned analyses are detailed in the SAP. As a result of the early closure of the trial, further ad hoc analyses and analysis populations were considered. Where appropriate, these are described in the results chapter (see *Chapter 3*).

All analyses were conducted with STATA 16 (StataCorp. Stata Statistical Software: Release 16. College Station, TX, USA: StataCorp LLC; 2019).

Sources of bias

It was a requirement of the trial eligibility criteria that participants must be and remain for the duration of their involvement in the trial, in secondary care mental health services. This was because of the complexity of the use of pramipexole and the risks of serious adverse effects including mania, psychosis and impulse control behaviours which potentially could require urgent specialist intervention. However, this means that the trial population did not include patients with BD being managed only in primary care, who probably constitute the majority of such patients. Further, participant identification was very dependent on on-site clinicians and they may well have biased selection in ways that we are unaware of.

The trial required participants to conduct repeated self-assessments of symptoms using online tools. While there were a few participants included who neither had access to a computer, tablet or smartphone, nor were computer literate, such situations made engagement in the trial much more difficult for participants and site trial staff. This may have been a factor contributing to the recruited population of participants having relatively high levels of education compared with the general population. In addition, all online assessment tools were only available in English. To have had all tools available in multiple languages not only would have been prohibitively expensive, but also would have required extensive validation testing before the tools could have been used. The consequence is that those for whom English was not their first language, or anybody with limited literacy, would have found participation challenging if not impossible. This further limits the generalisability of the results.

Health economic analysis

A health economics analysis was included in the PAX-BD trial in order to examine the quality of life, well-being, health and social care and broader societal costs of participants randomised to either pramipexole or placebo.

The aim was to establish the incremental cost-effectiveness of pramipexole in comparison to placebo primarily over 12 weeks with secondary analysis exploring the cost-effectiveness over longer follow-up based on available data from the trial. In order to achieve this, a HEQ was utilised to capture information on health and social services use and broader societal costs. In addition, the EQ-5D-5L,[78] captured HRQoL and the ICECAP-A,[79,80] and OxCAP-MH,[81,82] instruments captured broader well-being information.

Qualitative substudy

Qualitative interviews were conducted by the trial RAs and qualitative researchers. Interviews included both site staff and participants.

Staff interviews included PIs, clinicians and CRN staff (such as CSOs/Research nurses/trial co-ordinators) at participating sites that were open to recruitment.

The purpose of these interviews was to discuss any barriers and facilitators to recruitment and retention that sites experienced while taking part in PAX-BD. Verbal consent was obtained from staff over the phone prior to the interview.

For the participant interviews, it was intended that a selection of participants that were recruited to pre-randomisation and a selection of participants that were randomised would be interviewed.

The purpose of the interviews in pre-randomisation was to review how many participants were on antipsychotics and on mood stabilisers at the point of consent, the time taken to adjust antipsychotics and their success rates, and the time taken to establish participants on an alternate mood stabiliser and its success rate.

The purpose of interviewing those randomised was to explore retention rates and reasons for discontinuation where applicable. These interviews would primarily include participants still taking part in the trial at the week 12 primary outcome point.

Verbal consent was obtained from participants over the phone prior to the interview. Interviews were directed by two themes: barriers and facilitators. Interviews were transcribed and transcripts were coded and reviewed by clinical and non-clinical staff. Then, the interpretation of the transcripts was guided by an a priori framework of subthemes (see *Appendix 5*, *A priori framework for analysis of barriers and facilitators to recruitment and retention to PAX-BD trial*) from a meta-analysis of studies in depression.[83]

Ethics and governance

The sponsor for the trial was CNTW NHS Foundation Trust (reference RES-17-031). Clinical Trial Authorisation was received from the MHRA on 5 August 2019 (Eudract Reference 2018-002869-18). A Favourable Opinion was granted by the North East – Newcastle and North Tyneside 2 Research Ethics Committee on 4 September 2019 (REC reference 19/NE/0233). Approval was also sought and received from the Health Research Authority (HRA) on 4 September 2019. Local approval was subsequently granted by each participating trust.

All required approvals were sought prior to any protocol amendments being implemented throughout the duration of the trial.

Participant expenses

Trial participants received three £25 gift vouchers as a token of thanks for their participation. These were distributed at 12, 36 and 52 weeks/final trial visit. Following the decision to close the trial early, these timings may have differed slightly by participant. Participants received a total of £75 in gift vouchers.

Trial management and oversight

A TMG met regularly throughout the trial. The TMG was responsible for the day-to-day management of the trial and for monitoring the conduct and progress of the trial. The TMG comprised the CI, co-applicants, statisticians, health economists, qualitative researchers, project manager, CRN representative, sponsor representative, pharmacy representative, patient representative and NCTU trial management team [Trial Manager, Senior Trial Manager, Clinical Trial Administrator, and Data (base) Manager].

Both a DMC and a TSC were established as part of the PAX-BD trial.

The role of the TSC was to act as the oversight body on behalf of the Sponsor/Funder. The TSC comprised an independent clinical Chairperson, two further independent clinicians, an independent statistician, an independent health economist, and an independent lay member. The TSC met at the start of the trial and then three further times throughout the duration of the trial. A joint TSC/DMC was also held at the end of the trial to go over the initial analysis and results.

The role of the DMC was to monitor the key trial outcome measures including safety and efficacy and monitor overall trial conduct. The DMC comprised an independent clinical Chairperson, an independent Psychiatrist, an Independent Statistician and an Independent PPI member. The DMC met at the start of the trial and then three further times throughout the duration of the trial. As mentioned above, a joint TSC/DMC meeting was also held at the end of the trial.

Patient and public 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. A trial PPI group was set up and it met numerous times during the trial. The group was involved in protocol development, reviewed patient-facing documents and inputted into discussions regarding ethical issues around recruiting and retaining participants in the trial. The group was also involved in training the central RAs before the trial commenced. The PPI group lead was invited to all TMG and core team catch-up meetings as an equal partner, with PPI as a standing agenda item.

Changes to trial design

Significant Protocol amendments made during the trial are listed in *Table 27* within *Appendix 2*. All amendments received HRA approval, favourable Research Ethics Committee opinion and MHRA approval as applicable prior to implementation.

Impact of COVID-19

In line with the COVID-19 national guidelines for pausing recruitment and prioritising resources to pandemic essential clinical trials, the trial submitted amendment 5 to formally pause the trial to recruitment as of 23 March 2020. In order to enact necessary changes and introduce greater flexibility for face-to-face versus remote activities, amendment 7 was given approval on 17 August 2020. Approval from the MHRA to lift the pause of recruitment was given on 28 August 2020.

The amendments to the protocol allowed for greater flexibility in trial processes and comprised:

- removal of blood pressure and pulse measurements as agreed by the DMC. Additional updates to safety measures for monitoring
- updating of the protocol and consent procedures to allow for remote discussions and completion of questionnaires
- introduction of doorstep collection by CSOs for used medication and empty bottles, urine samples, provision of diaries and collection of completed diaries
- update to methods of provision of trial information and completion of additional forms by post
- update to pharmacy processes regarding methods of returning empty bottles.

Additional administrative changes took place to reflect the changes to practice across trial documents.

Trial registration and protocol availability

PAX-BD was registered via International Standard Randomised Controlled Trials Number under ISRCTN72151939 on 28 August 2019.

The trial protocol was published in *BMC Psychiatry* in 2021.[57]

Chapter 3 Results

The analysis presented here is reported according to the CONSORT flow diagram in *Figure 1* and is based on the SAP version v2.0 (20 October 2022, *Report Supplementary Material 6*) which was in turn based on protocol version v11.0 (6 June 2022). Any analyses that were not pre-specified in the SAP are denoted as 'unplanned' or 'ad hoc'. The main clinical outcomes from the PAX-BD study have previously been published.[84]

Recruitment

- Number of sites: 21 opened, 14 recruiting into the pre-randomisation and 12 into the randomisation stage.
- Date first site opened: 28 November 2019.
- Date first participant randomised: 31 January 2020.
- The trial did not recruit to target and was closed to recruitment as of 15 June 2022.
- Date last recruited into pre-randomisation: 28 April 2022.
- Date last participant randomised: 26 May 2022.
- Date of last participant follow up: 7 September 2022.
- Date of final data set download: 5 and 6 December 2022.

Participant flow – Consolidated Standards of Reporting Trials flow diagram

Recruitment and participant flow through the trial is reported in the CONSORT diagram (see *Figure 1*).

Pre-randomisation stage

A total of 102 patients were assessed for entry into the trial. Fifty per cent of these (51 participants) were found to be eligible and entered pre randomisation. Demographic (see *Table 28*), illness characteristics (see *Table 29*) and medication history (see *Table 30*) can be found in *Appendix 3*.

The mean age of participants was around 47 years old (range 26–68), with slightly more men than women included. Most were non-smokers. The population studied was more highly educated than the general population with around half having achieved either an undergraduate or postgraduate university level. The majority of recruited participants were bipolar type I (73%) with a mean age of onset of BD was 28.3 years and duration of the current episode of 27.6 months. For just over half (51%) this was the only episode of BD in the last year, while eight (16%) participants would meet the criteria for rapid cycling bipolar disorder of four or more episodes in the last 12 months.[85]

On entry to the trial, 42 (82%) were on a mood stabiliser, 29 (57%) an antipsychotic, 29 (57%) an antidepressant, 25 (49%) an anxiolytic/hypnotic, 10 (20%) another psychotropic and 33 (65%) on a non-psychotropic. The specific drugs and doses are shown in the *Appendix 3* in *Table 30*. The population appeared to be one with clinically difficult-to-treat BD as evidenced by 10 (20%) being on 2 mood stabilisers and the number on antidepressants (29; 57%), including five on two and several being on high doses and/or drugs, such as venlafaxine and tricyclic antidepressants (TCAs), believed to be associated with a high risk of precipitating mania.[10]

The criteria needed to meet the trial definition of TRBD, in terms of non-response, intolerance, declined/not clinically indicated in relation to the four guideline-recommended treatments for BD (olanzapine, quetiapine, lamotrigine and lurasidone),[3,10] are shown in *Appendix 3*, *Table 32*. As can be seen, the most common drugs to which there was a recorded non-response were lamotrigine (41%) of pre-randomisation sample and quetiapine (39%). The most reported as associated with intolerance or declined/not clinically indicated were olanzapine (20% and 51%, respectively) and quetiapine (31% and 51%). The least commonly reported drug in all categories was lurasidone, consistent with this drug not being included in NICE guidelines.[3] The number of NICE and BAP recommended medications to which there was an inadequate response in the current episode is shown in *Table 33* in *Appendix 3*. The majority had failed to respond to one or none (65%), and only a small minority had failed to respond to three or four medications (6%).

Twelve participants recruited into the pre-randomisation stage (23.5%) did not progress to the randomisation. The time spent in pre-randomisation for the 12 participants who did not, and the 39 who did, progress to the randomised

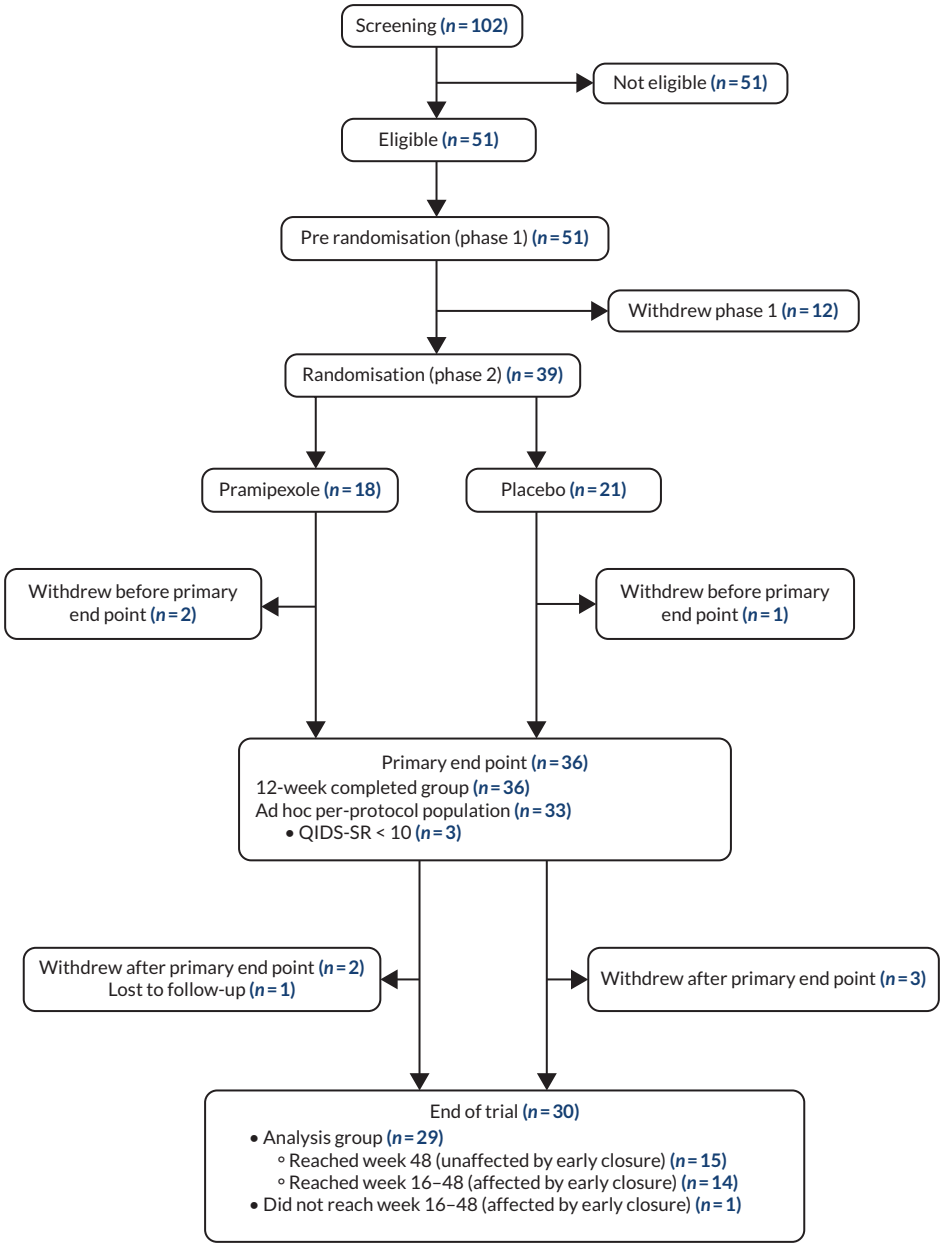

FIGURE 1 Consolidated Standards of Reporting Trials diagram illustrating flow of participants through the PAX-BD Trial. Reproduced with permission from McAllister-Williams *et al.*[84] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, in any medium and for any purpose, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original text.

phase of the trial are shown in *Figure 2* (with summary statistics for the latter in *Appendix 3*, *Table 34*). For those not randomised, the mean (SD) and median durations were 16.9 (16.6) and 8.6 weeks, respectively (range 2.7–52.4), while that for the randomised participants were 9.9 (7.8) and 8 weeks (range 3.9–43.9). There was little difference between the time in pre-randomisation between those randomised to pramipexole and those randomised to placebo (see *Table 34*, *Appendix 3*).

Reasons for lack of continuation to randomisation were varied. One participant tragically died during the pre-randomisation stage. One was not yet meeting eligibility criteria for randomisation at the point when the study had to be closed down. Three no longer met eligibility criteria for randomisation (two due to no longer meeting criteria for a current episode of depression and one due to a relapse in alcohol use). Three were not able to tolerate withdrawal from an antipsychotic and/or commencement of a non-antipsychotic mood stabiliser. Two withdrew because of COVID infections. Two withdrew for other/personal reasons.

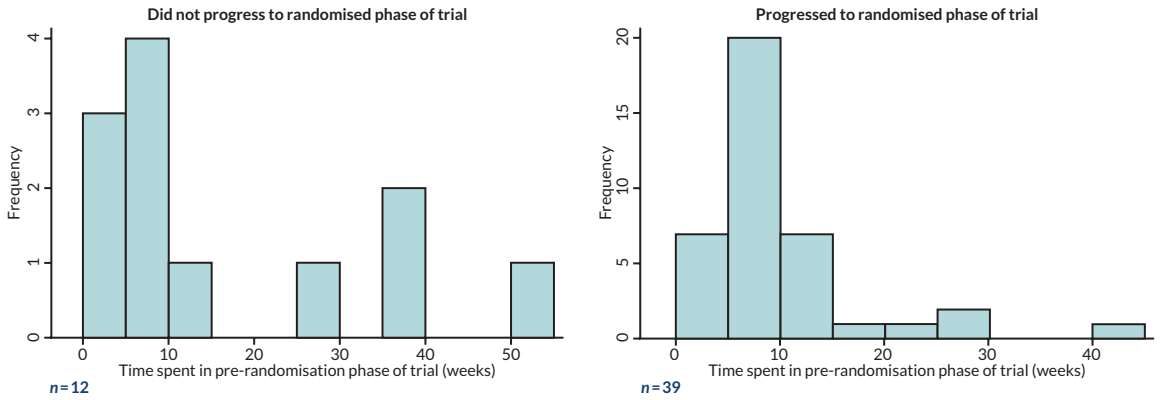

FIGURE 2 Time in pre-randomisation stage for participants who did not progress to randomisation stage (*n* = 12), and those that did (*n* = 39).

In terms of demographics, there was a higher proportion of women in those who did not progress to randomisation (75%) compared with those who did (46%) and more only had a basic level of education (25% vs. 10%), although numbers in each group are small making comparisons potentially unreliable. However, in all other respects, the participants who did or did not progress to randomisation appeared very similar with regard to their demographics and illness characteristics. It is, however, noteworthy that a higher proportion of participants not randomised were on an antipsychotic (75% vs. 51%) but not on a (non-antipsychotic) mood stabiliser (58% vs. 5%). This is to be expected. Any participant not on a mood stabiliser at recruitment was required to commence one to be eligible for randomisation, with those that struggled to tolerate the introduction of such medication not progressing. Similarly, at the start of the trial, a requirement for randomisation was to not be taking an antipsychotic, so any participant recruited on one had to have this withdrawn, and if this led to clinical problems, the participant potentially had to be withdrawn from the study.

Trial analysis populations

Of the 39 participants who were randomised, 54% were male and 26% were smokers. The primary analysis for this trial was carried out on those participants in the ITT population who provided a 12-week score on the primary outcome measure: the QIDS-SR (*n* = 36). Three participants withdrew from the trial prior to the 12-week time point: two in the pramipexole (who withdrew at 3 and 6 weeks) and one in the placebo treatment arm (who withdrew at 6 weeks). As can be seen from *Tables 28–30* in *Appendix 3*, there were few differences in participant demographics, illness characteristics or medication histories. Baseline scores in the various rating scales used in the trial were also similar between all those randomised and those who contributed data to the primary outcome analysis (see *Table 31*, *Appendix 3*).

One of the eligibility criteria for randomisation was a QIDS-SR score of 10 or more. All participants randomised were assessed as meeting this criterion. However, at the point of 'baseline', the point at which trial medication was started, three participants no longer met this criterion (two with scores of 9 and one with a score of 3). A review of these participants' scores before and after the eligibility check and baseline QIDS-SR assessment is shown in *Table 35* in *Appendix 3*. All three had scores of < 10 before the randomisation eligibility check, between 10 and 31 days prior to starting medication, though two scored 10, 4–5 days after starting medication (both of these had a baseline QIDS-SR of 9). It is possible there was some 'inflation' of QIDS-SR scores to enable participants to enter randomisation. However, the variability in scores may simply reflect fluctuations in symptom severity or be within the measurement error of the scale. However, a 'per protocol' population (*n* = 33) was analysed, excluding participants whose baseline QIDS-SR score was < 10.

Randomisation and minimisation factors

Participant characteristics with regard to the minimisation factors are shown in *Table 36*, *Appendix 3*. Close balance over minimisation factors was not achieved due to the trial closing early, though most factors were similar between treatment arms.

Treatment at the point of randomisation

As per the eligibility criteria, all participants who were randomised were taking a mood stabiliser. The most commonly taken were lithium and valproate (see *Appendix 3*, *Table 30*). Two participants had a mood stabiliser started, one had the dose of their drug increased and one was switched from one mood stabiliser to another, prior to randomisation. However, the vast majority (90%) were on the same medication at the same dose as at the point of recruitment to pre randomisation.

At the point of randomisation, 18 (46%) participants were taking an antipsychotic (with 2 participants taking 2), with the details of these shown in *Appendix 3*, *Table 30*. Ten of the participants in the ITT population were recruited to the pre-randomisation stage, of whom three had been randomised, prior to the protocol amendment allowing for participants to continue on antipsychotics into the randomisation stage. Three of the randomised participants discontinued an antipsychotic during the pre-randomisation stage. Of those participants taking an antipsychotic at the point of randomisation, 11 (61%) remained on the same dose as at the point of recruitment. Five had their dose lowered to comply with the maximum dose allowed in the amended protocol, and one had their dose increased.

Fifty-six per cent of participants were taking an antidepressant at the point of randomisation (drugs and doses shown in *Table 30*, *Appendix 3*).

Study medication received

Of the 39 participants randomised to IMP, 18 received pramipexole and 21 placebo. The dose of medication achieved at the end of the titration phase and used for the fixed-dose period was 2.18 mg/day (SD: 0.58; range: 0.75–2.50) for the pramipexole arm and 2.25 mg/day (SD: 0.55; range: 0.50–2.50) for the placebo arm. By the end of the flexible-dose phase, the doses were 2.02 mg (SD: 0.64; range: 0.25–2.50) for pramipexole and 1.66 mg (SD: 0.55; range: 0.25–2.50) for placebo, indicating a degree of dose reduction during this phase of the trial, interestingly more so in the placebo arm. The maximum doses achieved by participants were similar in both treatment arms: 2.50 mg (range: 0.75–2.50) versus 2.50 mg (range: 2.25–2.50) for pramipexole and placebo, respectively. It is noteworthy that the lowest maximum dose for any participant on pramipexole was 0.75 mg, but 2.25 mg on placebo.

Note: all doses are based on salt, rather than base, weights.

Missed doses

Fifteen participants (38%) recorded in their diaries that they had missed at least one dose of trial medication, nine (50%) in the pramipexole group and six (29%) in the placebo group. Details of the number of missed doses recorded by these individuals are reported in *Table 37* in *Appendix 3*.

Duration of trial follow up

The initial protocol detailed follow-up for 48 weeks post randomisation followed by up to a 4-week taper of trial medication. However, because of the early closure of the trial, a protocol amendment allowed for participants to be withdrawn from the trial once the last participant randomised had reached the 12-week primary outcome time point while maximising the number reaching 24-, 36- and 48-week time points when there was extra data collection (see *Chapter 2* and *Table 26*).

The duration of follow-up for the participants in each of the treatment arms, defined as the time they started taking the trial medication to week 48 adjusted for withdrawal and early closure of the trial, is shown in *Figure 3* (with summary statistics in *Appendix 3*, *Table 38*). As can be seen, the duration of follow-up was similar between groups.

Outcome data quality and completeness

There was a high rate of completion by participants of the online weekly rated scales (78% for the QIDS-SR across both treatment arms) with full details provided in *Appendix 3*, *Table 39*. Return rates for other scales are reported in *Appendix 3*, *Table 40*, where it can be seen that completion rates were, if anything, even higher.

For the primary analysis, the QIDS-SR score completed during week 12 after the commencement of trial medication was used where available. Where this score was missing, the score closest in time to 12 weeks within the range of 10–14 weeks was used as pre-specified in the protocol and SAP. If data collected before and after were equidistant

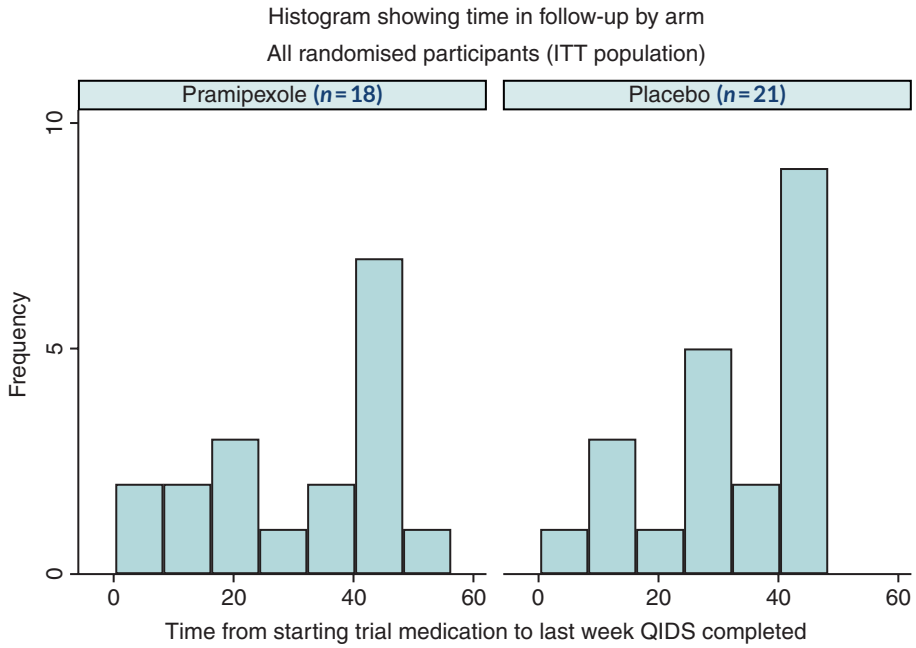

FIGURE 3 Duration of follow-up by treatment arm.

from the 12-week time point, then the later data within the compliance window were used. Note that in the ITT analysis, the nearest score to 12 weeks for one participant was recorded at 9 weeks and 3 days (i.e. 4 days outside of the 10–14-week compliance window). Summary statistics for the timing of the 12-week primary outcome measure can be found in *Appendix 3*, *Table 41*.

Descriptive analysis of the primary outcome measures

The distribution of QIDS-SR scores at baseline by treatment arm is shown in *Appendix 3*, *Figure 26*. Scores at baseline and the primary end point (12 weeks) are summarised in *Table 1*. Slight differences in summary measures between treatment arms are observed at baseline, probably reflecting the small sample size due to the early closure of the trial. The raw data show an apparent difference between the arms with lower scores (i.e. less depressive symptoms) in the pramipexole arm. Data for baseline and 12, 24, 36 and 48 weeks are shown as a box plot in *Figure 4*.

The change in QIDS-SR scores from baseline to 12 weeks is presented in *Table 2*. As can be seen, the decrease in QIDS-SR score in the pramipexole arm was over twice as great as in the placebo arm (means of −4.4 and −2.1, respectively). The reduction of over four QIDS-SR points in the pramipexole arm would be judged as being a clinically meaningful reduction.[65,66]

TABLE 1 Quick Inventory of Depressive Symptoms, Self-Rated summary statistics at baseline and primary end point (12 weeks) by treatment arm

	Pramipexole		Placebo	
Time point	**Baseline**	**12 weeks**	**Baseline**	**12 weeks**
Median (IQR)	15.5 (12–19)	10 (8.5–14.5)	17.5 (15.5–21)	16.5 (12.5–19)
Mean (SD)	15.1 (5.2)	10.7 (5.4)	17.3 (4.7)	15.2 (6.4)
95% CI about mean	12.4 to 17.9	7.8 to 13.6	15.1 to 19.5	12.2 to 18.2
Range (min–max)	(3–24)	(0–21)	(9–25)	(2–24)

CI, confidence interval; IQR, interquartile range; max, maximum; min, minimum.

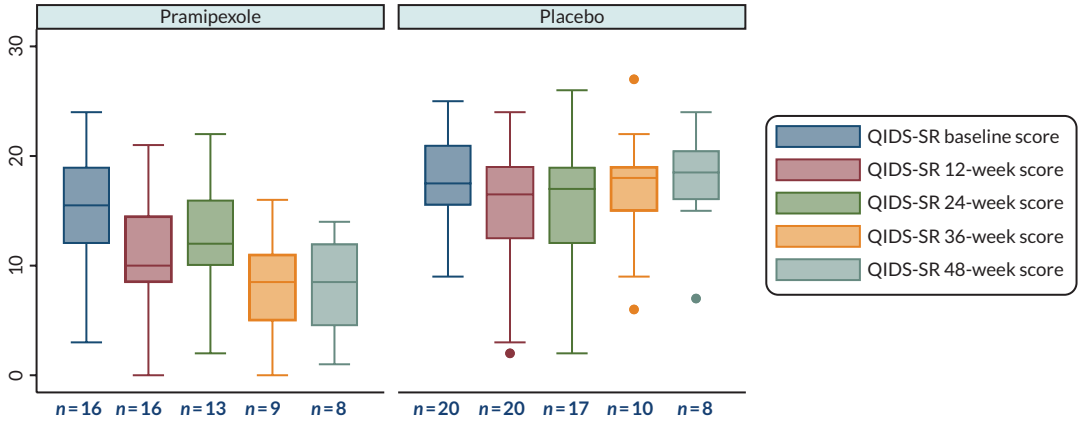

FIGURE 4 Box plots of QIDS-SR scores at baseline, 12, 24, 36 and 48 weeks (n = 36). Reproduced with permission from McAllister-Williams *et al.*[84] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, in any medium and for any purpose, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The text below includes minor additions and formatting changes to the original text.

TABLE 2 Summary statistics of change in QIDS-SR between baseline and primary end point (12 weeks) by treatment arm (12-week completion population)

	Pramipexole (N = 16)	Placebo (N = 20)
Median (IQR)	−3 (−7.5 to −1.5)	−1.5 (−5.5 to + 0.5)
Mean (SD)	−4.4 (4.8)	−2.1 (5.1)
95% CI about the mean	−7.0 to −1.9	−4.5 to + 0.3
Range (min–max)	(−15 to + 2)	(−14 to + 6)

CI, confidence interval; IQR, interquartile range; max, maximum; min, minimum.

Efficacy analysis – primary outcome

Univariable analysis

A two-tailed t-test was used to compare the two treatment arms. The null hypothesis was that there was no difference between means at the 12-week primary outcome time point. The two-sided t-test revealed p = 0.0303, with lower average QIDS-SR scores in the pramipexole compared to the placebo group (10.7 vs. 15.2), so the null hypothesis was rejected. This could have resulted from a baseline difference between groups. As a result, this univariate analysis was repeated for the change in QIDS-SR scores between the baseline and the 12-week primary end point. In this case, the two-sided t-test resulted in a p-value of 0.1689, so the null hypothesis of there being no difference between treatment arms is accepted.

Multivariable analysis

Analysis of covariance conducted according to the SAP demonstrated a non-statistically significant difference in QIDS-SR score at 12 weeks, adjusted for the effects of baseline QIDS-SR, 2.9 points higher for participants randomised to placebo [unadjusted mean (SD) for pramipexole: 10.7 (5.4) and placebo: 15.2 (6.4); p = 0.087, 95% confidence interval (CI) −0.4 to 6.3; d = −0.72]. The unadjusted results are presented in *Table 1* and the results of the ANCOVA analysis are presented in *Table 3*.

Further to the above ANCOVA analysis on the primary outcome at 12 weeks, it was intended to consider further adjustment for the minimisation factors used during randomisation. However, due to the trial closing early and the reduced sample size, this work could not be fully completed.

TABLE 3 Quick Inventory of Depressive Symptoms, Self-Rated ANCOVA analysis (n = 36)

Primary outcome measure QIDS-SR at 12 weeks	Coefficient[a]	SE of coefficient	p-value	95% CI coefficient	
				Lower	Upper
Difference between treatment arms	2.939	1.664	0.087	−0.445	6.324
Baseline QIDS-SR	0.723	0.168	< 0.001	0.381	1.066
Constant	−0.253	2.819	0.929	−5.988	5.483

SE, standard error.
Adjusted R^2 = 0.4087. *Prob* > *F* = 0.0001.

The first stage of assessing the minimisation factors for inclusion, as specified in the SAP, was to consider each individually to assess their influence on QIDS-SR at 12 weeks while adjusting for baseline scores following the earlier analysis showing this to be significant. Any factors that appeared potentially important (with $p < 0.1$) would then have been considered for inclusion in the forward stepwise selection procedure to identify the most parsimonious final model. The results of this can be seen in *Appendix 3*, *Table 42* which reports the results of the analysis of each variable, adjusting for baseline QIDS-SR, alone and when also including the treatment arm in the regression. None of the minimisation variables appeared to have a statistically significant influence on the difference in QIDS-SR score at 12 weeks between treatment arms, and the difference between treatment arms remained non-significant and generally close to that in the uncorrected ANCOVA as reported above (see *Table 3*).

A further analysis, similar to that conducted to assess each minimisation factor, was employed to assess the influence of GAD-7 baseline scores (see *Table 42* in *Appendix 3*). Baseline GAD-7 score was found to be related to the primary outcome measure when adjusted for baseline QIDS-SR scores. However, when added to the above regression model, the difference between treatment arms remained not statistically significant. Note that at baseline, 12-, 24-, 36- and 48-week time points there was a statistically significant correlation between QIDS-SR and GAD-7 scores with correlation coefficients of between 0.4 and 0.7 (see *Appendix 3*, *Table 43*).

The next step undertaken was to assess the baseline demographic variables for relationships with the primary outcome and to consider their inclusion in the final parsimonious model. The procedure for this was identical to that used to assess the minimisation factors. The results of this assessment can be found in *Table 44*, *Appendix 3*. As with the minimisation factors, none of the baseline variables assessed impacted the primary outcome.

As described in the *Chapter 2*, sensitivity and additional analyses were performed.

Ad hoc end-point analyses

On the basis of observation of *Figures 4* and *6*, it appeared that the effects of pramipexole had not plateaued at week 12, perhaps as a result of the 4-week up-titration phase. As a result, ad hoc analyses of QIDS-SR scores at 24, 36 and 48 weeks were carried out, including those participants still in the trial at these times. Each of these time-points' data were determined in the same manner as the primary end point with a ± 2-week compliance window with the exception of week 48 where this was specified in the protocol as −3/+ 1 weeks. The results can be found in *Table 4*. There are diminishing numbers of participants at each time point.

The primary QIDS-SR outcome at 12 weeks for participants who had a baseline QIDS-SR score of 10 + at the point of starting medication were almost identical to that of the ITT population (see *Table 45* in *Appendix 3*).

Secondary analysis of depressive symptomatology

Observer rated depressive symptom severity

The MADRS and QIDS-C were completed via the phone by the central trial RAs and administered at baseline and week 12, with scores reported in *Tables 46* and *47* in *Appendix 3*, with the MADRS data shown in *Figure 5*.

TABLE 4 Summary of analysis of QIDS-SR scores at ad hoc end points of 12, 24, 36 and 28 weeks

QIDS-SR	Number with data (*n*)			95% CI	
Time point	Pramipexole	Placebo	Coefficient[a]	Lower	Upper
12 weeks	16	20	2.939	−0.445	6.324
24 weeks	13	17	1.185	−2.275	4.645
36 weeks	9	10	6.278	1.850	10.707
48 weeks	8	8	5.478	−0.045	11.002

a Adjusted for baseline. Reference category is pramipexole.

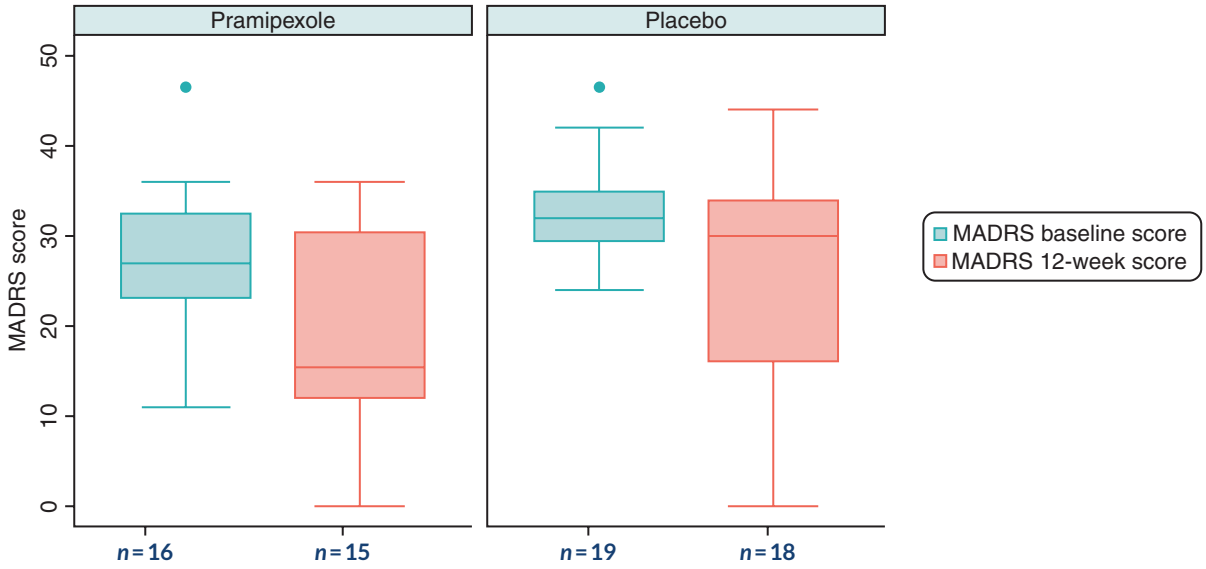

FIGURE 5 MADRS scores at baseline and week 12.

The non-statistically significant difference in the change in scores from baseline to week 12 for MADRS was a 2.59-point larger reduction (95% CI −4.54 to 9.72; *d* = 0.65) for the pramipexole arm. Similarly, for QIDS-C the non-significant change in scores was 2.30 points (95% CI −1.72 to 6.32; *d* = 0.34) greater in the pramipexole arm.

Depression response

At 12 weeks, 4 of 16 in the pramipexole arm met response criteria compared to 3 of 20 in the placebo arm. Fisher's exact test shows no significant difference in these rates. The response was also examined at the point participants exited the trial or began tapering down trial medication. This was planned to be at 48 weeks. However, the trial was closed early and, as a result, many participants exited early, with this ranging between 16 and 48 weeks. At this time, rates were 6 of 13 (46%) in the pramipexole arm compared to 1 of 16 (6%) in the placebo arm. Fisher's exact test showed this to be a statistically significant difference ($p = 0.026$). Full details of response rates are provided in *Table 48* in *Appendix 3*.

Remission of depressive symptoms

Remission was defined as a QIDS-SR score ≤ 5. There were 2 of 16 participants in remission in the pramipexole arm compared to 3 of 20 in the placebo arm. Fisher's exact test shows no significant difference between treatment arms. At exit from the trial, 4 of 13 (31%) were in remission in the pramipexole arm compared to 0 of 16 (0%) in the placebo arm. Fisher's exact test showed a statistically significant difference ($p = 0.03$) in these proportions, in favour of pramipexole. Full details of the remission data are presented in *Appendix 3*, *Table 49*.

Weekly ratings of depression symptoms

During the trial, participants completed weekly QIDS-SR ratings (see *Figure 6*) allowing for an examination of the proportion of time participants were free of significant depressive symptoms (defined as scores of QIDS-SR ≤ 5). A table showing the proportion of weeks when participants were free of depression in each arm is reported in *Table 50* (see *Appendix 3*). The average proportions of weeks free of depressive symptoms reported were approximately twice as large for the pramipexole treatment arm (15.4%) as for placebo (7.1%), though a *t*-test showed differences were not statistically significant.

Overall summary of effect of pramipexole on depressive symptomatology

- No significant difference between pramipexole and placebo was detected for the primary outcome, although this may be a result of the small sample size. Pramipexole treatment was associated with a clinically meaningful reduction in QIDS-SR score from baseline to week 12, double the reduction seen with placebo. The effect size for the difference in reduction in depressive symptoms varied between 0.72, 0.65 and 0.34 for QIDS-SR, MADRS and QIDS-C, respectively.
- Similarly, participants in the pramipexole group had around twice as many weeks relatively free of symptoms during the trial as those in the placebo group, but this was not a statistically significant difference.
- Further analyses of depressive symptoms suggested that the 12-week primary outcome time point may have been too soon to assess the effectiveness of the treatment, with significant differences on baseline-adjusted ANCOVA of QIDS-SR scores at 36 weeks. There were also significantly greater numbers of participants meeting remission and response criteria at their exit from the trial.
- No difference between treatment arms was seen on the two observer rating scale scores (MADRS and QIDS-C) conducted at baseline and at week 12.
- The difference between treatment groups appeared largely unaffected by minimisation factors and baseline characteristics of participants.

Additional secondary outcomes related to efficacy

Generalised anxiety

The severity of generalised anxiety was assessed weekly using the GAD-7 self-report scale from baseline to week 48. Summary statistics of the data can be found in *Table 51* in *Appendix 3*. Scores over time are plotted in *Figure 27*,

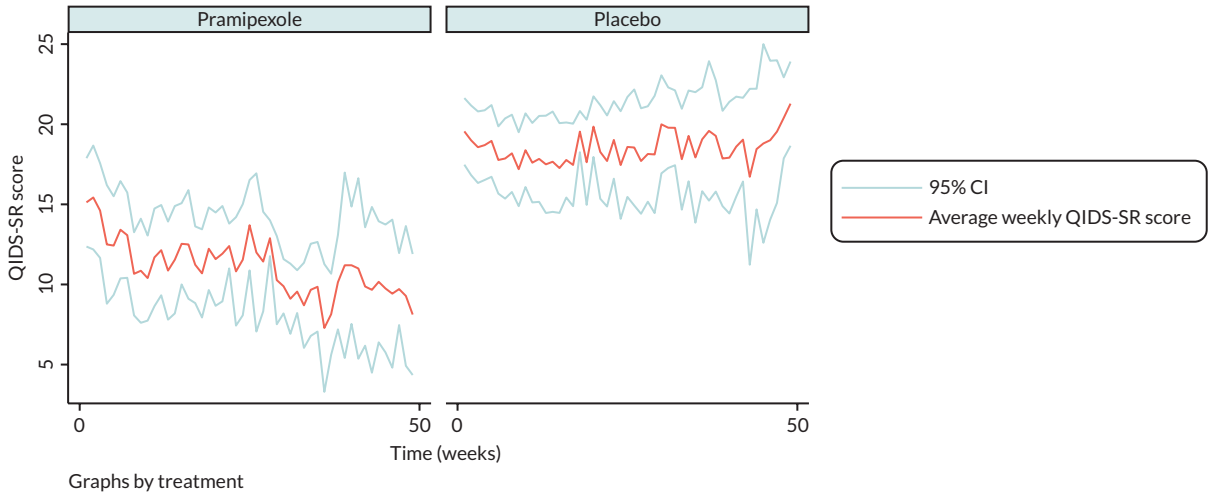

FIGURE 6 Weekly QIDS-SR scores from randomisation to a maximum of 48 weeks (n = 36). Reproduced with permission from McAllister-Williams *et al.*[84] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, in any medium and for any purpose, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original text.

Appendix 3, together with a box plot of the data at baseline, 12, 24, 36 and 48 weeks in *Figure 7*. As can be seen, there was no suggestion that pramipexole worsened anxiety.

Data were analysed as done for the QIDS-SR data, at 12, 24, 36 and 48 weeks using an ANCOVA covarying for baseline GAD-7 score. This demonstrated a non-significant difference between treatment arms at 36 weeks (p = 0.0564; *Table 5*). Although not significant, this finding is in line with the QIDS-SR scores where a statistically significant benefit of pramipexole was seen at 36 weeks on ANCOVA analysis (see *Table 3*). As noted previously, and detailed in *Table 43*, *Appendix 3*, there were significant correlations between QIDS-SR and GAD-7 scores at all time points.

Feelings of pleasure

The SHAPS was completed at baseline, 6 and 12 weeks and is shown in *Figure 8* with summary statistics reported in *Table 52* (see *Appendix 3*).

Analysis of the SHAPS scores found a non-significant difference between treatment arm at 6 weeks with pramipexole being associated with an increase of 2.04 (95% CI −0.11 to 4.20; d = −0.76) in experiences of pleasure (*Table 6*).

Psychosocial function

Potential effects of pramipexole on psychosocial function were assessed using the WSAS assessed at baseline, 6, 12, 24, 36 and 48 weeks, with the data shown in *Figure 9* and summary statistics in *Table 53* in *Appendix 3*.

Statistical comparison of the effect of the treatment arm on WSAS is shown in *Table 7*. Statistically significant advantage of pramipexole over placebo was seen at weeks 36 with 5.36 (95% CI 0.38 to 10.34; d = 0.80) and 48 with 9.63 (95% CI 0.25 to 19.02; d = −0.98) higher scores on ANCOVA adjusting for baseline scores.

Secondary outcomes regarding expected adverse effects of pramipexole

Pramipexole is known to be associated with an increased risk of manic symptoms and impulse control problems.[86] These symptoms were systematically assessed.

Manic and hypomanic symptoms

Manic and hypomanic symptoms were assessed weekly using the self-reported ASRM. Weekly scores are shown in *Figure 10*.

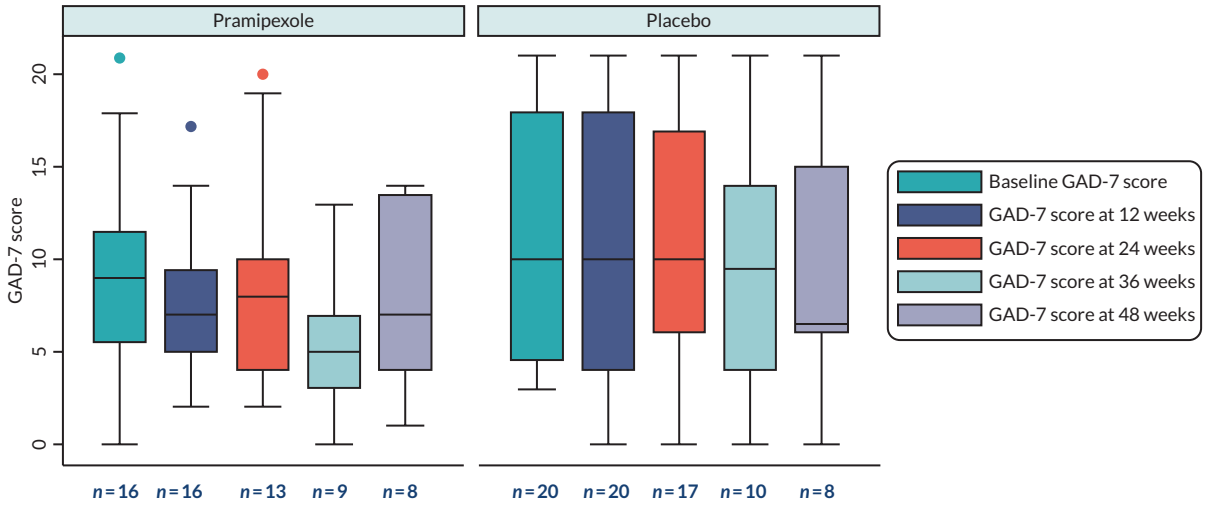

FIGURE 7 Box plot of GAD-7 scores at baseline, 12, 24, 36 and 48 weeks (n = 36). Reproduced with permission from McAllister-Williams *et al.*[84] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, in any medium and for any purpose, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original text.

TABLE 5 Analysis of covariance of GAD-7 scores at 12, 24 and 36 weeks comparing treatment arms and controlling for baseline scores

GAD-7	Number with data (*n*)			95% CI	
Time point	Pramipexole	Placebo	Coefficient[a]	Lower	Upper
12 weeks	16	20	1.317	−0.867	3.501
24 weeks	13	17	1.774	−2.040	5.587
36 weeks	9	10	3.440	−1.06	6.986
48 weeks	8	8	0.182	−6.046	6.410

a Adjusted for baseline. Reference category is pramipexole.

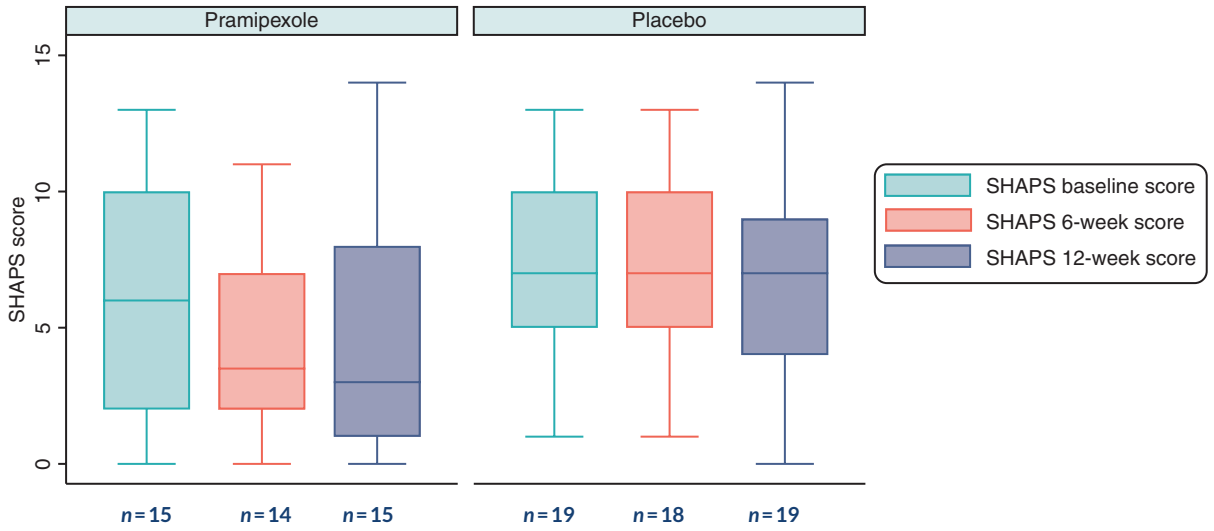

FIGURE 8 Baseline and weeks 6 and 12 SHAPS scores (*n* = 36). Reproduced with permission from McAllister-Williams *et al.*[84] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, in any medium and for any purpose, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original text.

TABLE 6 Analysis of covariance of SHAPS scores at 6 and 12 weeks comparing treatment arms and controlling for baseline scores

SHAPS	Number with data (*n*)			95% CI	
Time point	Pramipexole	Placebo	Coefficient[a]	Lower	Upper
6 weeks	14	18	2.043	−0.110	4.197
12 weeks	15	19	0.757	−1.779	3.293

a Adjusted for baseline. Reference category is pramipexole.

Being free of manic symptoms is defined as ASRM ≤ 5, with similar proportions of time seen in both treatment arms: pramipexole (88%) and placebo (96%; see *Table 54* in *Appendix 3*), with a *t*-test showing no statistically significant difference.

The ASRM data were also analysed in line with that of other scales, assessing scores at 12, 24, 36 and 48 weeks, with this shown in *Figure 28*, *Appendix 3* and summary statistics in *Table 55* in *Appendix 3*. ANCOVA analysis of these data revealed statistically significant lower scores in the placebo group −1.22 (95% CI −2.42 to −0.02; *d* = 0.85) at week 12, adjusting for baseline score. However, there were no statistically significant differences between treatment arms at any other time point (*Table 8*).

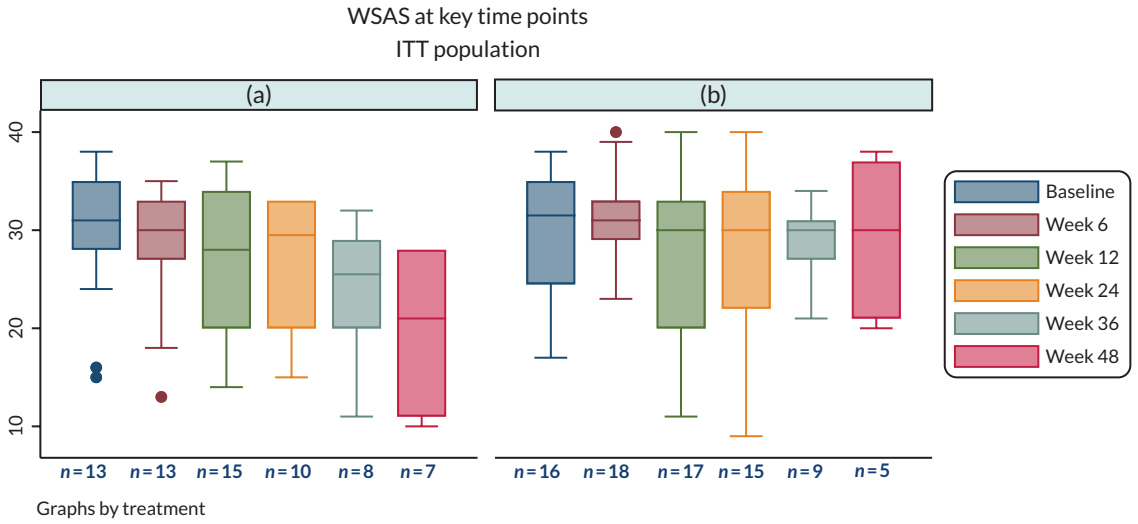

FIGURE 9 Baseline and 6-, 12-, 24-, 36- and 48-week WSAS scores (*n* = 36). Reproduced with permission from McAllister-Williams *et al.*[84] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, in any medium and for any purpose, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original text.

TABLE 7 Analysis of covariance of WSAS scores at 12, 24, 36 and 48 weeks comparing treatment arms and controlling for baseline scores

WSAS	Number with data (*n*)			95% CI	
Time point	Pramipexole	Placebo	Coefficient[a]	Lower	Upper
12 weeks	14	17	0.991	−4.160	6.142
24 weeks	10	15	2.210	−4.272	8.691
36 weeks	8	9	5.360	0.376	10.345
48 weeks	7	5	9.633	0.245	19.021

a Adjusted for baseline. Reference category is pramipexole.

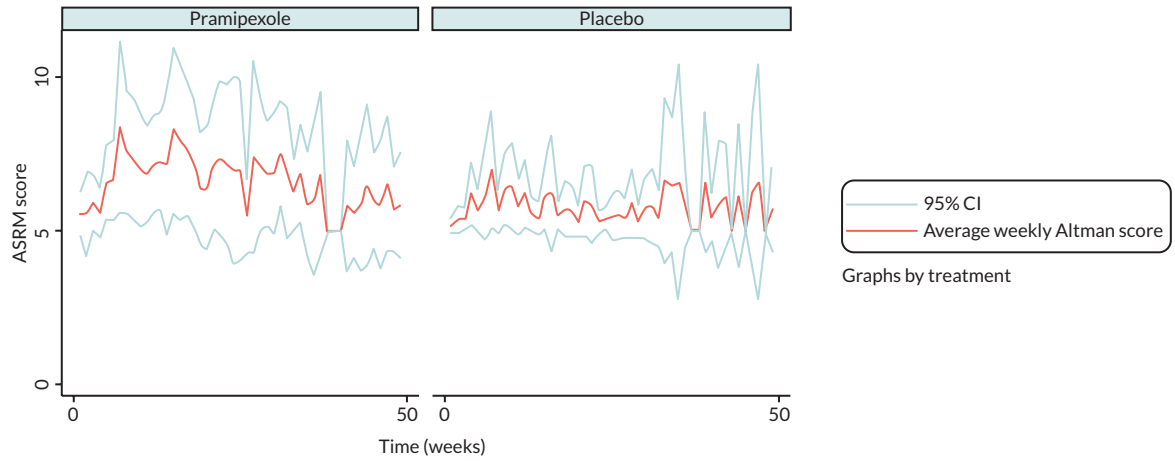

FIGURE 10 Weekly ASRM scores from randomisation to maximum of week 48 (*n* = 36). Reproduced with permission from McAllister-Williams *et al.*[84] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, in any medium and for any purpose, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original text.

TABLE 8 Analysis of covariance of ASRM scores at 12, 24, 36 and 48 weeks comparing treatment arms and controlling for baseline scores

ASRM	Number with data (*n*)			95% CI	
Time point	Pramipexole	Placebo	Coefficient[a]	Lower	Upper
12 weeks	16	20	−1.219	−2.415	−0.023
24 weeks	13	17	−0.919	−2.932	1.094
36 weeks	9	10	−0.979	−2.354	0.367
48 weeks	8	8	−0.560	−2.665	1.545

a Adjusted for baseline. Reference category is pramipexole.

Manic and hypomanic symptoms were also assessed using the observer-rated YMRS at baseline and week 12 by the trial RAs via phone. Summary statistics can be found in *Table 56* in *Appendix 3*. ANCOVA revealed no significant differences between treatment arms.

Impulsive and compulsive behaviour

Impulsivity was assessed using the QUIP-RS at baseline and then weeks 6, 12 and 4-weekly thereafter to week 48. Scores are shown in *Figure 11*, with summary data in *Appendix 3*, *Table 57*. Data at 12, 24, 36 and 48 weeks were analysed as for other scales, which did not indicate any differences between treatment arms (*Table 9*).

Impact of cotreatment with an antipsychotic

During the trial, a protocol amendment was approved allowing participants to remain on antipsychotics at randomisation. Post hoc analyses were conducted to assess the impact of this on both the efficacy of pramipexole in reducing depressive symptoms and the risk of inducing hypomania or mania. Sixteen participants from the pramipexole arm were included in the analysis, nine of whom were on an antipsychotic and seven who were not.

Weekly QIDS-SR scores are shown in *Figure 12*. This suggests that the effect of pramipexole on reducing QIDS-SR scores was similar in those participants who were, and who were not, taking antipsychotics. Due to the small numbers in each group (see *Table 58*, *Appendix 3*), limited statistical analysis was possible. Small coefficients for the difference

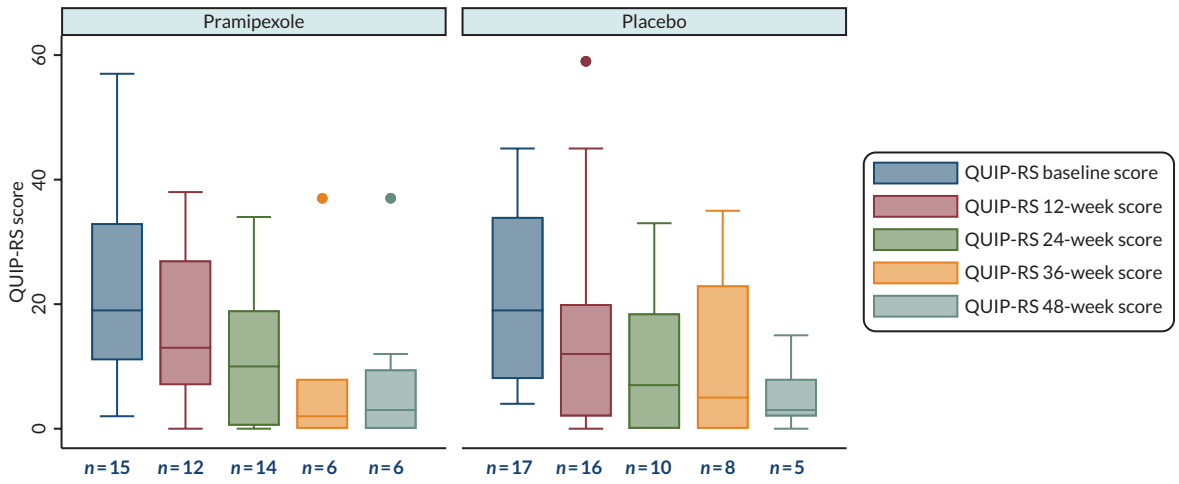

FIGURE 11 Questionnaire for Impulsive–Compulsive Disorders in Parkinson's Disease – Rating Scale box plots of baseline, 12, 24, 36 and 48 weeks (*n* = 36). Reproduced with permission from McAllister-Williams *et al.*[84] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, in any medium and for any purpose, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original text.

TABLE 9 Analysis of covariance of QUIP-RS scores at 12, 24, 36 and 48 weeks comparing treatment arms and controlling for baseline scores

QIPS-RS	Number with data (*n*)			95% CI	
Time point	Pramipexole	Placebo	Coefficient[a]	Lower	Upper
12 weeks	12	16	−2.714	−11.594	6.166
24 weeks	14	10	−3.789	−12.728	5.149
36 weeks	6	8	3.044	−12.478	18.566
48 weeks	6	5	−5.150	−17.522	7.222

a Adjusted for baseline. Reference category is pramipexole.

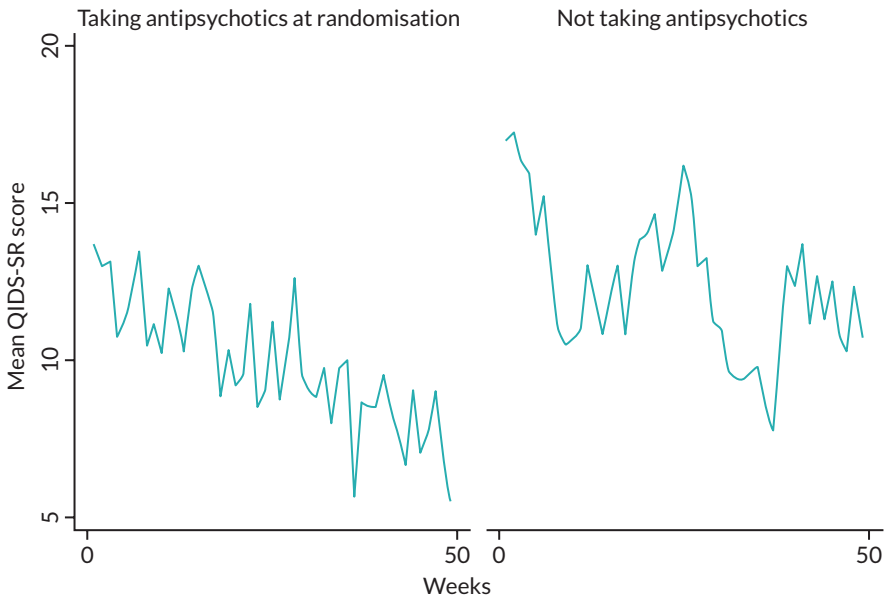

FIGURE 12 Quick Inventory of Depressive Symptoms, Self-Rated scores weekly from randomisation to a maximum of 48 weeks.

between arms indicate no difference in the reduction in QIDS-SR scores between those who were on, and not on, antipsychotics. A box plot for baseline, 12-, 24-, 36- and 48-week QIDS-SR scores for participants on and not on antipsychotics in the pramipexole arm is shown in *Figure 29* in *Appendix 3*.

Weekly ASRM scores are shown in *Figure 13*, with summary statistics in *Table 59*, *Appendix 3*. This appeared to suggest higher ASRM scores in those participants who were not on an antipsychotic. Again, due to the small numbers involved, analysis was limited, but there was no apparent significant difference between treatment arms (*Table 10*). A box plot for baseline, 12-, 24-, 36- and 48-week ASRM scores for participants on and not on antipsychotics in the pramipexole arm is shown in *Figure 30*, *Appendix 3*.

Overall safety and acceptability of treatment

Overall acceptability of treatment was assessed using the TSQM at weeks 6, 12 and then 4-weekly to week 48 (*Figure 14* and summary data shown in *Table 60*, *Appendix 3*).

Treatment Satisfaction Questionnaire for Medication scores were generally higher in the pramipexole arm (indicating better tolerability and acceptance of the treatment), though analysis of the data at 12, 24, 36 and 48 weeks (*Table 11*) found no difference between treatment arms. A figure of TSQM scores at weeks 6-, 12-, and then at 4-week intervals

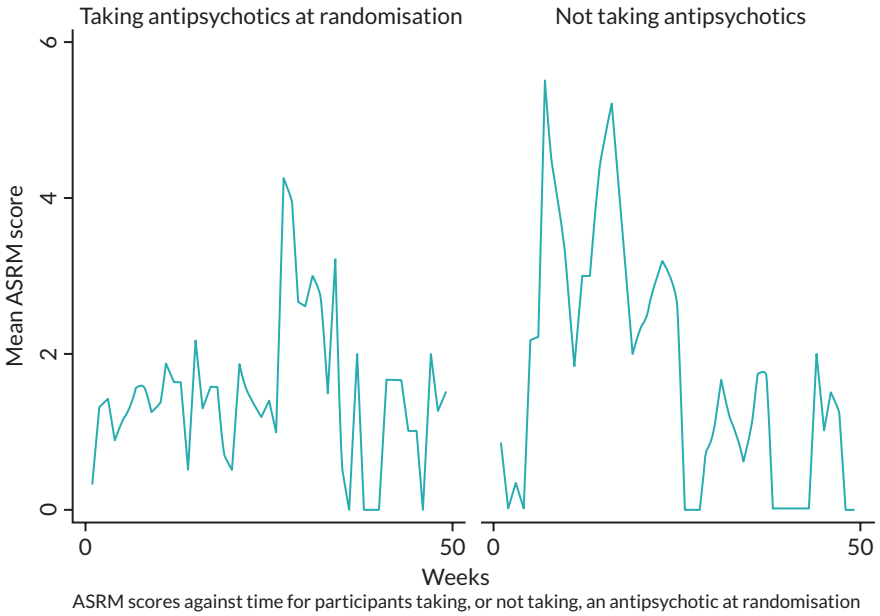

FIGURE 13 Altman Self-rating Scale of Mania scores weekly from randomisation to a maximum of 48 weeks, for participants on and not on antipsychotics in the pramipexole arm.

TABLE 10 Analysis of the effect of coadministration of an antipsychoticon the change in manic symptoms assessed by covariance of ASRM scores at 12, 24, 36 and 48 weeks comparing treatment arms and controlling for baseline scores

	Number with data (*n*)			95% CI	
Time point	AP at randomisation	No AP at randomisation	Coefficient[a]	Lower	Upper
12 weeks	9	7	0.994	−1.689	3.676
24 weeks	6	7	0.679	−4.396	5.754
36 weeks	4	5	−1.798	−4.921	1.325
48 weeks	4	4	−1.794	-5.644	2.056

AP, antipsychotic.
a Adjusted for baseline. Reference category is being on an antipsychotic at randomisation.

to week 48 is shown in *Figure 31*, *Appendix 3*. No adjustment for baseline and small sample size makes it difficult to establish the significance of observed differences.

Safety events

Adverse events

After removing entries that were errors or otherwise denoted as unintended entries, a total of 361 AEs remained. Of these, 71 were reported in pre-randomisation prior to any trial medication being taken, and 290 in the randomisation stage.

Adverse events in pre-randomisation stage

Thirty-five events (50%) were reported in five unique participants who did not enter the randomised phase of the trial. The remaining 36 (50%) were reported in 13 unique participants who were randomised, the severities of which are shown in *Table 61* in *Appendix 3*. Line listings of all AEs reported during pre-randomisation stage are line listed in *Table 62* in *Appendix 3*.

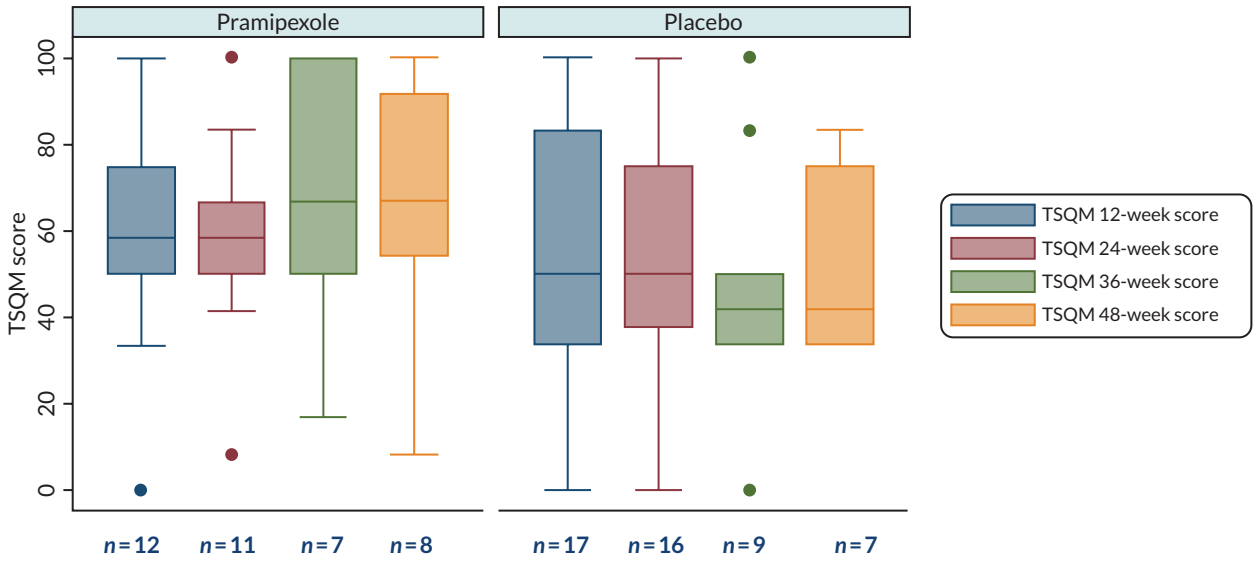

FIGURE 14 Treatment Satisfaction Questionnaire for Medication box plots for weeks 12, 24, 36 and 48 (n = 36). Reproduced with permission from McAllister-Williams *et al.*[84] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, in any medium and for any purpose, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original text.

TABLE 11 Two-tailed t-tests of TSQM scores at 12, 24, 36 and 48 weeks (n = 36)

TSQM	Number with data (n)			95% CI	
Time point	Pramipexole	Placebo	Coefficient[a]	Lower	Upper
12 weeks	12	17	−6.168	−27.201	14.864
24 weeks	11	16	−5.729	−26.533	15.074
36 weeks	7	9	−21.825	−54.071	10.420
48 weeks	8	7	−15.476	−44.811	13.858

a TSQM scores not collected at baseline so no adjustment for this. Reference category is pramipexole.

Adverse events in randomised phase of the trial

Two hundred and ninety AEs were reported by 36 (92%) of the 39 participants; 128 were reported by 17/18 unique participants in the pramipexole arm and 162 by 19/21 in the placebo arm. The severity, causality and status by the time of exit from the trial of reported AEs are shown in *Table 12*. Two hundred and sixty-five (91%) required no action to address the AEs, 22 (8%) had treatment interrupted/dose reduced or discontinued and 3 (1%) had IMP withdrawn. Listings of all AEs reported during randomisation are line listed in *Table 63* in *Appendix 3*. The AEs that occurred during the randomisation are further summarised in Medical Dictionary for Regulatory Activities terminology (MedDRA®, MedDRA, Herndon, USA) categories in *Table 64* in *Appendix 3*. The most common categories of AEs were those related to the psychiatric, gastrointestinal (particularly nausea) and the nervous system. Overall, for those rated as being definitely related to the IMP, there were few differences between rates of mild symptoms between treatment arms across all categories of AEs. There were, however, more moderately severe AEs in the pramipexole arm related to psychiatric and gastrointestinal symptoms. These findings are as expected. The *British National Formulary*[87] listed psychiatric and neurological symptoms (behaviour abnormal; confusion; dizziness; drowsiness; fatigue; hallucination; headache; movement disorders; psychiatric disorders; sleep disorders; vision disorders) and symptoms related to the gastrointestinal tract (appetite abnormal; constipation; nausea; vomiting; weight changes) as common or very common side effects of pramipexole.

TABLE 12 Severity, causality and status at exit from the trial, of AEs in the randomisation stage (*n* = 290) by treatment arm

Severity	Pramipexole (%)	Placebo (%)	Combined (%)
Mild	76 (59)	105 (65)	181 (62)
Moderate	48 (38)	49 (30)	97 (33)
Severe	4 (3)	8 (5)	12 (4)
Causality	**Pramipexole**	**Placebo**	**Combined**
Definitely related to IMP	48 (41)	43 (27)	91 (31)
Unable to determine if related	27 (21)	37 (23)	64 (22)
Unrelated	53 (41)	82 (51)	135 (47)
Status at exit from trial	**Pramipexole**	**Placebo**	**Combined**
Recovered	53 (41)	79 (49)	132 (46)
Condition improved	41 (32)	36 (22)	77 (27)
Condition unchanged	23 (18)	34 (21)	57 (20)
Condition stable and no change anticipated	11 (9)	13 (8)	24 (8)
Total	128 (100)	162 (100)	290 (100)

Serious adverse events

There were six SAEs reported by six unique participants. One SAE (suicide by drug overdose) was reported in the pre-randomisation stage in January 2022. Of the remaining five, all were reported by different participants, two in the pramipexole arm and three in the placebo arm. Details of all SAEs occurring during the randomisation stage are presented in *Table 65* in *Appendix 3*. Of those participants experiencing a SAE, three (one randomised to pramipexole and two to placebo) completed their 12-week primary outcome measures. Of the other two, one withdrew (from the pramipexole arm) 7 weeks after randomisation and the other (in the placebo arm) died after 8 weeks.

Of the two participants in the pramipexole arm who experienced a SAE, for one the event was judged to be unrelated to trial medication. The other participant with a SAE judged as related to study mediation experienced an episode of mania that led to hospitalisation.

Other safety events

For the period from the date of first randomisation to the last patient's last visit, there were no reported SUSARs, SARs or Urgent Safety Measures. One suspected SUSAR was downgraded to an AE.

Safety events related to hypomania, mania and impulsivity

Given the known risk of hypomania and mania with treatment with pramipexole,[86] which might be expected to be high in patients with bipolar disorder , and observations of ASRM scores (see *Figure 10*), all AEs, SAEs and withdrawals that related to this were examined, particularly in relation to whether or not the participant was taking an antipsychotic in addition to trial medication. *Table 13* details this review.

It is interesting that there was one SAE and two withdrawals (one of whom was the same participant who experienced the SAE) related to manic symptoms in the pramipexole arm, but no similar situations in the placebo arm. In addition, AEs related to hypomanic/manic symptoms were more common for participants in the pramipexole arm [11 AEs reported by 8 participants (44%)] compared with the placebo arm [12 AEs reported by 6 participants (29%)].

It is noteworthy that of the 18 unique participants involved who experienced one or more events related to hypomania or mania, only 3 were taking an antipsychotic. Of these, two were on relatively low doses (risperidone 1 mg and quetiapine 100 mg).

TABLE 13 Withdrawals, SAEs and AEs related to hypomania or mania

	Pramipexole		Placebo		Pre randomisation (not randomised)	
	N	AP information	*N*	AP information	*N*	AP information
Withdrawal	2	• Risperidone[a] • No AP	0	N/A	0	N/A
SAE	1[b]	Risperdone[a]	0	N/A	0	N/A
AE in pre randomisation	0	N/A	1	• No AP	1	• Lurasidone[c]
AE in randomised phase	8	• No AP • No AP • No AP • No AP • No AP[d] • No AP[d] • No AP[d] • Quetiapine[e]	6	• No AP • No AP • No AP • No AP • No AP • No AP	N/A	N/A

N, number of unique participants; AP, antipsychotic.
a Risperidone 1 mg/day.
b Same person as withdrew when on risperidone.
c Lurasidone 74 mg/day.
d Was on an antipsychotic in the pre-randomisation stage, but withdrawn prior to randomisation.
e Quetiapine 100 mg/day.

There was less evidence of significant issues with regard to impulsivity when reviewing the routinely collected QUIP-RS scores (see *Figure 11* and *Table 9*). However, there were 11 AEs related to impulse control behaviours reported by 6 unique participants in the pramipexole arm (i.e. 33% of participants in the arm) compared with and 8 from 4 unique participants in the placebo arm (19% of participants), hinting at a possibly higher rate with the active drug.

Summary of key findings

Efficacy of pramipexole

- Pramipexole was associated with clinically meaningful reduction in QIDS-SR score between baseline and 12 weeks, twice that seen in the placebo arm. It was also associated with twice the number of depression-free weeks during follow-up compared with placebo. However, neither of these changes were statistically significant possibly due to the small sample size. There were, however, statistically significant greater reductions in QIDS-SR scores at 36 weeks of follow-up, and higher rates of response and remission at exit from the trial, compared with placebo.
- While pramipexole can be activating, there was no increase in GAD-7 scores over the course of the trial. Indeed, there was a near significant reduction in scores at 36 weeks compared with placebo, in line with the QIDS-SR finding.
- There was an increased ability to experience pleasure at 6 weeks in the pramipexole compared with placebo group which was not statistically significant.
- There was a statistically significant benefit of pramipexole on work and social function at 36 and 48 weeks of follow-up.

Safety of tolerability of pramipexole

- Overall tolerability and acceptability of pramipexole were good, with this being rated (non-significantly) higher in the pramipexole arm.
- Rates of AEs were similar between treatment arms, with 91% not requiring any action and only one in the pramipexole arm being adjudged as severe. There were two SAEs in the pramipexole arm, one adjudged as unrelated to medication and the other an occurrence of a manic episode.

- Pramipexole treatment was associated with significantly higher rates of hypomanic symptoms at 12 weeks compared with placebo. This effect was not seen at later time points.
- There was no apparent difference in the rates of impulse control problems on structured testing between pramipexole and placebo treatment arms, but a higher proportion of participants in the pramipexole compared with the placebo arm (33% vs. 19%) experienced at least one AE related to impulse control problems.
- Comparing participants who were and who were not taking an antipsychotic in combination with trial medication, it appears that the reduction in depressive symptoms with pramipexole is not affected, but the severity of hypomanic symptoms may be reduced by coadministration with an antipsychotic, at least from observations of AE rates.
- Of 18 participants who withdrew from follow-up and/or experienced an AE or SAE related to mania, only 3 were taking an antipsychotic (compared with around half of the ITT population who were). Of these, two were taking doses that might be considered low.

Chapter 4 Health economics

Introduction

The aim of this health economic evaluation is to assess whether the treatment of patients with TRBD with pramipexole in addition to mood stabilisers (treatment) is cost-effective compared to placebo (control). For this purpose, the following section presents a detailed within-trial outcome, cost and incremental cost-effectiveness analysis of the PAX-BD randomised, double-blind, placebo-controlled trial conducted in the UK between 2018 and 2022. Most of the trial was conducted during the COVID-19 pandemic facing major challenges and had to be terminated early due to funding reasons. Therefore, care contacts and cost information are representative of this given time period and the sample size available for the economic evaluation is much more limited than originally foreseen.

Methods

The health economic analysis plan was published in the PAX-BD trial protocol paper,[57] and is reported following the Consolidated Health Economic Evaluation Reporting Standards guidelines.[88]

Study population

All base-case economic analyses focused on the same ITT population with 12-week outcomes (n = 36) as used for the main efficacy analysis. Further sensitivity analyses were conducted on a per-protocol health economic (PP-HE) sample including those participants who had at least moderate-level depression at treatment initiation (baseline) and had some follow-up health economic data beyond baseline, and excluding one participant in the placebo arm whose 12-week QIDS-SR score was completed outside of the compliance window (note that this participant was NOT excluded from the per protocol population used in the sensitivity analysis in *Chapter 3*). For a detailed description of the samples analysed, see *Appendix 4*, *Tables 68* and *69*.

Economic evaluation methods

The economic evaluation compared the within-trial patient-level costs, outcomes and incremental cost-effectiveness between the pramipexole and the placebo arms using current gold standard methods.[89] Relevant outcome and resource use data were collected electronically through the TrueColours clinical platform,[90] at baseline and at weeks 12, 24, 36 and 48.

As per the NICE health technology evaluation manual (NICE 2022), the economic evaluation was conducted primarily from the NHS and PSS perspective. A secondary evaluation from a broader societal perspective included also lost productivity and informal care costs since these were shown as major cost components in the latest cost-of-illness trial for bipolar disorder in the UK.[91] Due to the limited sample size, results are reported not only for the full 48 weeks trial follow-up, but also for the first 12 weeks trial period matching the primary clinical end point. Since the time horizon of the analyses did not exceed 1 year, no discounting of either the costs or the outcomes results was necessary.

Outcome measurement and valuation

The base-case health economic analysis is a cost–utility analysis with quality-adjusted life-years (QALYs) gained and calculated based on utility values developed from HRQoL information collected via the EQ-5D-5L questionnaire as recommended by most health technology institutes.[89,92,93] UK-specific health state utilities were calculated using the 'EQ-5D-5L Crosswalk Index Value Calculator' tool provided by the EuroQol Group as currently required by NICE.[92] Outcome results for the EQ visual analogue scale (EQ VAS) are also reported.

Due to known limitations of the EuroQol-5 Dimensions (EQ-5D's) sensitivity for capturing broader quality-of-life benefits in mental health,[82] secondary cost-effectiveness analyses using patient-reported capability well-being measurement tools previously validated within the mental health context were also carried out.[94,95] For this purpose, we measured broader capability well-being based on the generic ICECAP-A questionnaire valued by its UK tariff set,[96,97] and

based on the more mental health-specific OxCAP-MH questionnaire using its standardised scores,[81,82] and calculated capability-weighted life-years (CWLYs) gained.[91]

Costing methods

In terms of treatment costs, pramipexole was prescribed electronically and posted out to participants. The prescription of the trial drug hence did not require regular direct specialist contact. Instead, participants were regularly contacted and followed up by trial researchers with additional psychiatrist supervision and information review. Treatment costs in the current economic evaluation reflect the given care provision in the PAX-BD trial and may not be fully representative outside of the trial setting.

The cost analysis used further resource use data collected with an adapted version of the HEQ.[98,99] The HEQ's development was based on previous versions of the Client Service Receipt Inventory instrument[100] and the Trimbos/iMTA questionnaire for Costs associated with Psychiatric illness (TiC-P).[101] Collected resource use data included all hospital and community health and social care services, medication, productivity losses and informal care. For medication costs, only mental health-relevant prescription medications were considered and categorised as antipsychotics, mood stabilisers, antidepressants, hypnotics or other mental health-related medications. Additional cost categories for the broader societal perspective included the costs of informal care provided by family members or friends as well as costs due to absenteeism from work for participants who were employed or self-employed.

Costing was conducted using UK national-level unit costs for a common costing year of 2020–1 as reported in *Table 66* in *Appendix 4*. Lost productivity costs were estimated using the human capital approach where time off work was multiplied by the average daily national salary for participants who were employed or self-employed.[102,103] All costs are expressed in Great British pounds (GBP) for the financial year 2020–1. Unit costs referring to earlier years were inflated using the NHS Cost Inflation Index (NHSCII) as reported in the Personal Social Services Research Unit (PSSRU) Cost of Health and Social Care 2021 report.[104]

Data processing

All available outcome and resource use data underwent thorough plausibility checks. Furthermore, three forms of missing data were encountered and underwent imputation. Firstly, participants did not always submit their self-reported outcome information at the planned follow-up time point within the compliance period of ± 3 weeks. When reported outcome data were available outside this window, we used linear extrapolation between the previous and the given data reporting time point and imputed missing outcome data points according. For the calculation of QALYs or CWLYs gained, all available and extrapolated outcome data points were taken into consideration. Secondly, participants may have submitted incomplete HEQ data where key information was based on more than one question. For instance, the frequency of visits was reported but not their length. In these cases, missing length information was derived from the mean of the available observations in the relevant trial arm. All other missing data were imputed using the gold standard method of multivariate imputation via chained equations based on the missing at random assumption.[105,106] Missing values were filled in based on predictive mean matching adjusted for age, sex and trial arm using three donors and repeated for $M = 24$ sets of imputed values, where M as a rule-of-thumb corresponded to the percentage of missing values in the data set.

Cost-effectiveness analysis

For the economic analyses, outcomes were adjusted to their baseline values and reported as difference-to-baseline to avoid any potential bias due to the considerable observed difference in the mean baseline EQ-5D-5L, ICECAP-A and OxCAP-MH levels between the pramipexole and placebo arms. Difference in HRQoL and capability well-being gains between the groups over time was analysed using multiple regression analysis with age, sex and trial arm as explanatory variables. For the calculation of QALYs and CWLYs gained, HRQoL and capability well-being states were assumed to change linearly between the two data collection points.

Cost-effectiveness results were expressed as incremental cost-effectiveness ratios (ICERs) which correspond to the difference in costs divided by the difference in the given outcome between the pramipexole and the placebo arms, and are reported also as net monetary benefits (NMBs) and net health benefits (NHBs) for the base-case analysis at threshold values of GBP20,000/QALY gained and GBP30,000/QALY gained.

Non-parametric bootstrapping was used to generate a joint distribution of the mean incremental costs and effects through 1000 simulations based on random draws.[107] The bootstrapping approach allows calculating the 95% uncertainty intervals of the ICERs to represent uncertainty around the point estimate and controls for data outliers. As per probabilistic medical decision-making techniques, uncertainty around the main cost-effectiveness estimates is also presented on the cost-effectiveness plane and by cost-effectiveness acceptability curves (CEACs).[108,109] The cost-effectiveness plane has four quadrants, each representing a different decision-making scenario. Bootstrapped ICERs falling in the SE quadrant show pramipexole being more effective and less costly than placebo (dominant), falling in the NW quadrant show pramipexole being less effective and more costly than placebo (dominated), falling in the SW quadrant show pramipexole being less effective and less costly than placebo, and falling in the NE quadrant show pramipexole being more effective and more costly. CEACs are based on the net benefit principle and show the probability that pramipexole is cost-effective at a range of maximum threshold values (ceiling ratio) that a decision-maker might be willing to pay for an additional unit of improvement in outcomes.

For all statistical analyses, a two-tailed p-value of < 0.05 was used as the threshold for statistical significance. To compare trial arm means, paired two-tailed t-tests were applied. All analyses were carried out in Excel (Microsoft Office 2016, Microsoft Corporation, Redmond, WA, USA) and STATA version 15 (2017. StataCorp LLC, TX, USA).

Sensitivity analyses

We investigated the potential impact of linear extrapolation in HRQoL and capability well-being between health states by assuming the alternative that these changes happen at the beginning of each given time period in a sensitivity analysis. Further sensitivity analyses in terms of clinical patient characteristics were carried out for the PP-HE sample that excluded three participants whose depression severity was below 11 on the QIDS scale at treatment initiation (baseline), and one patient who did not provide any health economic data beyond the baseline. All methods and scenarios otherwise mirrored the main health economic evaluation. Due to the low number of trial participants who provided complete data (no single missing data point) over the entire 48-week follow-up (a total of 15 participants), a complete case analysis was not carried out.

Results

Study population

The demographic and main clinical characteristics of patients included in the ITT sample at baseline (total: $n = 36$, pramipexole: $n = 16$, placebo: $n = 20$) are shown in *Table 28* and *Table 29* in *Appendix 3*. Socioeconomic characteristics are described in *Table 67* in *Appendix 4*. The same baseline patient characteristics of the PP-HE sample (total: $n = 32$, pramipexole: $n = 15$, placebo: $n = 17$) are provided in *Table 68* in *Appendix 4*. As described in *Chapter 3*, there were no significant differences between the arms except in the case of depression severity being lower in the pramipexole arm.

Missing data

The level of missingness for all used outcome and resource use data is reported in *Appendix 4*, *Table 69*. Overall, missingness was below 5% at 12 weeks and around 25% of all planned health economics-related data points over 48 weeks including missingness as a result of withdrawal due to early closure of the trial.

Outcome results

The two arms differed considerably (but not significantly) in all health economic outcome measures at baseline with participants in the pramipexole arm having on average higher HRQoL and capability well-being outcomes at treatment initiation (see *Appendix 4*, *Table 70*). Observed HRQoL and capability well-being (EQ-5D-5L, EQ VAS, ICECAP-A, OxCAP-MH) all improved for both arms at 12 weeks and over the entire 48 weeks follow-up when taking the mean over all available data collection points at 12, 24, 36 and 48 weeks for the available cases into consideration (*Figure 15*). None of the observed changes at 12 weeks relative to baseline were statistically significant at the 95% confidence level due to the comparatively large confidence bounds corresponding to the small sample size. However, average improvement was more dominant in the pramipexole arm for the later follow-up stages, resulting in statistically significantly higher incremental HRQoL (EQ-5D-5L index) gain (+ 0.07, 95% CI 0.01 to 0.13) in comparison to placebo over 48 weeks as shown in the multiple regression analysis adjusted for age, sex and baseline values (*Table 14*).

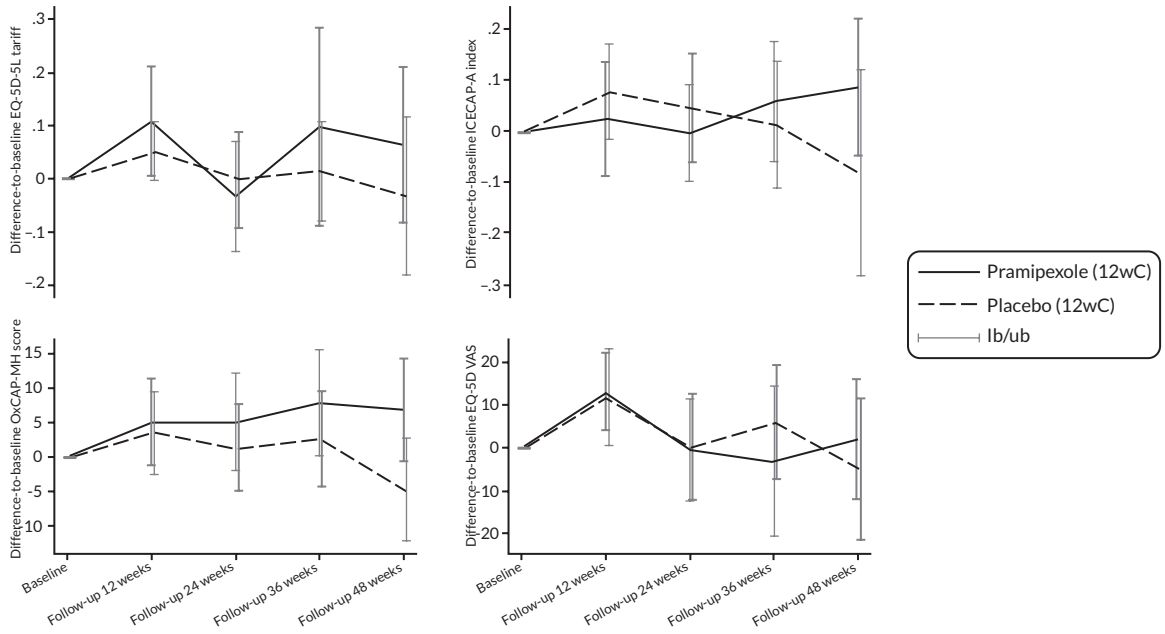

FIGURE 15 Health economic outcome results. (a) EQ-5D-5L (NW); (b) ICECAP-A (NE); (c) OxCAP-MH (SW); and (d) EQ VAS (SE) for the comparative ITT sample.

TABLE 14 Health economic outcome results at 12 weeks and over 48 weeks: EQ-5D-5L index, ITT sample, regression with robust standard errors

	Ordinary least squares		Generalised least squares	
Outcome: difference-to-baseline EQ-5D-5L index		**Controlling for baseline EQ-5D-5L**		**Controlling for baseline EQ-5D-5L**
Follow-up	12 weeks	12 weeks	48 weeks	48 weeks
Data type	Cross section	Cross section	Panel	Panel
Age	−0.000176	−0.000108	−0.000596	0.000425
	(−0.00142, 0.00106)	(−0.00150, 0.00129)	(−0.00397, 0.00278)	(−0.00228, 0.00313)
Female	0.00173	0.00114	−0.0754	−0.0843
	(−0.0435, 0.0469)	(−0.0429, 0.0451)	(−0.165, 0.0140)	(−0.145, −0.0233)
Pramipexole	0.00833	0.0137	−0.0113	0.0680
	(−0.0346, 0.0513)	(−0.0446, 0.0719)	(−0.0963, 0.0737)	(0.00847, 0.128)
EQ-5D-5L tariff level at baseline		−0.0366		−0.546
		(−0.147, 0.0734)		(−0.750, −0.342)
Constant	0.00431	0.0182	0.0695	0.277
	(−0.104, 0.113)	(−0.0655, 0.102)	(−0.126, 0.265)	(0.105, 0.448)
Time-fixed effects	–	–	Yes	Yes
Observations	36	36	144	144

The secondary health economic outcomes showed a similar significant added benefit of pramipexole over 48 weeks for the ICECAP-A index (+ 0.08, 95% CI 0.02 to 0.15) (*Table 15*) and for the OxCAP-MH score (+ 4.03, 95% CI 0.24 to 7.81) (*Table 16*).

Cost results

Observed level of resource use

Resource utilisation is shown in *Appendix 4*, *Table 71*, while *Appendix 4*, *Table 72* shows the main cost results. The two arms did not differ significantly in their baseline costs measured over 4 weeks prior to treatment initiation. Other than in the case of direct treatment costs (£20.00, 95% CI £17.47 to £22.53), the two arms did not differ in any of the measured cost categories significantly during the trial period corresponding to the small sample size either. When looking at total health and social services costs, the pramipexole arm in comparison to the placebo arm was on average cost saving both over 12 weeks (−£52.48, 95% CI −£391.64 to £286.67) and over 48 weeks (−£798.65, 95% CI −£1882.17 to £284.87), although the differences were not significant. From the societal perspective, the pramipexole arm was on average more costly both over 12 weeks (£794.73, 95% CI −£2698.82 to £4288.29) and over 48 weeks (£1170.73, 95% CI −£8941.89 to £11,283.35), although the differences were not significant.

Cost-effectiveness results: base-case analysis (QALY gained)

Mean incremental costs, QALYs and cost–utility results are reported in *Table 17* both over 12 weeks and over 48 weeks. From the NHS + PSS perspective, we found pramipexole on average more effective and cost saving than placebo for both time periods. From the societal perspective, pramipexole was shown being on average more effective and more expensive. Uncertainty around the mean ICERs was large with statistically non-conclusive 95% CIs in all cases.

Uncertainty in the cost-effectiveness results is also presented probabilistically via the cost-effectiveness plane and CEAC based on bootstrapped results from the NHS + PSS perspective in *Figure 16* and from the societal perspective in *Figure 17* for both time periods.

TABLE 15 Health economic outcome results at 12 weeks and over 48 weeks: ICECAP-A, ITT sample, regression with robust standard errors

	Ordinary least squares		Generalised least squares	
Outcome: difference-to-baseline ICECAP-A index		**Controlling for baseline ICECAP-A**		**Controlling for baseline ICECAP-A**
Follow-up	12 weeks	12 weeks	48 weeks	48 weeks
Data type	Cross section	Cross section	Panel	Panel
Age	−0.00143	−0.00155	0.00192	0.000950
	(−0.00533, 0.00248)	(−0.00563, 0.00254)	(−0.00267, 0.00651)	(−0.00237, 0.00426)
Female	−0.0417	−0.0429	−0.0498	−0.0595
	(−0.127, 0.0439)	(−0.131, 0.0450)	(−0.153, 0.0532)	(−0.133, 0.0136)
Pramipexole	−0.0133	−0.00896	0.0458	0.0811
	(−0.0919, 0.0653)	(−0.0847, 0.0668)	(−0.0515, 0.143)	(0.0175, 0.145)
ICECAP-A index level at baseline		−0.0667		−0.540
		(−0.201, 0.0674)		(−0.737, −0.343)
Constant	0.109	0.144	−0.0738	0.212
	(−0.179, 0.396)	(−0.193, 0.481)	(−0.349, 0.201)	(−0.0324, 0.457)
Time-fixed effects	–	–	Yes	Yes
Observations	36	36	144	144

TABLE 16 Health economic outcome results at 12 weeks and over 48 weeks: OxCAP-MH score, ITT sample, regression with robust standard errors

	Ordinary least squares		Generalised least squares	
Outcome: difference-to-baseline OxCAP-MH score		**Controlling for baseline OxCAP-MH**		**Controlling for baseline OxCAP-MH**
Follow up	12 weeks	12 weeks	48 weeks	48 weeks
Data type	Cross section	Cross section	Panel	Panel
Age	−0.0825	−0.0534	−0.0207	0.0876
	(−0.299, 0.134)	(−0.254, 0.147)	(−0.311, 0.270)	(−0.101, 0.276)
Female	−0.550	−0.00315	−4.115	−2.081
	(−6.115, 5.016)	(−5.247, 5.241)	(−11.73, 3.500)	(−6.300, 2.138)
Pramipexole	−1.001	0.142	−0.231	4.026
	(−6.091, 4.088)	(−4.698, 4.983)	(−7.500, 7.038)	(0.241, 7.811)
OxCAP-MH score at baseline		−0.164		−0.611
		(−0.350, 0.0220)		(−0.771, −0.451)
Constant	5.402	12.11	3.785	28.75
	(−11.31, 22.12)	(−8.190, 32.41)	(−14.08, 21.65)	(14.36, 43.14)
Time-fixed effects	–	–	Yes	Yes
Observations	36	36	144	144

TABLE 17 Cost-effectiveness results (pramipexole vs. placebo) with QALYs as outcome measure based on the ITT sample

Perspective	Cost difference (95% CI)	QALY gain difference (95% CI)	ICER (95% CI)	Interpretation
Weeks 1–12				
NHS + PSS	−£52.48 (−£393.94 to £238.56)	0.006 (−0.005 to 0.017)	−£9253.92/QALY (−£186,950.40/QALY to −£20,180.85/QALY)	Pramipexole on average saves costs and is more effective than placebo
Societal	£794.73 (−£2428.52 to £4181.67)	0.006 (−0.005 to 0.017)	£140,128.83/QALY (−£551,419.39/QALY to −£1,012,159.77/QALY)	Pramipexole on average is more expensive, but more effective than placebo
Weeks 1–48				
NHS + PSS	−£798.65 (−£1763.75 to £69.27)	0.032 (−0.038 to 0.101)	−£24,592.70/QALY (−£265,810.47/QALY to £7503.59/QALY)	Pramipexole on average saves costs and is more effective than placebo
Societal	£1170.73 (−£7989.04 to £10,871.54)	0.032 (−0.038 to 0.101)	£36,050.09/QALY (−£552,661.13/QALY to −£615,990.70/QALY)	Pramipexole on average is more expensive, but more effective than placebo

In *Figure 16*, we can see that from the NHS + PSS perspective bootstrapped ICERs mainly fall within the SE quadrant of the cost-effectiveness plane for both time periods resulting in an around 90% probability of pramipexole being cost-effective at £30,000/QALY gained.

In *Figure 17*, we can see that from the societal perspective most bootstrapped ICERs fall within the NW quadrant of the cost-effectiveness plane and the probability of pramipexole remains under 50% at £30,000/QALY gained.

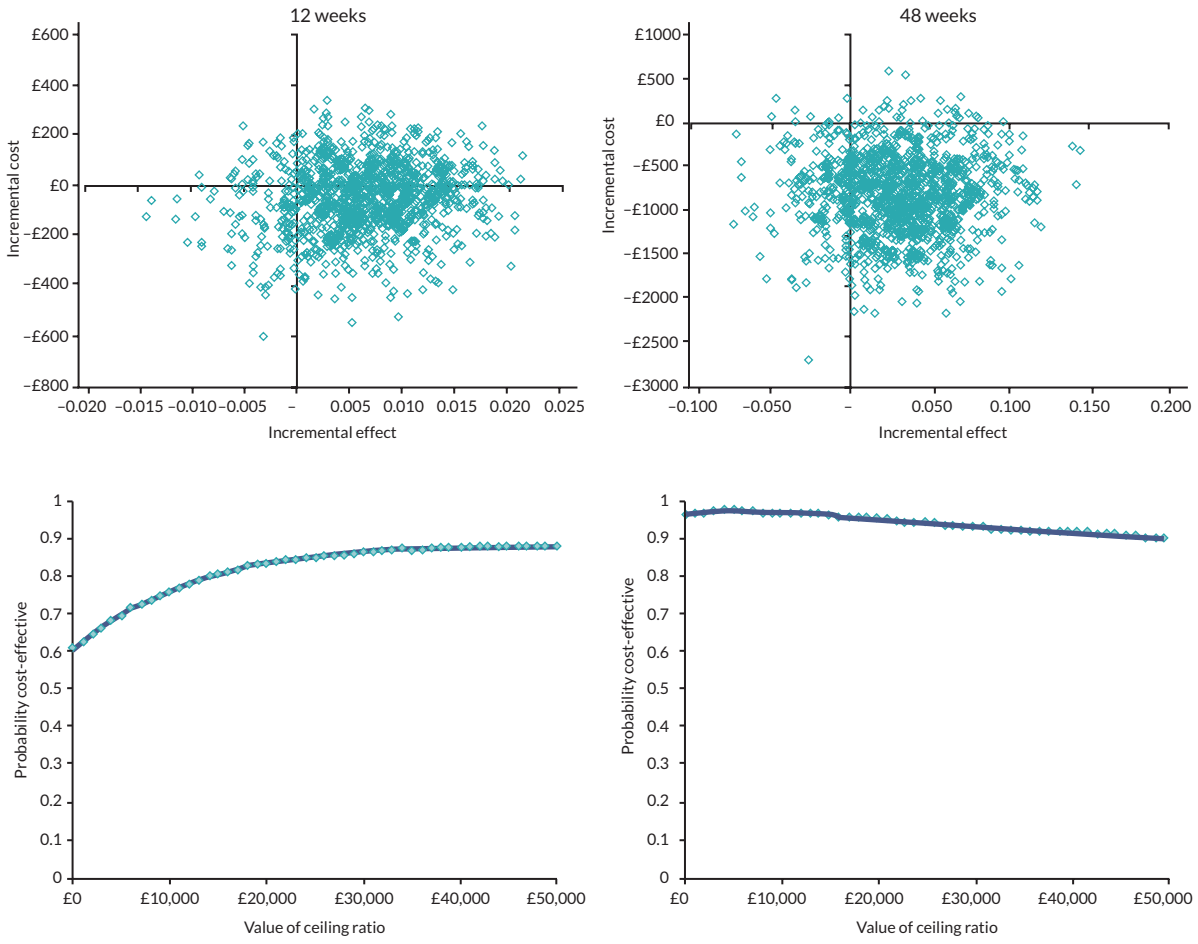

FIGURE 16 Uncertainty in the cost-effectiveness results (NHS + PSS perspective). Note: cost-effectiveness plane with bootstrapped ICERs for pramipexole vs. placebo treatment (left: 12 weeks, right: 48 weeks); CEAC showing the probability of pramipexole being cost-effective in comparison to placebo treatment at different willingness-to-pay thresholds for QALY gained (left: 12 weeks, right: 48 weeks).

The NMB at 12 weeks (NHS + PSS perspective) was £165.91 (95% CI −£177.08 to £536.21) assuming a willingness-to-pay (WTP) threshold of £20,000, and £222.63 (95% CI −£205.54 to £672.53) assuming a WTP threshold of £30,000. The corresponding NHB was 0.01 QALY (95% CI −0.01 QALY to 0.03 QALY) and 0.01 QALY (95% CI −0.01 QALY to 0.02 QALY), respectively. In line with the findings presented above, the NMB and NHB for pramipexole improve when considering the longer follow-up period of 48 weeks, for example, with an NMB of £1448.15 (95% CI −£295.39 to £3057.81) at £20,000 and £1772.90 (95% CI −£542.81 to £3964.20) at £30,000, respectively. *Appendix 4*, *Tables 73* and *74* provide summaries of the NMB and NHB results for the main analyses of the ITT and PP-HE patient samples.

Cost-effectiveness results: secondary outcome analyses (CWLYs gained)

The secondary cost-effectiveness analyses used CWLYs gained based on the ICECAP-A index and the OxCAP-MH score as alternative outcome measures.

ICEpop CAPability measure for Adults

The secondary cost-effectiveness analysis results based on CWLY gained using the ICECAP-A are shown in *Table 18*, *Figures 18* and *19*. In line with the health outcome analysis results, the probability of pramipexole being cost-effective is somewhat lower than in the base-case analysis, but still around 70% over 48 weeks from the NHS + PSS perspective.

Oxford CAPabilities questionnaire-Mental Health

The secondary cost-effectiveness analysis results based on CWLY gained using the OxCAP-MH are shown in *Table 19*, *Figures 20* and *21*. In line with the primary health outcome analysis results, we found the probability of pramipexole being cost-effective about the same as in the base-case analysis, around 90%, over 48 weeks from the NHS + PSS perspective.

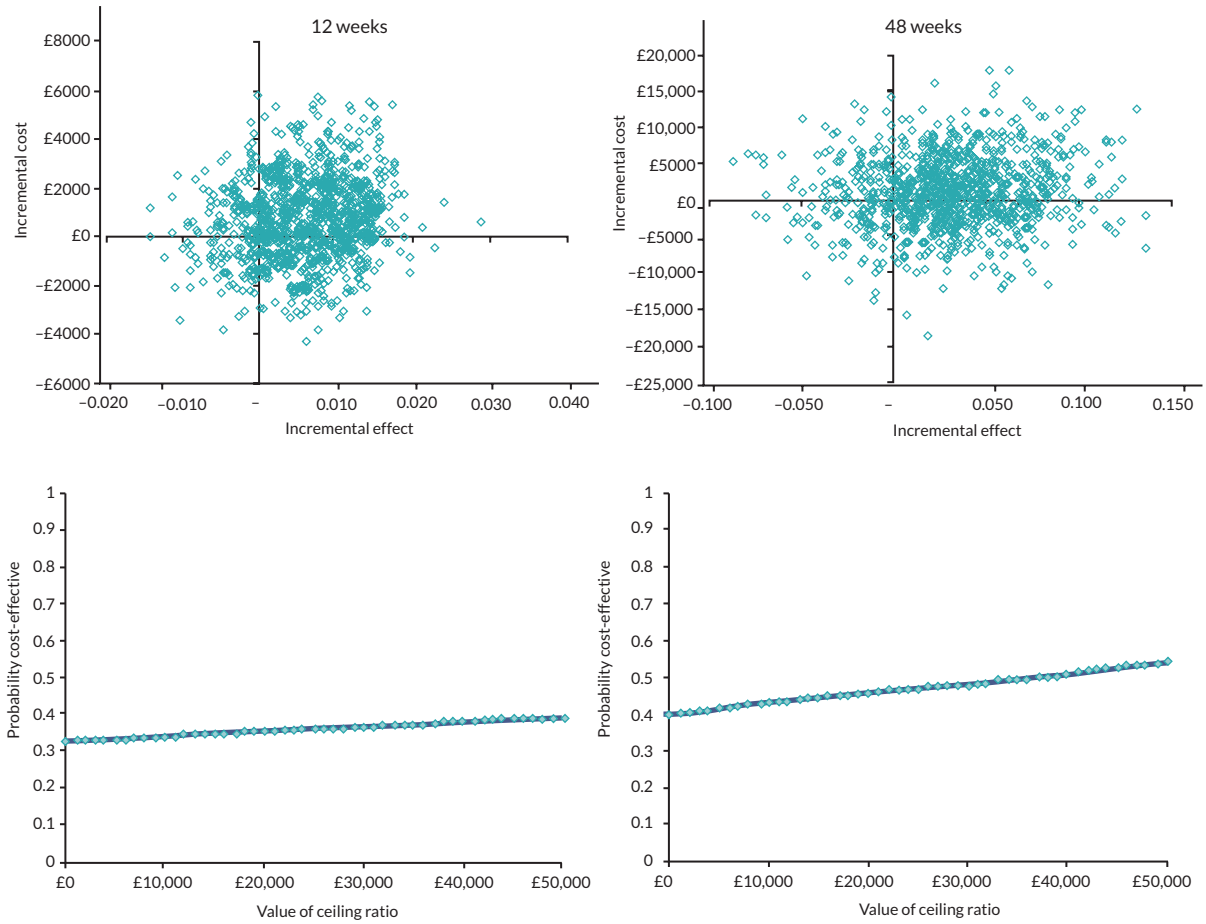

FIGURE 17 Uncertainty in the cost-effectiveness results (societal perspective) over 12 weeks and 48 weeks follow-up for the comparative ITT sample. Note: cost-effectiveness plane with bootstrapped ICERs for pramipexole vs. placebo treatment (left: 12 weeks, right: 48 weeks); CEAC showing the probability of pramipexole being cost-effective in comparison to placebo treatment at different willingness-to-pay thresholds for QALY gained (left: 12 weeks, right: 48 weeks).

TABLE 18 Cost-effectiveness results (pramipexole vs. placebo) with CWLYs based on the ICECAP-A outcome measure for the ITT sample

Perspective	Cost difference (95% CI)	CWLY gain difference (95% CI)	ICER (95% CI)	Interpretation
Weeks 1–12				
NHS + PSS	−£52.48 (−£393.94 to £238.56)	−0.006 (−0.020 to 0.008)	£9096.39 (−£128,587.56 to −£48,533.32)	Pramipexole on average saves costs, but is less effective than placebo
Societal	£794.73 (−£2428.52 to £4181.67)	−0.006 (−0.020 to 0.008)	−£137,743.44 (−£343,034.39 to −£1,730,450.12)	Pramipexole on average is more expensive and less effective than placebo
Weeks 1–48				
NHS + PSS	−£798.65 (−£1763.75 to £69.27)	−0.003 (−0.078 to 0.072)	£256,378.74 (−£352,407.26 to £820.17)	Pramipexole on average saves costs, but is less effective than placebo
Societal	£1170.73 (−£7989.04 to £10,871.54)	−0.003 (−0.078 to 0.072)	−£375,821.91 (−£560,843.46 to −£1,014,617.01)	Pramipexole on average is more expensive and less effective than placebo

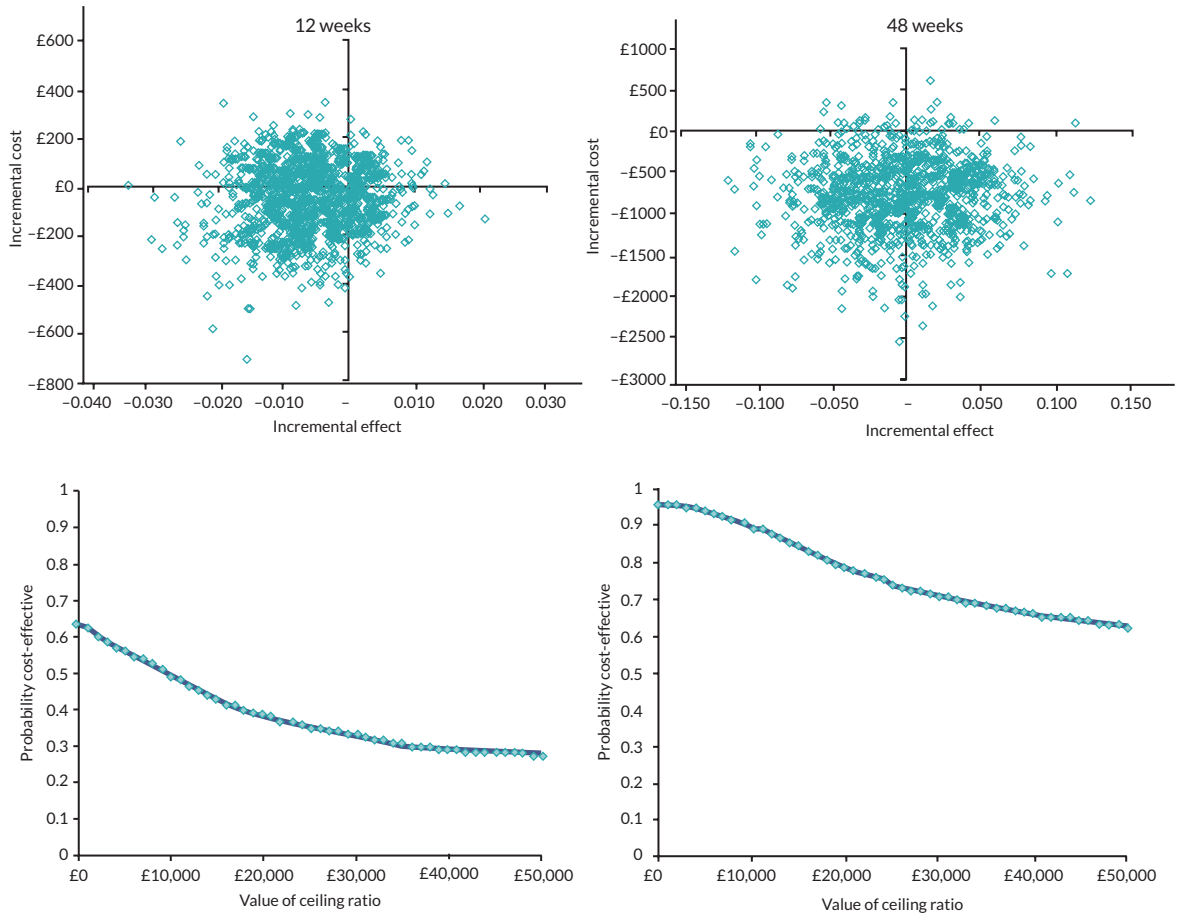

FIGURE 18 Uncertainty in the cost-effectiveness results (NHS + PSS perspective) over 12 and 48 weeks follow-up for the comparative ITT sample based on the secondary ICECAP-A outcome measure. Note: cost-effectiveness plane with bootstrapped ICERs for pramipexole vs. placebo treatment (left: 12 weeks, right: 48 weeks); CEAC showing the probability of pramipexole being cost-effective in comparison to placebo treatment at different WTP thresholds for CWLY gained (left: 12 weeks, right: 48 weeks).

Sensitivity analyses

Per-protocol health economics sample

Including in the economic evaluation only participants who fulfilled the 'per protocol' criteria had considerable impact on the cost-effectiveness results. In the PP-HE analysis, pramipexole was shown being significantly more effective than placebo in terms of QALYs gained over 48 weeks with the probability of being cost-effective from the NHS + PSS perspective increasing close to 100%. Relevant results are reported in *Table 20*, *Figures 22* and *23*. Separate trial population, outcome and cost results for the PP-HE analysis are shown in *Appendix 4*, *Figure 32*, *Tables 68*, *75* and *76*.

Alternative quality-adjusted life-year calculation (change-at-beginning)

Assuming changes in health status at the beginning of each time period rather than linearly between time points had no impact on the results or conclusions, the probability of pramipexole being cost-effective remained around 90% over 48 weeks from the NHS + PSS perspective. Relevant results are reported in *Appendix 4*, *Table 77*, *Figures 33* and *34*.

Discussion

This health economic evaluation assessed whether pramipexole treatment of patients with treatment-resistant BD in addition to mood stabilisers (treatment) is cost-effective compared to placebo (control) as administered within the PAX-BD trial.

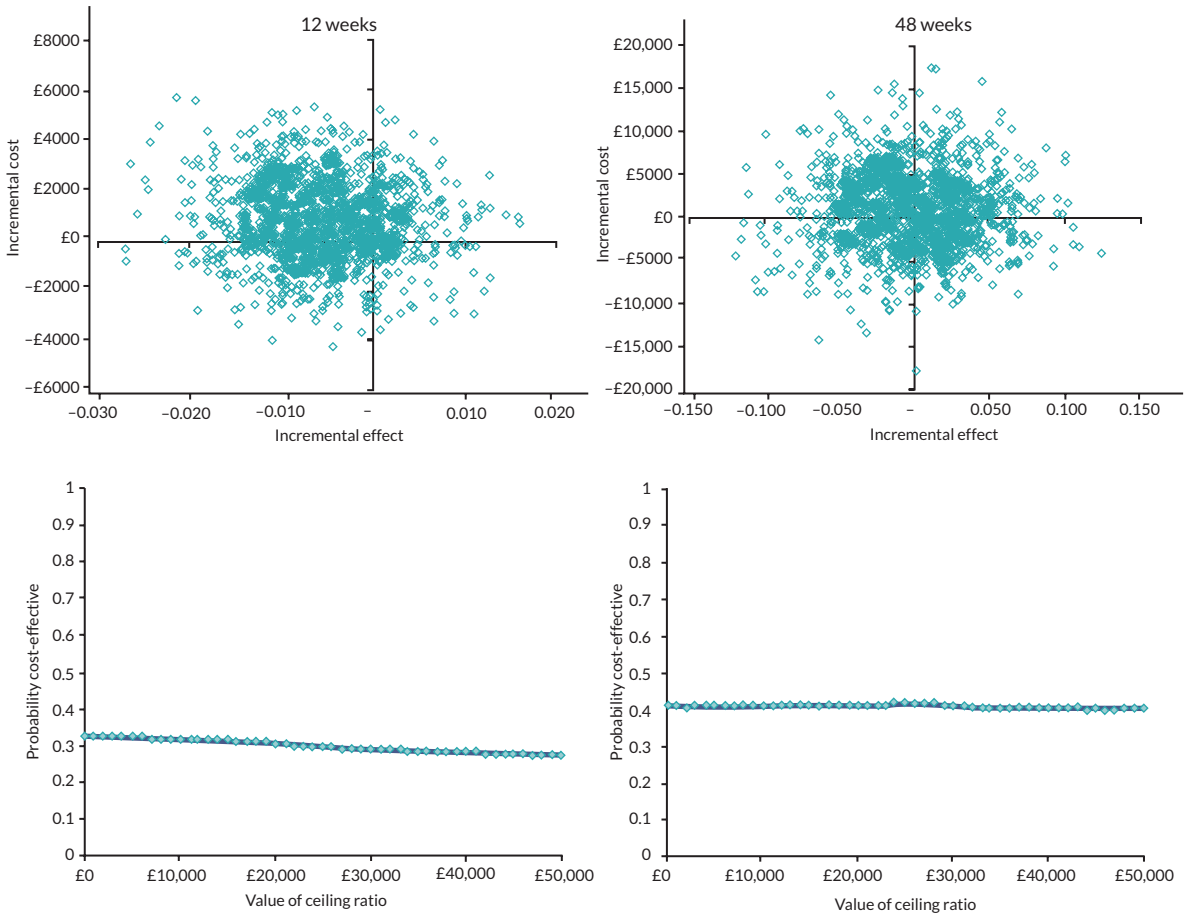

FIGURE 19 Uncertainty in the cost-effectiveness results (societal perspective) over 12 and 48 weeks follow-up for the comparative ITT sample based on the secondary ICECAP-A outcome measure. Note: cost-effectiveness plane with bootstrapped ICERs for pramipexole vs. placebo treatment (left: 12 weeks, right: 48 weeks); CEAC showing the probability of pramipexole being cost-effective in comparison to placebo treatment at different WTP thresholds for CWLY gained (left: 12 weeks, right: 48 weeks).

TABLE 19 Cost-effectiveness results (pramipexole vs. placebo) with CWLYs based on the OxCAP-MH outcome for the ITT sample

Perspective	Cost difference (95% CI)	CWLY gain difference (95% CI)	ICER (95% CI)	Interpretation
Weeks 1–12				
NHS + PSS	−£52.48 (−£393.94 to £238.56)	0.001 (−0.007 to 0.009)	−£40,424.12/CWLY (−£363,687.98/CWLY to −£86,657.72/CWLY)	Pramipexole on average saves costs and is more effective than placebo
Societal	£794.73 (−£2428.52 to £4181.67)	0.001 (−0.007 to 0.009)	£612,128.30/CWLY (−£343,034.39/CWLY to −£1,730,450.12/CWLY)	Pramipexole on average is more expensive, but more effective than placebo
Weeks 1–48				
NHS + PSS	−£798.65 (−£1763.75 to £69.27)	0.017 (−0.035 to 0.068)	−£46,042.72/CWLY (−£452,409.50/CWLY to £10,935.76/CWLY)	Pramipexole on average saves costs and is more effective than placebo
Societal	£1170.73 (−£7989.04 to £10,871.54)	0.017 (−0.035 to 0.068)	£67,493.36 (−£978,183.14/CWLY to −£821,899.03/CWLY)	Pramipexole on average is more expensive, but more effective than placebo

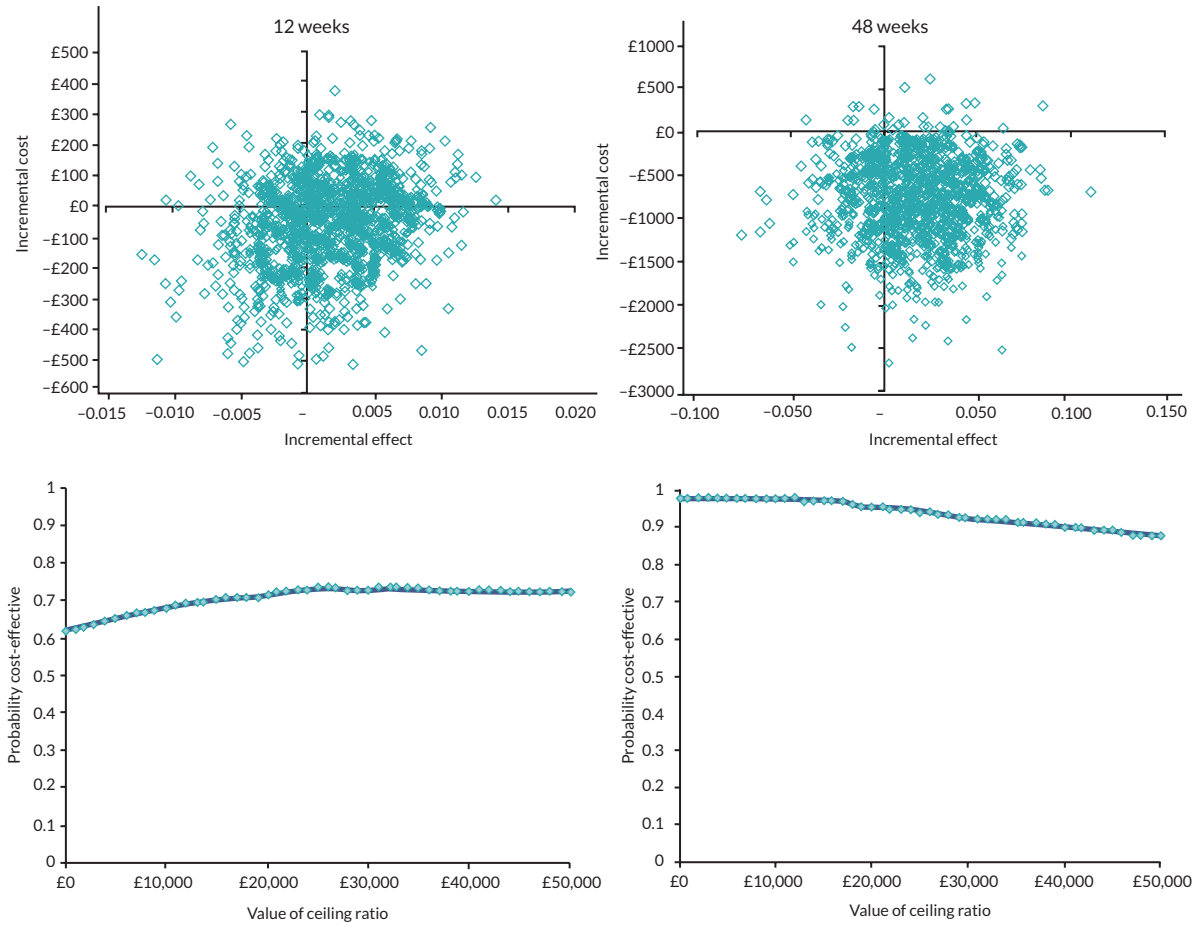

FIGURE 20 Uncertainty in the cost-effectiveness results (NHS + PSS perspective) over 12 and 48 weeks follow-up for the comparative ITT sample based on the secondary OxCAP-MH outcome measure. Note: cost-effectiveness plane with bootstrapped ICERs for pramipexole vs. placebo treatment (left: 12 weeks, right: 48 weeks); CEAC showing the probability of pramipexole being cost-effective in comparison to placebo treatment at different WTP thresholds for CWLY gained (left: 12 weeks, right: 48 weeks).

Since the PAX-BD trial was terminated early, the health economic evaluation suffered from the same limitation in terms of sample size as the main clinical analysis. Furthermore, the two arms of the trial had some imbalance in their health economic outcomes at baseline which we had to adjust for in our analyses. Addressing these limitations statistically, we found pramipexole being significantly more effective in terms of HRQoL and capability well-being over 48 weeks, but not over 12 weeks, which corresponds to the observed pattern of increasing pramipexole benefits over a longer duration. The additional health outcome gain over 48 weeks ranged between 4% and 8% depending on the outcome measure used. Cost-effectiveness analyses based on QALYs and CWLYs showed the probability of pramipexole being cost-effective in comparison to placebo over 48 weeks from the health and social care perspective being around 70–90%. In terms of the base-case analysis (QALY, NHS + PSS perspective), we found that almost 80% of the bootstrapped ICER estimates indicated pramipexole being more effective and less costly than placebo over 48 weeks (*Table 21*).

Since most of the PAX-BD trial was conducted during the COVID-19 pandemic, resource use and (treatment) cost results are indicative of the type of (mental) health care provided at that time and cannot be generalised to bipolar treatment costs outside the given context. On the other hand, these conditions equally impacted both arms of the trial. Since the economic evaluation looked at incremental effects and costs between the two trial arms, it is unlikely that any COVID-19-related resource use patterns impacted the incremental cost-effectiveness results from the NHS + PSS perspective significantly. This may not be true for broader societal costs such as lost productivity and informal care which could have been more significantly influenced by patients' individual circumstances during the COVID-19 pandemic. We also observed large differences between the two arms in terms of the number of patients reporting informal care support or employment (see *Appendix 4*, *Table 71*). Therefore, given the small sample size and the added

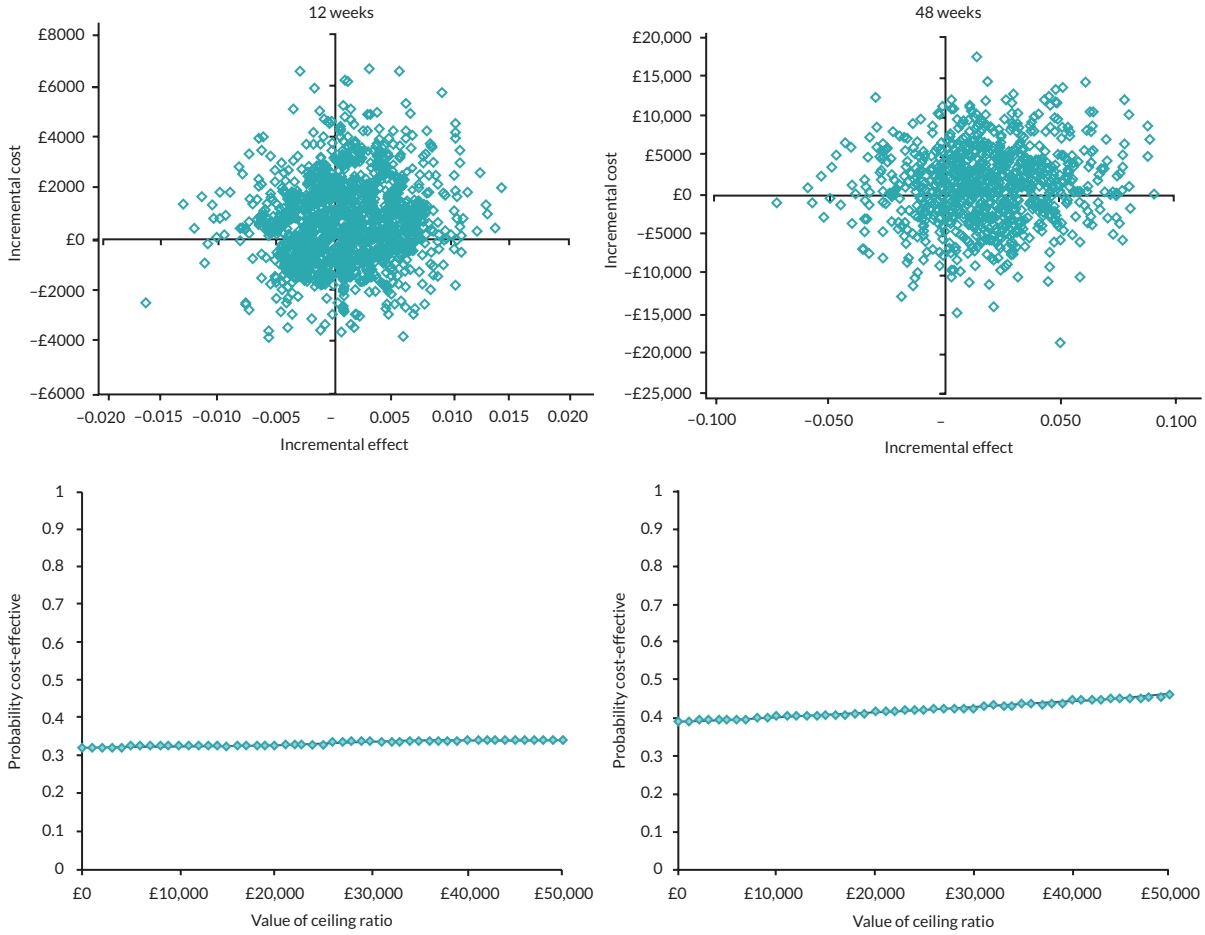

FIGURE 21 Uncertainty in the cost-effectiveness results (societal perspective) over 12 and 48 weeks follow-up for the comparative ITT sample based on the secondary OxCAP-MH outcome measure. Note: cost-effectiveness plane with bootstrapped ICERs for pramipexole against placebo treatment (NW: 12 weeks, NE: 48 weeks); CEAC showing the probability of pramipexole being cost-effective in comparison to placebo treatment at different WTP thresholds for CWLY gained (SW: 12 weeks, SE: 48 weeks).

TABLE 20 Cost-effectiveness results (pramipexole vs. placebo) with QALYs as outcome measure based on the PP-HE/MI sample

Perspective	Cost difference (95% CI)	QALY gain difference (95% CI)	ICER (95% CI)	Interpretation
Weeks 1–12				
NHS + PSS	−£60.42 (−£458.12 to £234.03)	0.009 (−0.002 to 0.018)	−£6742.96/QALY (−£117,616.02/QALY to £38,091.11/QALY)	Pramipexole on average saves costs and is more effective than placebo
Societal	£1649.56 (−£1568.33 to £5081.10)	0.009 (−0.002 to 0.018)	£184,099.59/QALY (−£256,450.30/QALY to −£231,891.82/QALY)	Pramipexole on average is more expensive, but more effective than placebo
Weeks 1–48				
NHS + PSS	−£890.40 (−£2105.02 to £58.64)	0.060 (0.000 to 0.112)	−£14,960.98/QALY (−£129,931.13/QALY to £7876.34/QALY)	Pramipexole on average saves costs and is statistically significantly more effective than placebo
Societal	£1997.75 (−£8639.48 to £12,275.65)	0.060 (0.000 to 0.112)	£33,567.42/QALY (−£238,771.39/QALY to £648,137.62/QALY)	Pramipexole on average is more expensive, but statistically significantly more effective than placebo

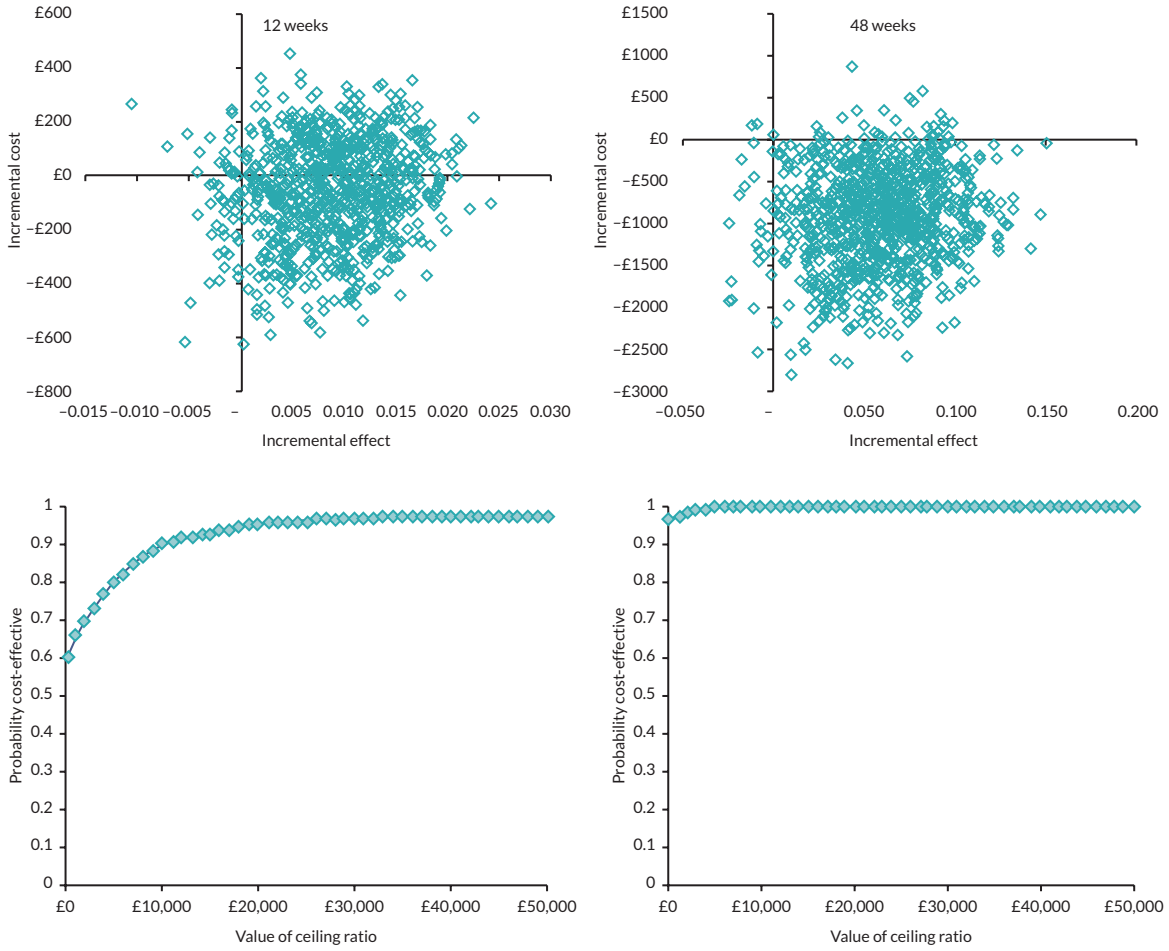

FIGURE 22 Uncertainty in the cost-effectiveness results (NHS + PSS perspective) over 12 and 48 weeks follow-up for the PP-HE sample. Note: cost-effectiveness plane with bootstrapped ICERs for pramipexole vs. placebo treatment (left: 12 weeks, right: 48 weeks); CEAC showing the probability of pramipexole being cost-effective in comparison to placebo treatment at different WTP thresholds for QALY gained (left: 12 weeks, right: 48 weeks).

uncertainty, cost and cost-effectiveness estimates from the societal perspective should be treated with extreme caution. We nevertheless report these estimates as outlined in our original analysis plan.[57]

Besides the above limitations, the economic evaluation has multiple strengths. Health economic analyses were carried out fully blinded to group allocation and independently of the main clinical statistical analysis. Furthermore, a respectively low total of 25% missing data points across all variables needed imputation. In addition, we conducted cost-effectiveness analyses not only with QALYs based on the EQ-5D-5L but also using CWLYs based on two validated capability well-being measures (the generic ICECAP-A and the more mental-health-specific OxCAP-MH) and found the same outcome results and cost-effectiveness conclusions with all three outcome measures.

Furthermore, the conclusions were insensitive to the outcome extrapolation methods used. Including only patients with at least moderate depression at baseline (PP-HE sample) increased the probability of cost-effectiveness even further.

In summary, our results based on the PAX-BD trial suggest added benefits of pramipexole in comparison to placebo in terms of HRQoL and capability well-being and suggest a tendency towards reduced health and social care costs with a high probability of overall cost-effectiveness over 48 weeks. Ideally, these findings would have to be confirmed in a larger sample size.

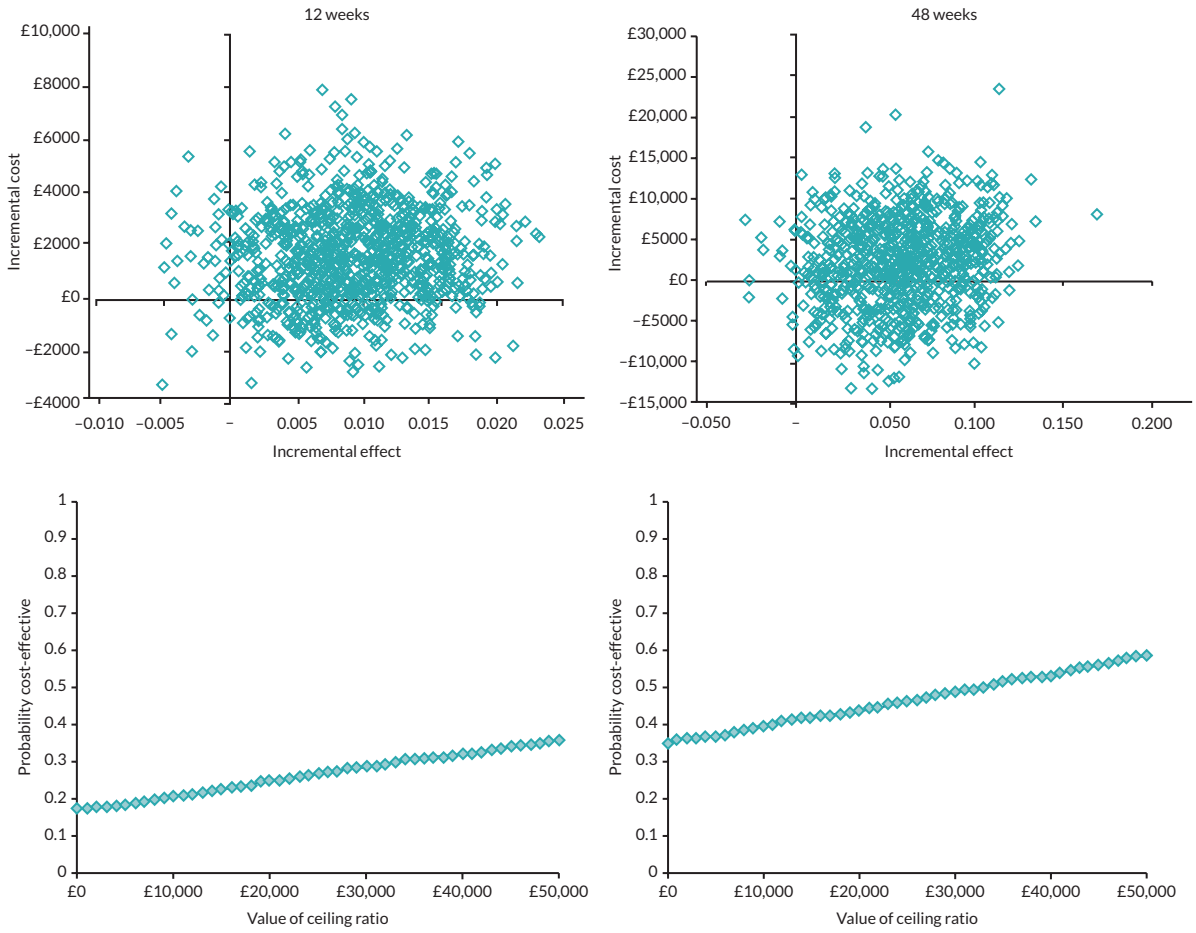

FIGURE 23 Uncertainty in the cost-effectiveness results (societal perspective) over 12 and 48 weeks follow-up for the PP-HE sample. Note: cost-effectiveness plane with bootstrapped ICERs for pramipexole vs. placebo treatment (left: 12 weeks, right: 48 weeks); CEAC showing the probability of pramipexole being cost-effective in comparison to placebo treatment at different WTP thresholds for QALY gained (left: 12 weeks, right: 48 weeks).

TABLE 21 Distribution of the base-case cost-effectiveness results across the four quadrants of the cost-effectiveness plane: QALYs, ITT population

Perspective	Quadrant I (NE)	Quadrant II (SE)	Quadrant III (SW)	Quadrant IV (NW)
Interpretation	Δ effect > 0	Δ effect < 0	Δ effect < 0	Δ effect < 0
	Δ costs > 0	Δ costs > 0	Δ costs < 0	Δ costs < 0
Weeks 1–12				
NHS + PSS	35.3%	51.0%	9.6%	4.1%
Societal	57.1%	24.8%	7.8%	10.3%
Weeks 1–48				
NHS + PSS	3.1%	78.2%	17.8%	0.9%
Societal	49.0%	31.8%	8.4%	10.8%

Chapter 5 Qualitative substudy

Aim and objective

The purpose was to explore the barriers and facilitators to recruitment and retention of participants in the PAX-BD trial. Initially, the qualitative component was intended to collect feedback specifically for the pilot phase of the trial. However, due to early trial closure, the applications of the qualitative substudy were broadened to encompass more general insights that could be applied to similar studies in future.

Method

Semistructured interviews were conducted by central researchers via telephone. Topic guides were used to cover areas of interest, as well as allowing openings for emergent topics (see *Appendix 5*, *Qualitative study topic guides for interviews*). Interviews were audio-recorded and outsourced to UK Transcription for transcribing. HCP participants verbally consented to interview and patient participants optionally consented at the pre-randomisation and randomisation consent visits.

Sample

A total of 26 participants were interviewed, comprising 15 HCPs (4 PIs and PI delegates, 11 non-clinical research staff including CSOs, nurses and RAs) and 11 randomised patient participants (1 withdrawn prior to week 12 and 10 retained until at least week 12). It was not possible to interview patient participants who were withdrawn in pre-randomisation as some had declined consent or disengaged with trial activities after withdrawal; similar issues were experienced for participants withdrawn prior to week 12.

Analysis

Barriers and facilitators were the key directing themes (*Table 22*) for interviews and analysis. More focused interpretation of the transcripts was guided by an a priori framework of subthemes (see *Appendix 5*, *A priori framework for analysis of barriers and facilitators to recruitment and retention to PAX-BD trial*) from a meta-analysis of studies in depression.[83] Interview transcripts were independently coded using NVivo Release 1.6.1 (QSR International, Warrington, UK) by at least one clinical and one non-clinical researcher to generate codes with an expanded span of interpretation. Initial codes were reviewed by a wider collective of clinical and non-clinical researchers, as well as the PPI group. Codes were modified on an ongoing basis to reach consensus and inform subsequent transcript analysis. Once all transcripts had been coded, analysis shifted to the interpretation of indexed codes assisted by the Hughes-Morley *et al.* framework;[83] subthemes were inductively revised, and emergent themes were added per recurring discussions. Homogeneity within the subthemes and heterogeneity across them was established and attributed to the three key themes: Barriers, Facilitators and Suggestions for Future Improvement. A summary framework of themes and codes is presented in *Table 22*.

Results

The results presented here are a summary of the findings from the qualitative research conducted. Fuller details of all sections, including verbatim quotations from participants, are included in *Appendix 5*.

TABLE 22 Summary framework of themes and codes

Themes	Subthemes and codes
Barriers	Expression of symptomatology: *Profile of BD; Patient presentation at recruitment; Determining causality of AEs*
	Presenting the trial to participants: *Impact of COVID-19 on services; Research prioritisation; Trial promotion strategies; Access to eligible patients; The term 'Treatment-resistance'; Uncertainty about research; Relationship with care team; Trial material*
	Treatment profile: *Clinician attitudes; Medication changes in pre-randomisation; Placebo; Pramipexole*
	Views of trial processes and procedures: *Administrative duties; Eligibility criteria; Medication processes; Safety monitoring*
Facilitators	Marketing: *Promoting to clinicians; Promoting to patients*
	Trust: *Trial design; Central research team; Relationship with care team; Informed consent; Attitude to risks; Central RAs*
	Perceived benefits: *Access to treatment; Altruism; Safety monitoring and support; Treatment response*
	Ability to conduct study: *Trial information; Reflective protocol amendments; Remote design; Medication processes; Flexibility in trial processes; HCP attributes and attitudes*
Suggestions for future improvement	Organisational issues
	Trial design
	Trial processes

Barriers to recruitment and retention

Expression of symptomatology

This subtheme considered the profile of TRBD, interplay from comorbid conditions and the clinical challenges these factors present in identifying eligible participants and engaging them.

Profile of bipolar depression

Healthcare professionals highlighted that BD has a complex profile with symptoms overlapping other disorders such as emotionally unstable personality disorder, and patient presentation can be compounded by lifestyle stressors. These nuances contribute to difficulties in identification of participants for the trial. Subsequent determination of treatment resistance poses further challenges in clinical practice. The exclusion criteria included comorbid substance misuse and impulse control issues. HCPs highlighted that such comorbidities were prevalent among the bipolar patient group, narrowing the pool of eligible participants.

Patient presentation at recruitment

Transcript analysis suggested an interplay between previous treatment failures and chronicity of BD, which appeared to yield a sense of desperation for active treatment. This made it difficult to accept the possibility of placebo. Participants were required to be in a current mood episode, contingent on the periodic nature of BD, and this could change while they were in the pre-randomisation stage. The impact of depressive symptoms and side effects of medication were recognised as barriers to patients' capacity to process trial material. Similarly, poor motivation could also lead to difficulties completing trial activities and engagement with HCPs. Overall, recruiting patients from the TRBD cohort posed complex clinical challenges in considerations of eligibility and ability to safely participate in the PAX-BD trial.

Determining causality of adverse events

During the randomisation stage, it was difficult to ascertain the causality of AEs due to similarities between common side effects of pramipexole and psychotropic concomitant medications, as well as bipolar symptoms of hypomania, mania and impulse control.

Presenting the trial to participants

Impact of COVID-19 on services

COVID-19 posed significant challenges to the PAX-BD trial. Although many trial activities were conducted remotely, sites were required to obtain consent in-person while adhering to strict guidelines around face-to-face contact. After restrictions became more lenient, there was a lengthy adjustment period post pandemic. Overall, HCPs widely expressed the view that recruitment would have been more successful if not for the COVID-19 pandemic.

Research prioritisation

Some PIs reported use of personal time for conducting research suggesting a workplace ethos that research is not a routine activity integrated into clinical care. HCPs employed at these sites reported limited recruitment and research experience, citing lack of staff capacity, resources and networks with clinical services as barriers to research involvement. Reflecting on the trial, HCPs stated they would reconsider involvement in research, particularly later in their careers, due to mounting clinical pressures.

Trial promotion strategies

Non-medical staff across sites emphasised the importance of engaging clinicians to gain access to eligible participants. This was challenging due to the limited availability of PIs, which shifted the burden of marketing and recruitment to CSOs. They reported that clinicians were less receptive to promotion from non-clinical colleagues; therefore, peer-to-peer trial endorsement was critical in imbuing credibility, especially in relation to a Clinical Trial of Investigational Medicinal Product (CTIMP). Overall, HCPs described the approach to recruitment as proactive and were perplexed when these attempts did not produce more referrals.

Access to eligible patients

Logistical issues in the care pathway structure were widely noted by HCPs who believed that patients with BD were largely under primary care, despite the nature of treatment resistance necessitating management under a community mental health team. HCPs used patient databases and case notes for pre-screening but noted a lack of informative detail. CSOs additionally encountered gatekeeping of clinical caseloads. Ultimately, CSOs focused screening to the caseloads of PIs who were already involved in the trial and with whom they had an existing working relationship. The pool of prospective patients, and scope for professional development, was therefore limited.

The term 'Treatment resistance'

One patient stated that learning about the 'treatment-resistant' label was surprising, indicating this may have been a somewhat confronting experience. Given the nihilistic and stigmatising overtones of the phrase patient-facing documents and clinic discussions might be better using the alternative 'difficult to treat bipolar depression', mirroring the use in major depressive disorder.[110] Treatment failures prior to the trial appeared to contribute to scepticism about the efficacy of pramipexole. Conversely, one HCP believed patient cost–benefit appraisals did not swing in favour of participation for those who had not exhausted all treatment options.

Uncertainty about research

The profile of research was raised in public consciousness because of the COVID-19 pandemic. Some patients were cautious of partaking in PAX-BD due to the view that research is experimental with unknown drug characteristics and potentially harmful side effects. Some participants expressed general apprehension, particularly around the RCT design.

Relationship with the care team

A patient with a negative view of their care team declined the opportunity for participation. The prospect of closer monitoring by the research team highlighted frustrations around the lack of sufficient support from their clinical team. During the trial, some patient participants reported a lack of direct involvement from their local site teams. Overall, patient views of their local team influenced their general level of satisfaction, perception of support and ability to carry out trial activities with ease.

Trial material

Some participants highlighted the complexity and amount of trial material they received. They felt overwhelmed by it, particularly at the beginning of the trial. Some admitted that rather than refer to the information sheet, they relied on conversations with HCPs leading to an added burden on staff time.

Treatment profile

Clinician attitudes

Clinical Studies Officers noted that sceptical clinicians viewed research as detrimental and/or disruptive to patients' mental health, thereby withholding access out of desire to protect the vulnerable patient. One PI expressed general anxiety about the experimental nature of pramipexole for the treatment of BD.

Medication changes in pre-randomisation

Prior to the amendment allowing antipsychotics use in the randomisation stage, there was a reluctance to withdraw antipsychotics due to the possibility of destabilising patients and triggering relapse of manic or psychotic symptoms. HCPs reported many patient refusals due to the requirement to withdraw antipsychotics. Patient views suggested that those who were required to make changes to existing medication were likely to express stronger concerns about placebo. The obligation to commence a mood stabiliser was challenging for patients who had experienced intolerable side effects in the past and/or felt they had been ineffective.

Placebo

The possibility of being randomised to placebo appeared to give many patients pause when considering participation in PAX-BD. The resistance to placebo appeared to be exacerbated by the length of the trial.

Pramipexole

Healthcare professionals expressed major concerns about impulsivity and mania as potential side effects of pramipexole in bipolar patients. For some clinicians, this was compounded by the view that they could not intervene per usual clinical care due to restrictions in the first 12 weeks of the trial. Hence, a risk-averse approach was employed with patients perceived to be more vulnerable but not definitively ineligible.

View of trial processes and procedures

Administrative duties

During the trial, HCPs reportedly found it difficult to keep abreast of the numerous protocol changes and maintain administrative files, particularly in line with pandemic guidelines. PIs struggled to complete research tasks within trial timelines, especially when accounting for their restricted availability.

Eligibility criteria

Although reflective amendments were made to the eligibility criteria, some HCPs stated this did not significantly increase recruitment. HCPs thought the eligibility criteria were limiting and did not accurately represent the normative bipolar patient. Criteria around comorbid conditions, manic and psychotic symptoms, and treatment resistance were repeatedly flagged as stringent and restrictive.

Medication processes

Healthcare professionals expressed concerns about the capability of patients to independently manage study medication, particularly if they were in remission from substance misuse and/or experiencing impulse control issues related to BD or as a side effect of pramipexole. In these cases, they appeared to regard the independent management of medication as a risk factor. For participants in the trial, challenges were oriented around managing the large supplies of trial medication. Challenges in the 4-week titration phase related to the complexity of dosing.

Safety monitoring

Remote trial monitoring in PAX-BD was a barrier for patients who were reportedly lacking computer literacy or access, fearful of technology and/or had anxieties around answering the telephone. Central RAs observed that if participants

experienced issues with the digital platform on first use, frustration developed at an early stage which meant they were likely to be less tolerant of continuing faults. Patient participants reported that the frequency and volume of questionnaires were time consuming. Some participants felt that the questions were not representative of their experiences. Weekly calls were unappealing to some patients.

Healthcare professionals noted difficulties engaging participants, and the reliance on a remote design led to gaps in crucial safety monitoring which resulted in recommendations to withdraw participants if they did not re-engage.

Facilitators to recruitment and retention

Marketing of the trial

Promoting to clinicians

The central research team regularly contacted sites about PAX-BD, which served as ongoing reminders and helped HCPs maintain recruitment goals. CI involvement in promoting the trial was highlighted by HCPs who expressed the effectiveness of a credible expert outlining limitations in the treatment of BD and emphasising the subsequent salience of trial objectives. Locally, PI networks seemed to be especially important in raising the profile of the trial. Research-active trusts had dedicated teams, and HCPs at such sites seemed better able to promote the trial. HCPs at less established research sites mitigated lack of prioritisation by proactively using special interest time for the trial. An additional appeal of PAX-BD was the opportunity for professional development from upskilling research and clinical competencies.

Promoting to patients

Healthcare professionals found the ability to promote the trial in clinical appointments efficient and effective. Some PIs adopted the strategy of framing PAX-BD as a 12-week trial and found this approach was more palatable to patients compared to the somewhat daunting prospect of 48-week participation. Patients generally reported positive impressions of the trial design and that although the trial processes were vast and complex, the language in the documents was clear.

Trust

Trial design

One patient response indicated that the research focus on treatment for BD validated their experiences of chronicity and debilitation; HCPs also recognised the salience of this in a professional capacity. Pramipexole has an existing profile of product characteristics, side effects and previous research and is also prescribed off-licence for mood disorders.[27] This evidence base was accessible to HCPs and patients; combined with trial information and discussions with HCPs, this may have perpetuated a perception of pramipexole as relatively low risk.

Central research team

During the trial, the central team organised regular teleconferences attended by multiple sites to discuss progress and provide updates. They were understanding of recruitment challenges and collaborated with sites to implement alternative strategies, rather than applying idealistic pressure. This approach was particularly beneficial to less-experienced sites. Reflective amendments to trial processes and the eligibility criteria in response to challenges at site demonstrated that HCP feedback was valued and tangibly implemented.

Relationship with care team

Positive and trusting patient relationships with secondary care teams was a key facilitator of recruitment and engagement throughout the trial.

Informed consent

A strong sense of autonomy was emphasised by patient participants, achieved by extended discussions with an emphasis on their right to exercise agency and withdraw consent at any time. Access to support systems outside the trial enabled some trial participants to join the trial and engage with trial activities.

Attitude to risks

Some participants de-emphasised potential risks of the trial, adopting the stance that consequences of participation would be either neutral or beneficial. Participants felt they had fostered acute awareness of their response to drugs and felt confident in their ability to quickly identify side effects to prevent escalation. In terms of antipsychotic and mood stabiliser adjustments, some indicated that they were more receptive to changes as the current medication was ineffective. Many patients also appeared to have an implicit belief in HCPs' duty of care, diminishing excessive concerns about trialling an experimental drug or the severity of side effects.

Central research assistants

Constructive relationships and rapport were established with weekly calls during pre-randomisation and the first 12 weeks of randomisation. Demonstrations of reliable assistance and patient-centred care acquired participant trust.

Perceived benefits

Access to treatment

PAX-BD provided clinicians the opportunity to access a new medication option and medical expertise. HCPs anticipated that demonstrating treatment efficacy would strengthen the evidence base for pro-dopaminergic strategies. For participants, a strong component of hope was present.

Altruism

Many participants expressed altruistic motives for participation.

Safety monitoring and support

Compared to routine clinical practice, follow-up in PAX-BD was more robust, frequent and personalised, providing quick intervention in matters of patient safety. This was reassuring to participants and HCPs. Central RAs flagged any cause for concern to PIs indiscriminately, which inadvertently facilitated regular holistic clinical input.

Treatment response

A large component of participant retention and motivation for continuation in the trial centred on treatment response. HCPs similarly indicated that observing a decline in symptoms reinforced the possible benefits of the trial, potentially encouraging them to continue recruitment. Some participants ascribed improvements in facets of quality of life to trial participation.

Ability to conduct trial

Trial information

Many HCP participants cited the trial protocol and Clinician Manual as comprehensive base reference resources. Other trial resources such as training videos, newsletters, information sheets, participant diaries and the trial website were similarly highlighted as useful source material.

Reflective protocol amendments

The PAX-BD protocol was reflectively amended in response to feedback from sites; this resolved some eligibility constraints and expanded the pool of prospective participants, as well as mitigating clinician and patient concerns around medication changes.

Remote design

Prior to the COVID-19 pandemic, the PAX-BD trial utilised remote means of data collection and monitoring. Post-COVID-19 remote monitoring additionally increased the feasibility of the trial. Participants described the ease of online self-reported data compared to clinic visits.

Medication processes

Healthcare professionals indicated that regular updates from central RAs provided comprehensive oversight of trial participants, thus prescribing processes felt well informed. The use of the central CNTW pharmacy was noted to expand

feasibility for sites, as this streamlined trial set-up and dispensing processes. Participants additionally highlighted the convenience of receiving trial medication directly to their homes, rather than travelling to collect them. The option for CSOs to collect unused medication and empty bottles provided an additional adherence check and assurance that participants were managing medication safely.

Flexibility in trial processes

The role of flexibility was identified as a pragmatic facilitator, for instance the ability to make dose adjustments and lenient guidelines for concomitant medication and psychotherapy post week 12 made the trial more acceptable to patients and HCPs.

Healthcare professional attributes and attitudes

Clinical experience with bipolar depressed patients and successful recruitment in previous studies appeared to expedite knowledge of effective strategies to identify, engage and recruit participants. HCPs with prior experience in research were also better able to grasp nuanced trial requirements to avoid deviations and manage administrative tasks effectively. HCPs widely reported the value of CSOs assisting screening. Working values of collaboration, proactivity and dedication to patients emerged as facilitators of participant engagement.

Chapter 6 Patient and public involvement

The PAX-BD PPI group undertook a comprehensive review of the involvement of PPI in the trial and concluded with a set of recommendations for future studies. The full PPI group report (authored by the group) can be found in *Appendix 6*. A brief summary is provided here, including the conclusions and recommendations as written by the group.

Background

Public involvement is requested by most funders. However, this has the potential to lead to tokenism and several reviews of PPI have concluded that evidence of impact is weak. More evidence is required of public involvement in research to identify challenges, barriers and methods to overcome these to ensure appropriate and impactful public involvement.

PAX-BD was a complicated trial with several challenges due to participant recruitment, the trial population itself, amendments being implemented throughout the trial, the pandemic restrictions, personnel changes at the NCTU, the passing of our PPI lead and the early closure of the trial. This all led to the patient and public involvement and engagement (PPIE) group being able to assess the public involvement in the trial through the lens of facing and overcoming challenges as well as more generalised public involvement in a RCT.

Methods

The core methodology used in the analysis of PPI was the Guidance for Reporting Involvement of Patients and the Public 2 (GRIPP2) tool which aims to improve reporting of PPI within research. The GRIPP2 checklist, however, does not take into account the quality and impact of PPI on a trial, so the PPIE group also reviewed evidence following the work of Wilson *et al.* and reviewing PPI contributions utilising the dialogue and change award criteria designed by Investing in Children and the NIHR Applied Research Collaborative, North East and North Cumbria (ARC NENC). A retrospective review of all documentation relating to the public involvement within the trial was conducted, as well as holding a meeting with the public contributors and members of the trial team to get their views on the impact.

Conclusion

The PPIE group's evaluation of the public involvement within the PAX-BD trial has been led by established PPI evaluation tools and frameworks. The group have identified numerous occasions of PPI impacting the trial as well as discussing the process of PPI integration within the trial and the personal impacts to the public contributors and the researchers. The group have created a list of recommendations to support future public involvement in research. The PPI within this trial was largely developed as it progressed which had both positive and negative impacts on the trial, the researchers and the PPI contributors and, with hindsight, there are some changes that the group would make.

Some limitations of this evaluation are that the group did not have the aim of writing this chapter/paper (i.e. as per *Appendix 6*) until towards the end of the trial, so some information may have been lost due to not being aware of the need for PPI record keeping. The original PPI lead sadly passed away in September 2021. She had been involved from the initial trial design and unfortunately was not able to participate in this assessment of the overall involvement which would have added more depth to the evaluation. A different PPI lead taking over created new ways of working which may have affected the views of and created a 'before and after' attitude towards PPI from the other PPI members and the researchers, possibly impacting the involvement from the group. The second PPI lead was not involved from the inception of the trial so has no reference for the period prior to funding being received and her joining the group in March 2019. There have been a number of different Trial Managers which could have impacted the level of PPI involvement in the trial due to a possible lack of consistency in contact for the PPI group.

Overall, the PPI input has been relevant, beneficial and impactful to the trial, the researchers and the public contributors, with one PPI group member with no previous research experience stating:

> *Actually, I've really enjoyed it. It's been so interesting to listen to. I mean the upshot of all that is that I would definitely volunteer for a similar thing in future for sure.*
>
> *PPI 4*

This was felt to be an endorsement of the PPIE group's contribution and conclude that the PPI input was successful. The detailed report of the positive and negative aspects of PPI within a RCT will hopefully help others to design and carry out effective and inclusive PPI to ensure that research is focused on creating improvements for the patients and public affected by the issues being investigated.

Recommendations

What worked well:

- Positive attitude of the trial team to PPI led by the CI.
- Flexibility for PPI members to be involved where they wanted to.
- Integration into the TMGs – status of PPI lead was never questioned as an equal partner in the group.
- Prioritising PPI as an agenda item for every TMG and CI catch-up meeting.
- Utilising people's different expertise.
- Listening to carers as well as people with lived experience of the condition.
- Reactive PPI for changes to patient documents, trial amendments and recruitment.
- Using PPI voices to challenge the funders regarding recruitment and trial amendments.
- Feedback actioned and changes made to aspects of the trial that the PPI group reviewed or discussed.
- Feedback on changes made to the trial after PPI feedback was given to the group at the next PPI meeting keeping us informed of our impact.
- There was diversity of gender, lived experience of depression and BD and carers of people with bipolar disorder, age, disability, and research experience within the group providing a range of perspectives.
- Accessibility of documents and meetings for all PPI Group members was implemented following identifying our individual needs.

What not to do:

- Create the PPI as the trial progresses. Having a plan and some structure would have been beneficial to getting PPI involved in the appropriate places. Having a PPI member at the TMG and catch-up meetings did go some way to addressing this, but it still could have been more organised and streamlined.
- Missed opportunities for PPI input, for example designing the qualitative questions and involvement in themes and analysis.

What would we do differently next time:

- Involve PPI in more aspects of the trial – qualitative planning, possibly use as peer researchers to complete qualitative interviews, trialling the participant questionnaires and software.
- Involve the PPI group at an earlier stage when drafting patient documents to reduce time spent redrafting.
- Due to COVID-19, many changes to the trial had to be made very quickly and the PPI members were not involved in these as much as the trial team would have liked.
- More in-depth planning for PPI activities, for example, role-play calls, qualitative interviews to ensure appropriate involvement and inclusion of PPI in important trial areas.
- Training on relevance for PPI group members when providing feedback to researchers.
- Have a dedicated PPI lead within the trial team.
- More admin support for PPI Lead.

- More diverse PPI group members. We were all North East based, White British, mainly middle class.
- Larger PPI group – creates more opportunity for diversity, a range of voices and new ideas.
- PPI Funding – needs to be established as part of the funding bid. Budgeting for any additional tasks and involvement, not just meetings. Budget to cover a larger and more diverse PPI group.
- Voucher payments made in a timelier manner. Cash payments available if preferred.
- Maintain PPI records with the goal of authoring a paper showing the impact and learnings for researchers to use to support more effective PPI in future trials.
- Funding applications need to allow room for innovation and flexibility in terms of PPI plans, inputs and altering trial design, outputs and dissemination. You do not know what you will produce until you have the conversations with people with lived experience.
- Prior contact of PPI Group with funders re trial recruitment challenges may have supported trial extension rather than closure.

Chapter 7 Discussion

Statement and interpretation of results

The primary outcome in the trial was negative with $p = 0.0865$, potentially reflecting the small sample size included in the analysis ($n = 36$) due to the trial being stopped prior to recruitment of the target sample size. Nevertheless, it does appear that pramipexole may well be having a positive effect on mood in participants with TRBD, in line with the two previously published pilot studies,[28,29] and clinical experience.[27] Numerically, the improvement in QIDS-SR score between baseline and 12 weeks averaged 4.4 points in the pramipexole arm. This magnitude of change would be regarded as clinically significant,[61,62] and was over double that seen in the placebo arm. Over the course of follow-up in the trial, participants taking pramipexole also experienced twice as many depression-free weeks as those on placebo, though this was not statistically significant. However, secondary and post hoc analyses revealed a statistically significantly greater reduction in QIDS-SR score at 36 weeks of follow-up and significantly greater rates of response (46% vs. 6%; $p = 0.026$) and remission (31% vs. 0%; $p = 0.030$) for participants taking pramipexole at the point of their exit from the trial.

A positive effect of pramipexole is also supported by the statistically significant improvement in work and social function at 36 and 48 weeks and HRQoL over the 48-week follow-up period compared with placebo. While not statistically significant the increase in ability to experience pleasure at 6 weeks, as shown by the SHAPS scores being 2.04 (95% CI −0.11 to 4.20; $d = -0.76$) lower, and improvement in anxiety symptoms at 36 weeks, shown by GAD-7 scores being 3.44 (95% CI −1.06 to 6.99; $d = -0.67$) lower, for participants in the pramipexole arm is consistent with the change in work and social function and quality of life. It is tempting to speculate that the early increase in pleasure may be a mediating factor related to improvement in mood. It is also perhaps not surprising if psychosocial function and quality-of-life measures take longer to change subsequent to an improvement in mood. Essentially, the relative time scales of the changes seen on the various measures have face validity.

While the overall tolerability and acceptability of pramipexole were good, its use is not without challenges. High rates of impulse control problems have been reported in patients with Parkinson's disease treated with pramipexole and other dopamine agonists.[111] While there were no significant differences in ratings of impulsivity between the two treatment arms, 33% of participants in the pramipexole arm reported an AE related to such problems, compared with 19% in the placebo arm. Interpretation of these data is complicated by the association between impulsivity with bipolar disorder per se,[112] and the overlap between such problems and hypomania/mania.

However, the biggest issue in the PAX-BD trial was the occurrence of hypomanic and manic symptoms which resulted in the only medication-related SAE and AEs in 8 of the 16 participants in the pramipexole arm compared with 6 out of 20 in the placebo arm. This increase in hypomanic/manic symptoms occurred early, as shown by the weekly ratings illustrated in *Figure 10*, and by the rate being significantly higher at 12 weeks in the pramipexole arm.

The use of an antipsychotic in combination with pramipexole is contentious. While it has been reported that the combination can be used successfully to treat BD in clinical practice,[24] the commissioned call for a study of pramipexole for the treatment of TRBD by the NIHR HTA panel specifically required participants to not be taking an antipsychotic. This, most probably, was due to the view that it was illogical to combine pramipexole (a dopamine agonist) with an antipsychotic (a dopamine antagonist). However, this takes a simplistic view of the drug's pharmacology. Pramipexole is a relatively 'clean' dopamine agonist, but it has activity at three dopamine receptors: D2, D3 and D4. The binding affinity of pramipexole is highest at the D3 receptor (Ki = 0.5 nM) – around an order of magnitude greater than at D2 (Ki = 3.9 nM) and D4 (Ki = 5.1 nM) receptors.[31–33] The pharmacology of antipsychotics varies, but in general, they have a higher affinity for D2 receptors compared with D3 (see *Table 23* in *Appendix 1*). Genetically modified mice that do not express D3 receptors have been reported to exhibit depressive and anxious features.[70] In addition, a wealth of data using highly selective D3 antagonists in animal models has demonstrated that D3 receptors play a critical role in reward processes.[71,72,113,114] Importantly, levels of baseline reward processing are associated with pramipexole response in those with depression.[115] Further, PET imaging data in humans suggest D3 receptor expression may be related to motivation

for rewards.[37] Such findings support a hypothesis that the mechanism of action of pramipexole in BD may be mediated via D3 receptors. On the basis of these arguments, and the high rate of use of antipsychotics in BD in clinical practice (data from POMH – reporting 80% usage in 6025 patients in 2018) hampering recruitment, the NIHR HTA panel agreed to a PAX-BD protocol amendment to allow participants to be randomised still taking an antipsychotic if this was with certain limits based on the drugs pharmacology (see *Table 24*, *Appendix 1*). While the numbers of those participants in the pramipexole arm who were and who were not taking an antipsychotic are small, it appears that coadministration had little impact on the positive effects on depressive symptoms, but probably reduced the risk of manic symptoms. It is noteworthy that the one participant experiencing a SAE, and seven who had an AE, related to mania while on pramipexole were not taking an antipsychotic. Conversely, only one participant on an antipsychotic experienced a hypomanic AE when taking pramipexole.

Health economic analysis is limited by the small sample size, but as stated above, there were significant advantages in favour of pramipexole in HRQoL over the 48 weeks of follow-up in the trial. With regard to health and social care, pramipexole was associated with a cost saving of £52 at 12 weeks and £798 at 48 weeks, with NMB of around £200 and £1500, respectively. This implies that the treatment is cost-effective. There was a 90% chance that the threshold for cost-effectiveness of £30,000/QALY gained was met. From a societal perspective, the situation was slightly different with pramipexole being more expensive than the control arm, with greater costs of £794 at 12 weeks and £1170 at 48 weeks. As a result, there was < 50% probability that the cost-effectiveness threshold would be met.

An extensive qualitative review of the PAX-BD trial was conducted, particularly focusing on the barriers and facilitators to both recruitment and conduct of the trial. Essentially this demonstrated the feasibility of the largely remote methodology used in the trial. This trial design was put into place pre-COVID-19 and required little adjustment following commencement of the pandemic. Dropout rates in the trial were similar or lower than in previous studies in similar populations of patients. In the pre-randomisation stage, the dropout rate was 24%, identical to the run-in phase prior to randomisation in the CEQUEL study,[59] and similar to the 28% in the BALANCE study,[58] which also required potential changes in participants medication prior to randomisation. The dropout rate prior to the primary outcome time point was low at 7.7%, below that seen over the same time period in the CEQUEL study (18.8%). This may have reflected the frequent contact with the study RAs. Completion rates of the participant-rated weekly questionnaires were high at around 80%, again similar to that seen in the CEQUEL study.[59] Again, this may have been related to the frequent contact between trial participants and the central trial RAs based in Newcastle. A concern regarding this was whether such frequent contact might increase the placebo response rate. However, there was relatively little evidence of much improvement in symptoms in the placebo arm. The trial required a large number of sites to attempt to recruit to target. One issue that became clear during the running of the trial was that there was a vast gulf in experience in research between the sites taking part in the trial. Some were highly expert in taking part in CTIMPs. For others, they had little or no such experience which contributed to the high rate of protocol deviations. By the end of the trial, 174 deviations had been recorded across the 15 sites that had recruited, with the number per site ranging from 0 to 48.

Comparison with the literature

The potential role of pramipexole as a treatment for depressive episodes in bipolar disorder is supported by several lines of investigation. Pre-clinical investigations have demonstrated that pramipexole can reverse stress-induced suppression of sucrose intake in rats,[11] a model of anhedonia which is a core diagnostic symptom of depression. Similarly, antidepressant-like effects of pramipexole have been observed in other animal models of depression or models known to be responsive to drugs with antidepressant efficacy, such as the forced swim test,[12,13] social interaction test[13] and olfactory bulbectomised rats.[14] It has also been shown to increase hippocampal neurogenesis,[13] 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 controlled trials of pramipexole for the treatment of motor symptoms in patients with Parkinson's disease reported an odds ratio of 2.41 (95% CI 1.78 to 4.13; $p < 0.001$) for improvement in depression severity as measured by a single item on the 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.[19] A significantly greater decrease in Beck Depressive Inventory score was seen from pramipexole compared to placebo

(difference 1.9, 95% CI 0.5 to 3.4; $p = 0.01$). Path analysis suggested that the effect was a direct one on depressive symptoms rather than secondary via effects on motor symptoms.

Such findings, together with hypothesised roles for a hypo-dopaminergic state underlying BD,[20] have led to studies of pramipexole in BD. The use of pramipexole in TRBD is supported by naturalistic and open trial data.[21–27] More robustly, two small pilot RCTs, conducted around two decades ago, have examined pramipexole in BD.[28,29]

Goldberg and colleagues undertook a RCT of 22 patients with BD.[28] Participants were mainly suffering from bipolar disorder type I, similar to the population in PAX-BD (72% bipolar type I). All patients had failed to respond to at least two adequate trials of standard antidepressants during the current episode, a slight difference from the way TRBD was defined in PAX-BD. They were treated with a mean of 1.7 mg/day (SD = 1.3) pramipexole per day (slightly lower than the 2.18 mg/day used in the fixed-dose period in PAX-BD) in combination with lithium or anticonvulsant mood stabilisers. The mean 17-item HDRS at baseline in the Goldberg *et al.*'s study was around 20, which is equivalent to 16 points on the QIDS-SR scale,[116] and similar to that in the PAX-BD study (15.1 in the pramipexole arm and 17.3 in the placebo arm). Mean improvements in HDRS scores at 6 weeks were 48% for pramipexole and 21% for placebo ($p = 0.05$). This equates to a 9-point improvement in HDRS score for participants treated with pramipexole, equivalent to 7 QIDS-SR points and so a greater improvement than seen after 12 weeks in PAX-BD (4.1 QIDS-SR points).

Zarate and colleagues' RCT included 21 patients with bipolar type II.[29] Patients had failed at least one trial of a standard antidepressant, which is a very different criterion to that used in PAX-BD and also somewhat contrary to the notion that antidepressants are ineffective as treatments for BD.[3] Study medication was given in combination with lithium or valproate. Similar to Goldberg *et al.*, the mean dose of pramipexole was 1.7 mg/day (range 0.375–4.5 mg/day). The baseline severity of illness was slightly greater than in the Goldberg *et al.* and PAX-BD study being rated as scoring around 32 on the MADRS, equivalent to 18 on QIDS-SR.[117] The reduction in severity of depressive symptoms at 6 weeks was also greater than the Goldberg and PAX-BD studies being around 15 MADRS points, equating to 9 QIDS-SR.

As can be seen, while the reduction in depressive symptoms in the pramipexole arm of the PAX-BD study was of a clinically meaningful magnitude, it was somewhat smaller than that seen in the two previous small RCTs in BD. This may reflect differences in study populations (UK vs. USA; how TRBD was defined), or possibly that some of the participants in PAX-BD were also taking an antipsychotic, though there did not appear to be any difference in reductions in depression in those who were and were not. While the primary outcome was after 12 weeks in the PAX-BD study compared with 6 weeks in the two previous RCTs, dose titration was somewhat slower in PAX-BD. It was noteworthy that the reduction in depressive symptoms appeared to continue to build beyond 12 weeks, with the biggest effect seen 36 weeks after randomisation. This raises questions as to what in fact might be the optimal time point to examine for effects of pramipexole in BD.

It is a challenge to ascribe changes in mood in bipolar disorder to medication, given the nature of the spontaneous fluctuations seen in the disorder. This is a particular issue when considering whether hypomanic/manic symptoms result from the use of pramipexole or are just coincidental. Zarate and colleagues found that while one participant in the pramipexole group experienced a manic relapse, two did so in the placebo arm. Goldberg *et al.* described one dropout due to a manic relapse but found that formal ratings of manic symptoms did not differ between treatment groups. These findings are in stark contrast to the PAX-BD study where we did observe a significantly greater increase in scores on the ASRM in the pramipexole arm, and the proportion of participants experiencing AEs related to mania was also higher compared with those in the placebo group (44% vs. 29%). This higher rate of problems with hypomania/mania compared with the two previous RCTs may relate to the higher dose used in PAX-BD, or differences in the population being studied.

Despite the major concern regarding impulse control problems in patients being treated with dopamine agonists, particularly pramipexole,[118] there was no mention of such problems occurring in the two previous RCTs, perhaps due to the short duration of follow-up. However, no difference was seen in the formal ratings of impulse control behaviours between pramipexole and placebo in the PAX-BD study even over 48 weeks. This may reflect an issue with the use of the QUIP-RS scale, which was designed for use in patients with Parkinson's disease, in individuals with BD due to

the high rate of inherent impulse control problems in BD[110] and the overlap with hypomanic/manic symptoms. It could also be that patients with Parkinson's disease are more prone to developing impulse control problems with dopamine agonists than those with BD. It would, however, be foolhardy to not consider this risk when using pramipexole clinically, especially given the observation in PAX-BD of the higher rate of AEs associated with pramipexole than in the placebo arm (33% vs. 19%).

Commissioned research in bipolar depression

In 2015, the HTA Panel put out a call for 'Promising pharmacological therapy for treatment-resistant bipolar depression' (15/33). There was, and remains, a significant clinical need for new medication options for BD, with NICE,[3] listing just three options, two associated with a significant side-effect burden (olanzapine and quetiapine) and the other with a limited effect size and slow onset of action (lamotrigine). The intervention described in the details of the HTA call was stated as 'One or more promising pharmacological therapies, such as pramipexole'. Experts in the clinical management and trial of BD within the NIHR Mental Health Translational Research Collaboration (MH-TRC) discussed the call and concluded that pramipexole was not the most sensible medication to investigate. This was due to the complexity of titration and optimal dose selection, the high rate of impulsivity seen with the drug in Parkinson's disease and the theoretical risks of a dopamine agonist precipitating mania/hypomania and possibly psychosis, particularly in a population vulnerable to such symptoms. Consequently, a multicentre collaborative group of experts submitted a proposal to undertake a trial of an alternative medication, lurasidone, a second-generation antipsychotic. Lurasidone is currently licensed in the UK for the treatment of schizophrenia, but not BD. Short-term data support the view that it may be an effective treatment for BD as monotherapy, or in combination with a mood stabiliser.[50,51] Additionally, its side-effect profile suggests benefits over those seen with quetiapine and olanzapine.[119] However, the published studies were not conducted in patients with TRBD, and there are very limited data regarding its longer-term efficacy.[120] As a result, lurasidone is not included in NICE guidelines for the management of BD,[3] though it is in the BAP guidelines (ref: note that lurasidone was included in the PAX-BD trial as one of the medications included in the criteria to determine TRBD, but it was the least used of the four medications included: < 20% reported either a failure to respond or tolerate the drug, compared with around double this for quetiapine). Critically, a positive finding for the long-term efficacy, safety and cost-effectiveness of lurasidone would have been relatively straightforward to implement in the NHS, with mental health services having expertise in the use of similar drugs and lurasidone itself, in schizophrenia. Unfortunately, the applicants were unable to persuade the HTA panel to fund a trial of lurasidone, with the feedback being that the case was not made that lurasidone was a novel option compared with other antipsychotics. This view is somewhat counter to the evidence that while there is a class effect of antipsychotics in treating bipolar mania, this is most definitely not the case for the treatment of BD, with some antipsychotics even exacerbating depressive symptoms.[10]

In 2016, the HTA panel were more explicit in their commissioned call 16/154 'Pramipexole for treatment-resistant bipolar depression'. Experts within the MH-TRC discussed the call. There was concern around whether a large, multicentre, trial could be conducted safely and effectively, and that even if there were positive findings that pramipexole would be challenging to use within routine secondary care mental health services. This was particularly the case regarding the requirement specified in the HTA call that the drug must be investigated without coadministration of an antipsychotic. As described above, while this appeared to superficially make sense, it ignores the precise pharmacology of pramipexole and most antipsychotics. However, it was agreed that a large, well-designed, trial of pramipexole could potentially provide proof of concept regarding the use of dopamine D3 agonists in the treatment of BD. As a result, the PAX-BD trial application was submitted and funded. Ultimately, the combination of the eligibility requirement for participants not to be on an antipsychotic and the occurrence of the COVID-19 pandemic made recruitment to the trial extremely challenging. Following approval from HTA to significantly modify the antipsychotic requirement (see above), recruitment to the trial increased, but there was limited time prior to the end of the original contract with NIHR and the trial was closed down with the reason being stated as one of the criteria for closure that was to be used in the review of all studies across the NIHR portfolio. However, since the decision was taken before this formal process began, there was no opportunity to appeal the decision.

The results from the PAX-BD study should be treated with caution due to the small sample size, including those that were significant. However, despite the lack of a statistically significant effect of pramipexole on the primary outcome

measure, the direction of effect coupled with a number of statistically significant secondary outcome measures are in line with previous small pilot studies,[28,29] and clinical anecdotes suggesting that pramipexole may have a positive effect in TRBD.[27] The trial also suggests that the drug would be challenging to implement in routine secondary care. Issues were found with the complexity of dosing the drug (20 AEs related to this reported by 9 participants – likely an underestimate due to missed and incorrect doses not being reported by participants), and with high rates of problems with hypomania/mania (particularly if participants were not taking an antipsychotic). Such findings are consistent with the concerns aired within the MH-TRC when the HTA call first came out, suggesting that it probably was not the most sensible medication for a NIHR HTA Panel commissioned call. However, once funded, the closure of the PAX-BD trial at the point where recruitment was occurring means that it is a lost opportunity for definitive evidence regarding the efficacy and safety of a D3 agonist in TRBD, which would have been of importance to highly specialised affective disorder clinics and from a mechanistic perspective.

Limitations and strengths

Limitations

There are a number of issues with the PAX-BD study which limit interpretation of the data. Most notable is the small sample size, with only 36 participants contributing primary outcome data. In addition, due to the early study closure, not all participants were able to continue follow-up to 48 weeks. This resulted in particularly small sample sizes at the 36- and 48-week assessment time points, of relevance since this is the time where some of the significant findings were reported.

The small sample size is likely to have also contributed to the baseline differences in QIDS-SR and HRQoL outcome measures. While analysis adjusted for these differences, there remains a concern that it may have biased the results. However, it should be noted that the baseline severity was lower in the pramipexole arm. In general, larger improvements in symptoms tend to occur in participants with higher baseline starting points and hence more 'room for improvement'. So it is possible that the baseline differences seen in PAX-BD, rather than contributing to the greater effect seen in the pramipexole arm, actually contributed to this effect not being greater.

The study was designed to investigate the efficacy of pramipexole in TRBD. There is some debate and relatively little consensus as to how TRBD is defined.[121] Definitions are complicated by whether lack of response to medications is only counted in the current episode of illness, or over a person's lifetime. Most commonly, as done in PAX-BD and the two previous RCTs of pramipexole for BD,[28,29] non-response is only considered for the current episode. In clinical practice; however, if a person had a previous episode of depression which did not respond to a drug, generally this is rarely tried again in a new episode, not least because it can be challenging for a patient to re-try a medication that they perceive themselves as having failed on. In addition, the challenge of finding an effective drug for a patient is not just limited by non-response to trials of certain medications, but also lack of tolerability. PAX-BD took a pragmatic, clinical approach to defining TRBD. When assessing for criteria of two 'failed' treatments in the current episode, in addition to non-response, lack of tolerability and patient refusal or clinical contraindication to a drug were also allowed. Clinical contraindication included a medication that a patient's depression had been unresponsive to in a previous episode, therefore ruling it out in the current one. This, together with allowing a patient to reject a particular treatment due to the risks associated with it, more approximates clinical reality than a definition of TRBD based solely on non-response in the current episode. However, it does mean that the population included in PAX-BD is likely to be somewhat different from those included in other studies with more conventional criteria of TRBD. Indeed, 24% of participants randomised in PAX-BD had not failed to respond to one of the four recommended drugs in the current episode, and 41% had failed to respond to just one. We do not have data for the lifetime number of failed treatments, but it could be that the PAX-BD population was at least partially as much intolerant of treatment as non-responsive to it.

During the course of the study, an amendment to the protocol allowed for participants to be randomised to study medication while being prescribed an antipsychotic. Around half the randomised participants ended up being coprescribed an antipsychotic. While observation and analysis of the data suggest that this did not reduce the effectiveness of pramipexole, the numbers of participants in each subgroup are such that it is not possible to definitively say that antipsychotic coprescription does not limit the effectiveness of pramipexole. This coprescription also

complicates the comparison of the PAX-BD results with those from the two previous small RCTs in which none of the participants were taking an antipsychotic.[28,29]

Key to achieving a response to medication is adherence to taking it as prescribed. Due to the need to run the study as remotely as possible, opportunities for objective assessments of medication adherence (e.g. plasma drug concentrations) were not possible. Instead, we have had to rely on participant self-report to the study RAs. It could therefore be that response to pramipexole was limited by less than ideally medication adherence rates.

The vast majority of outcome measures used in the study were participant self-reported, as opposed to observer-rated. While this does limit comparisons, for example, with the two previous RCTs of pramipexole in BD,[28,29] there are an increasing number of studies using self-report scales to assess mood, for example the CEQUEL study in a similar patient population.[59] Computer-administered self-report ratings can help avoid baseline score inflation seen in clinician-rated scores when there is a severity criterion for inclusion into studies,[122] and there are instances where self-rated mood is more sensitive to change with treatment than observer-rated scales.[123] Nevertheless, it should be noted that there was less evidence of a benefit of pramipexole on the observer-rated MADRS at 12 weeks than on the self-rated QIDS-SR in PAX-BD. This might be in part accounted for the MADRS being administered by phone rather than face to face.

It is important to highlight that the population included in the PAX-BD study is not representative of all patients suffering from TRBD. Many patients currently experiencing an episode of BD, indeed probably the majority, are being managed in primary (rather than secondary) care in the UK, if they are receiving any care at all. Indeed, it is estimated that as many as 10% of patients prescribed antidepressant medication in primary care for depression or anxiety actually have undiagnosed bipolar disoder.[124] The eligibility requirement that patients needed to be in secondary care to take part in PAX-BD therefore did not allow for a truly representative sample of all patients receiving care. This criterion was applied due to the complexity of using pramipexole and the need for participants to be carefully monitored for the occurrence of serious adverse effects (such as mania and impulse control problems) and that they could receive timely specialist intervention if needed.

The plan to conduct PAX-BD largely remotely proved to be a good one when the COVID-19 pandemic developed. However, the requirements for outcome measures to be completed online by participants potentially caused a bias in participant involvement. While a few participants did not have access to a computer, tablet or smartphone, and hence had to receive help to complete rate scales from site staff, the reality was that this was too labour intensive to recruit many people in this situation. As a result, the vast majority of participants were computer literate and had their own devices on which they could complete the outcome measures. This may be a factor that led to the population as a whole having a low rate of the most basic level of education. The issue was even more acute for potential participants who were not fluent in English. It would have been prohibitively expensive to have included the ability to complete the various questionnaires in a range of languages, and would have required extensive validation as well. As a result, the study population was unlikely to be fully representative of the UK population, though details of participant's ethnicity were not collected.

Strengths

The PAX-BD does have a number of strengths as well. Most obvious among these is that the study provides by far the longest follow-up of participants randomised to pramipexole or placebo of any RCT conducted to date (48 weeks vs. 6). As such, the study does provide valuable information regarding the longer-term use of the drug. In addition, relatively high doses of study medication were achieved (higher than the two previous RCTs). In addition, the PAX-BD study is the first RCT in BD to explore the effect of pramipexole on anxiety, pleasure, psychosocial function, HRQoL and cost-effectiveness as well as mood.

As described above, the definition of TRBD was clinically pragmatic and hence the population studies were made up of those for which there is current clinical equipoise as to how they should be treated.

While the sample size was small, the treatment arms were remarkably well balanced with regard to demographics, illness characteristics and medication usage, with the exception of baseline QIDS-SR and HRQoL differences.

Participants in the study had a high rate of completion of online self-related symptom severity scales, comparable with previous studies. In addition, dropout rates were similar, or lower, than seen in previous studies.

In addition to the main quantitative findings, the PAX-BD study was able to acquire qualitative information to help inform the conduct of future trials in this therapeutic area in terms of facilitators and barriers to recruitment and retention. In addition, there has been an extensive review of the PPI involvement in the study, again leading to recommendations for future studies.

Future research

Whether or not pramipexole could be implementable as a treatment for TRBD in routine secondary care, there remains a need for definitive evidence regarding its efficacy, safety and cost-effectiveness. It is likely that pramipexole will continue to be used in highly specialist mood disorder services, such as those in the USA that included patients in the case series described by Fawcett *et al.*[27] However, definitive evidence would aid our understanding of the pharmacological mechanisms that are able to treat BD. In particular, evidence regarding pramipexole would help clarify whether dopamine D3 agonists are of potential use, opening avenues for further drug development. The PAX-BD has established a methodology that allows the conduct of such trials in the UK NHS in a semiremote fashion.

While the PAX-BD study was ended early, the NIHR/Medical Research Council (MRC) Efficacy and Mechanism Evaluation (EME) programme-funded PAX-D study – a RCT of pramipexole in unipolar depression – continues. It will be of interest to compare its findings with those of PAX-BD. There are commonalities in study design and, for example, the SHAPS tool to examine pleasure was included in PAX-BD to enable this cross-comparison between the treatment of bipolar and unipolar depression with pramipexole. Increases in the ability to experience pleasure were seen after just 6 weeks of treatment, prior to improvements in mood and psychosocial function. It is of interest to speculate that this increase in pleasure may be of mechanistic relevance to the improvement in mood. PAX-D may provide further evidence in this regard, and further research in this area with pramipexole and other pro-dopaminergic treatments is warranted.

Given that there are now three completed RCTs of pramipexole in BD, in the absence of funding for a single large definitive trial, a meta-analysis of the data from the three studies would be of value.

The study raised questions regarding the use of antipsychotics in combination with pramipexole. This warrants further investigation, partly because of the inherent value of such information when pramipexole is being used in highly specialist centres, but also because this would further help clarify the relative roles of dopamine D2 and D3 receptors in the mechanism of action of pramipexole, which could inform future drug development.

Running similar studies in the future – lessons learnt

Insights to inform future trial design, from the qualitative data obtained in the trial from participants and HCPs, together with those from the central trial team, are reported below and in more detail in *Appendix 7*.

Sample size estimates for future studies

PAX-BD is able to provide evidence to help inform sample size calculations for future similar studies.

Examining the QIDS-SR at 12 weeks reveals an overall SD (combined groups) of 6.6, and a difference between arms (pramipexole arm with lower mean) of 8.6. This gives an effect size of 8.6/6.6 = 1.3. A power calculation reveals that 14 participants per arm (28 total) would need to provide 12-week data to detect this effect size with 90% power at a 0.05 significance level. However, this assumes that 8.6 is effectively the MCID. As discussed above, there is evidence to suggest that this is in the order of 4 points when using the QIDS-SR.[61,62] This was used for a revised sample size calculation when we were applying to the funder for a costed extension to the study (which was turned down) of needing 100 participants to complete 12 weeks for 80% power or 132 for 90% power. Adjusting this using a SD of 6.6

(rather than 7 as in the original calculation) would mean a sample of approximately 90 needing to complete 12 weeks for 80% power, or approximately 120 for 90% power. The current study would not have had to have continued for a great length of time further for this sample size to have been achieved, illustrating the lost opportunity of the early closure.

Insights from the qualitative analysis

The qualitative data obtained in the trial were examined to identify potential lessons for future studies in similar populations of patients and/or using similar methodology.

Organisational issues

Undertaking research, particularly something as complex as a CTIMP, alongside busy clinical services is a challenge. HCPs identified the importance of the research being seen as clinically important, having full staffing complements and protected time for research. The requirement to inform patients about ongoing trials to facilitate informed choices about treatment was also emphasised.

Given that specialist mental health care is increasingly provided on an episodic basis, with patients discharged back to their general practitioner (GP) in between, the ability to recruit participants from primary care has become more critical, as has the need to be able to advertise studies directly to patients. This can bypass barriers of patient gatekeeping and reliance on staff with low availability, as well as providing access to depressed patients who may otherwise remain without treatment or referral to secondary care. It is also hoped that developments in electronic health records and the ability to search these, in both primary and secondary care, would also greatly facilitate accurate participant identification.

Trial design

The dose titration of the trial medication was complex, and some participants would have benefited from additional support, for example more information, ready-filled dosette boxes and extended discussions about medication with RAs and/or CSOs as well as the involvement of carers in such conversations.

The remote nature of the trial required multiple questionnaires to be completed at regular intervals by participants. Many found that breaking the task up over several days, rather than completing all those required at one sitting, was easier to manage.

Some HCPs indicated that the option of face-to-face site training and participant visits would add a personal touch. This may have improved understanding of the trial, connectivity to the trial and engagement from both research personnel and PAX-BD participants, all of which can have positive implications for recruitment and retention.

Trial processes

A key element to the conduct of the trial was for flexibility to allow sites to use local knowledge to optimise participant identification, approach and recruitment.

Collaboration between the central team and site staff was highlighted as an important facilitator to recruitment and trial conduct. Sites reported benefitting from the CI and CI delegate interacting with their staff and presenting to colleagues at local site meetings. Central RAs also expressed they would value more site involvement with trial participants in terms of encouraging engagement with safety monitoring and highlighting the importance of this. In future trials, introductions or handovers with all parties could be arranged to bolster the sense of collaboration and continuity in care.

Insights from central trial team

Remote design

Remote designs can alleviate burden from busy site teams and optimise funding using central RAs. They are likewise appealing to participants with busy schedules or have limited scope for in-person visits. However, RAs observed that for some participants, completing trial tasks in their own time seemed to feel like an encroachment on their personal lives. A hybrid design with the option of face-to-face appointments with research staff could offer a more optimal solution and help minimise participants lost to follow-up.

The use of technology as the only means of data collection is inadvertently exclusionary. In addition, the choice of a digital platform is also vital; issues with systems can be frustrating and demoralising for participants, as well as tarnishing trial credibility and stagnating data collection. Comprehensive, accessible and established procedures for offline options (such as paper questionnaires and staff-assisted completion) are also required to provide a contingency in case of technical failures, as well as expanding inclusivity of the trial.

Trial management

Adverse events for the trial were collected by the RAs during weekly assessments with participants and recorded centrally. It was discovered at the end of the trial that some disparities existed between the data collected by the central team and those collected by clinicians locally. Future trial design should build in ways of confirming local data collected in clinical consultations with those collected centrally to ensure the quality and completeness of data collected. Many sites needed support in completing routine research activities such as the upkeep of an Investigator Site File (ISF) and paper archiving. This would be facilitated by utilisation of e-ISFs and e-archiving. An annual formal review of local site arrangements for upkeep of the ISF provided, planned archiving arrangements and provision of staffing would facilitate adherence to research requirements.

Central pharmacy

A central pharmacy had a series of positives over dispensing at a local level. Feedback from sites was positive as it took any potential burden away from the local sites which was particularly pertinent during COVID-19. As such, it meant that only one pharmacy organisation needed to enact amendments, whereas multiple organisations would be required to do so if prescribing at a local level. Key feedback for the trial and for setting up any future research would be to involve the pharmacy from the very beginning of the trial in all areas to create a robust trial design and to reduce the need for amendments later on.

There were, however, some drawbacks to a central pharmacy, namely around storage of stock, risk assessments and the need for clear trial roles. This trial was fortunate, in that the storage requirements for IMP did not require temperature or other special environmental considerations which would have otherwise rendered the central storage impossible due to the quantity of IMP. Delivery of IMP was disrupted by the COVID-19 pandemic as well as postal strikes. The central trial RAs were essential in keeping open lines of communication with participants during the weekly calls to ensure that IMP had arrived as well as the empty bottles being posted back to the pharmacy. Future studies should consider contingencies for IMP delivery when undertaking their initial risk assessments.

Equality, diversity and inclusion

Unfortunately, data on participant's ethnicity were not collected and so it is not possible to comment on the ethnic diversity of the population included. However, it would have been challenging to take part in the study for a participant who was not fluent in English. This may have limited the diversity of the study population.

Similarly, we did not collect data on neurodiversity, so are unable to comment on this.

In terms of age and gender, the mix of the study population was similar to the population with BD in general and those included in similar studies.

Data on the participants show that they were probably more highly educated than the general population. This may have been driven by the remote collection of outcome data online by participants. While there was not a requirement for participants to have a computer/tablet/smartphone and be computer literate, it was challenging for those who did have this to take part. This remains a challenge for remotely conducted studies.

Patient and public involvement

There was extensive PPI in PAX-BD, and this is described in detail in *Chapter 6* and *Appendix 6*.

Chapter 8 Conclusion

The PAX-BD trial does not provide a definitive answer, but it does provide some support for the hypothesis that pramipexole may treat TRBD. However, it is not a simple treatment to use. Dose titration was complex and there were errors made by participants and clinicians. There also appears to be a risk of hypomanic/mania early on in treatment, though this may be partially ameliorated by coadministration of an antipsychotic. The treatment does appear to improve not only mood but also psychosocial functioning and quality of life and is probably a cost-effective treatment. All of these conclusions must be considered extremely tentative given the small sample size and variable length of follow-up of participants due to the study being closed prior to achieving its target sample size.

The nature of the commissioned call (examining a drug that would always be extremely challenging to implement into routine clinical practice), requirements laid down in the call (that participants must not be on an antipsychotic when randomised) and then the emergence of the COVID-19 pandemic produced a perfect storm of issue hampering the prosecution of the PAX-BD study. Nevertheless, it was demonstrated that it was possible to successfully put into place systems to allow a study of a drug associated with several complex issues around dosing and monitoring to run largely remotely. In addition, a cogent scientific argument that allowing antipsychotic prescription alongside pramipexole was accepted by funder and ethics committee, with very tentative observations that this did not fully prevent the beneficial effects of pramipexole but may have reduced the occurrence of adverse effects. Unfortunately, the timing of approval of this amendment was not till during the pandemic which impacted on the ability to recruit.

Extensive PPI input to the application to proposed extension and completion of the trial. When the application was rejected, there was a great deal of unhappiness and feeling that the PPI voice was not being listened to.

The continuation of the PAX-BD study was considered by the funder due to the initial contract coming to an end, with the study not being as progressed as would be expected at that point, not least because of the period when the study was suspended along with all non-COVID-related research during the pandemic. Unfortunately, the request for a funded extension to complete the study with a revised target sample size of 100 was rejected, with no right of appeal. The results of the study demonstrate that with a short extension, the study could have been successfully completed. Data obtained suggest that in fact a sample size of just 90 would have been sufficient, with the study being 40% of the way to this target and recruiting 4–5 participants per month. As a result, the opportunity to obtain more definitive data regarding the efficacy and safety of pramipexole in TRBD was lost. The findings in the study confirm the concerns raised by the applicants when they first applied for funding for a study of lurasidone rather than pramipexole, in that it would be difficult to implement the treatment in routine care. However, this does not negate the fact that a definitive result regarding pramipexole would have had important implications for our understanding of BD and its treatment.

Interpretation

As things stand, the findings of the PAX-BD trial are insufficient to recommend changes in routine clinical practice. Where pramipexole is being used off-licence for the management of BD, for example in highly specialised, tertiary level, services, observations from the PAX-BD study tentatively suggest that clinicians, in addition to all of the usual considerations in using a drug with a limited evidence base off-licence, should consider the following:

1. It may take time for the beneficial effects of the drug to be seen – many of the beneficial effects seen in the trial were not evident until 36 weeks post randomisation.
2. Increases in the ability to experience pleasure may proceed improvements in mood.
3. Pramipexole does not seem to exacerbate comorbid anxiety, but this may improve with improvement in mood.
4. There appears to be a significant risk of increased hypomanic and manic symptoms with treatment, particularly in the first 6–12 weeks of treatment and great care is recommended in terms of patient monitoring at this time.
5. Coadministration of an antidepressant along with pramipexole may be possible. Consideration of the precise pharmacology and dose of the antipsychotic used seems parsimonious.

6. It is important to be vigilant for the emergence, or exacerbation, of possible impulse control problems, identification of which can be problematic given trait impulsivity associated with bipolar disorder and overlap with hypomanic symptomatology.
7. While complex, the dosing schedule used in PAX-BD may be an option to consider with patients. In the trial, if the dose was reduced due to tolerability issues in the titration phase, then it was not re-increased. In clinical practice, it may be possible to attempt this, as previously described.[27]

The inability to persuade the NIHR HTA panel to fund a study of the more easily implementable drug lurasidone in the first place, and not to challenge the requirement regarding antipsychotics in the commissioned call for a study of pramipexole, must be laid squarely at the door of the CI and applicants. However, the circumstances around the commissioned call that led to the PAX-BD do raise questions regarding the nature of how decisions are reached as to what the subject of commissioned calls should be, and the detail specified in them.

It is possible to run a trial, including of a drug that is complex to use, largely remotely. One significant challenge that relates to such trials in mental health is that there are only a relatively small number of NHS Trusts and health boards that have expertise in the conduct of CTIMPs. As a result, significant input is required to support less experienced sites to build up their expertise. This takes significant resources but has the potential to increase the UK's capacity to undertake CTIMPs in mental health.

Recommendations for research

Aside from repeating the trial and achieving an adequate sample size, there are a number of avenues for further research. These include:

- Undertaking a meta-analysis of the now three small RCTs undertaken of pramipexole in patients with BD.
- Investigating the impact of coadministration of an antipsychotic alongside pramipexole both in terms of efficacy and safety.
- Further exploration of the mechanisms of effect of pramipexole in improving mood, including the possible role of an early impact on the ability to experience pleasure.

Additional information

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Data Monitoring Committee members

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Patient data statement

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that they are stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

Data-sharing statement

Anonymised data from this trial may be available to the scientific community subject to regulatory and ethics approval. Requests for data should be directed to the corresponding author.

Ethics statement

This trial received ethical approval on 4 September 2019 from the North East – Newcastle and North Tyneside 2 Research Ethics Committee: 19/NE/0233.

Information governance statement

Cumbria, Northumberland, Tyne and Wear is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679. Under the Data Protection legislation, CNTW is the Data Controller, and you can find out more about how we handle personal data, including how to exercise your individual rights and the contact details for our Data Protection Officer here (www.cntw.nhs.uk/foi/data-protection/).

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/HBFC1953.

Primary conflicts of interest: Hamish McAllister-Williams reports acting as TSC chair for the NIHR HTA funded SNAPPER trial and DMC chair for the EU funded PReDicT study; Director of Education for British Association for Psychopharmacology; receiving support for meetings via Janssen-Cilag; receiving payments/consultation fees from LivaNova, Janssen-Cilag, Sage Therapeutics, P1Vital, Takeda and Lundbeck.

Thomas Chadwick reports payments from NIHR HTA and the following:

Member of Programme Steering Committee (ODDESSI: Open Dialogue: Development and Evaluation of a Social Network Intervention for Severe Mental Illness – University College London); Chair of Data Monitoring and Ethics Committee (SCENE: Improving quality of life and health outcomes of patients with psychosis through a new structured intervention for expanding social networks – Queen Mary University of London); Member of Data Monitoring and Ethics Committee (SUMMIT: SUpporting Mothers' Mental health with Interpersonal Therapy – University College London).

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Publications

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Appendix 1 Additional information relating to the introduction

TABLE 23 Affinity of pramipexole and various antipsychotics for dopamine D2 and D3 receptors

Drug	D2 Ki (nM)	D3 Ki (nM)	D2 : D3 affinity ratio	Reference
Pramipexole	*3.9*	*0.5*	*7.8*	*See text in Chapter 1*
Aripiprazole	0.95	4.5	0.21	[73]
Chlorpromazine	2.0	5.0	0.4	[73]
Flupenthixol	0.35	1.75	0.2	[74]
Haloperidol	2.0	4.0	0.5	[75]
Lurasidone	1.0	15.7	0.06	[75]
Olanzapine	21	49	0.43	[75]
Paliperidone	2.8	6.9	0.41	[75]
Quetiapine	245	240	1.0	[75]
Risperidone	4.9	4.4	1.11	[75]
Zuclopenthixol	0.03	0.3	0.1	[76]

The lower the Ki, the greater the affinity, and for ratio numbers < 1 indicates greater affinity for D2 and numbers > 1 indicates greater affinity for D3. For comparison, the affinity and ratio are also shown for pramipexole at the top of the Table.

TABLE 24 Maximum daily dose of various antipsychotics allowed for eligibility to randomisation in PAX-BD following protocol amendment

Drug	Maximum daily dose allowed for eligibility to randomisation stage
Aripiprazole	15 mg
Aripiprazole depot	400 mg every 4 weeks
Chlorpromazine	200 mg
Flupentixol depot	200 mg every 4 weeks
Haloperidol	2 mg
Haloperidol depot	100 mg every 4 weeks
Lurasidone	111 mg
Olanzapine	10 mg
Olanzapine depot	150 mg every 2 weeks
Paliperidone	3 mg
Paliperidone monthly depot	75 mg every month
Paliperidone 3 monthly depot	263 mg every 3 months
Quetiapine	300 mg
Risperidone	1 mg
Risperidone depot	25 mg every 2 weeks
Zuclopenthixol depot	500 mg every 4 weeks

Note

Appendix 2 Additional methodological information

Additional figures

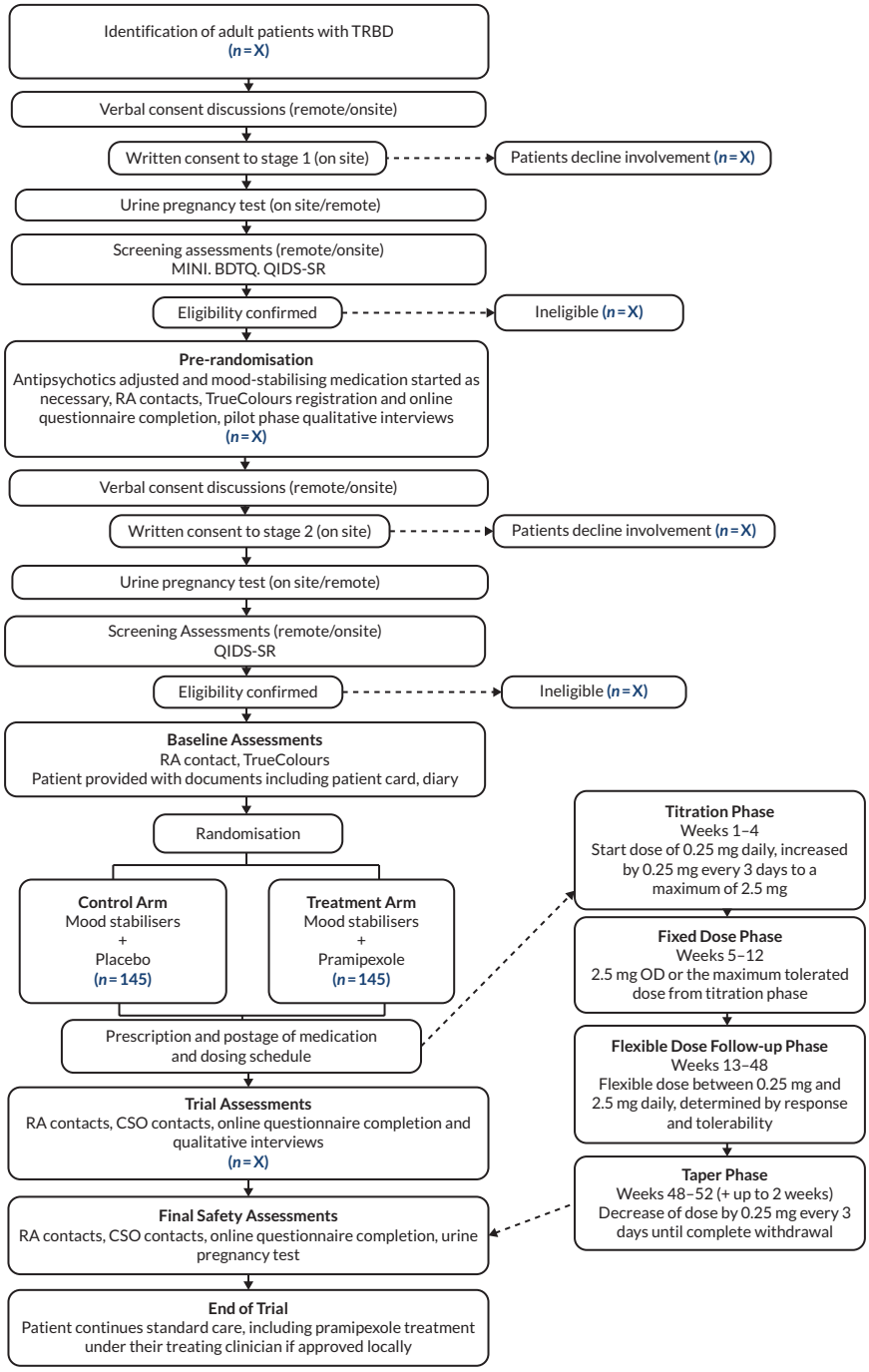

FIGURE 24 A priori CONSORT diagram. Note that this is an a priori diagram and hence the numbers of participants at each stage were unknown. For the post hoc CONSORT diagram, see *Figure 1*.

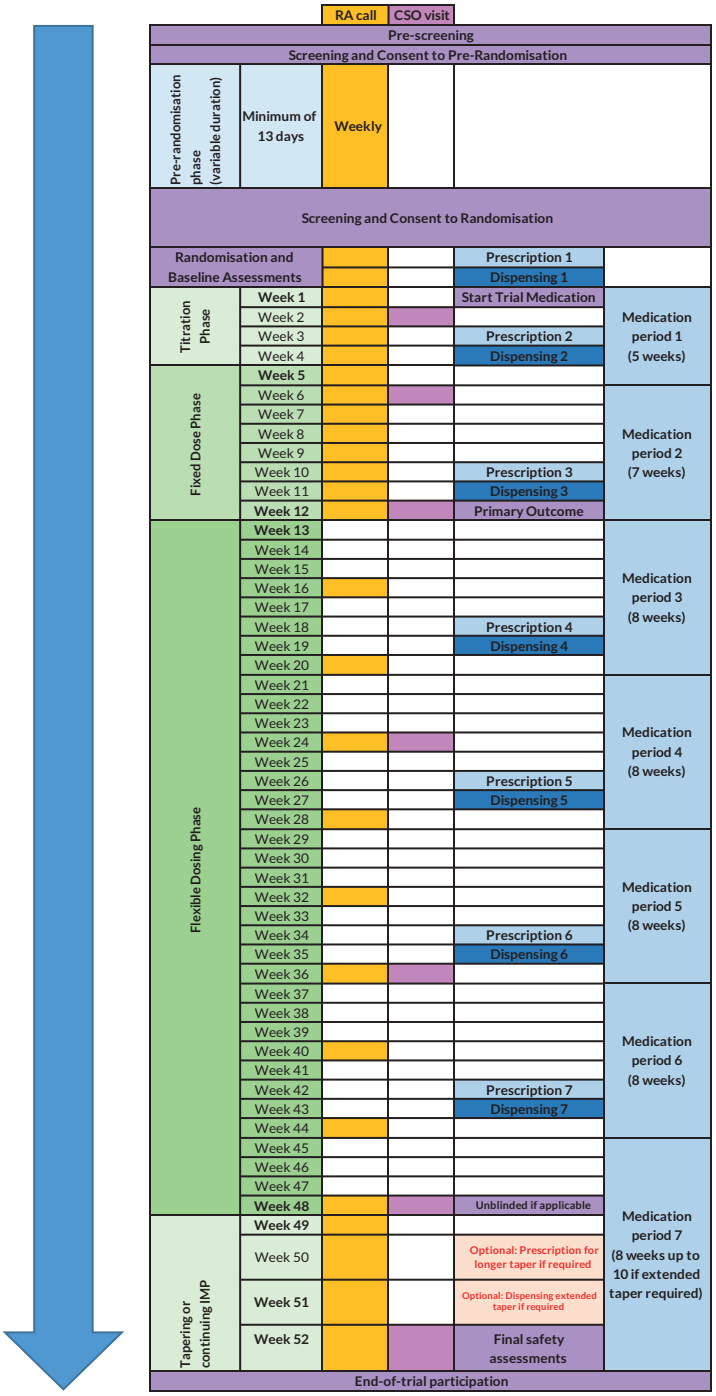

FIGURE 25 Patient flow diagram.

Additional tables

TABLE 25 Study sites and recruitment figures

	Open	Recruited to pre randomisation	Recruited to randomisation
Avon and Wiltshire Mental Health Partnership NHS Trust	9 July 2021	2	1
Cheshire and Wirral Partnership NHS Foundation Trust	20 February 2020	5	2
Cumbria, Northumberland, Tyne and Wear NHS Trust	28 November 2019	9	8
Derbyshire Healthcare NHS Foundation Trust	20 December 2019	0	0
Devon Partnership NHS Trust	3 February 2020	1	0
Essex Partnership University NHS Foundation Trust	23 June 2021	1	1
Kent and Medway NHS and Social Care Partnership Trust	28 January 2020	2	1
Lancashire and South Cumbria NHS Foundation Trust	20 January 2022	0	0
Leicestershire Partnership NHS Trust	26 July 2021	2	1
Lincolnshire Partnership NHS Foundation Trust	2 January 2020	1	0
NHS Lothian	8 April 2021	0	0
NHS Greater Glasgow and Clyde	25 March 2022	0	0
NHS Tayside	17 February 2022	0	0
Nottinghamshire Healthcare NHS Foundation Trust	12 October 2020	6	6
Oxford Health NHS Foundation Trust	28 April 2021	1	1
Sheffield Health and Social Care NHS Foundation Trust	28 January 2020	7	5
South London and Maudsley NHS Foundation Trust	24 May 2021	2	2
Surrey and Borders Partnership NHS Foundation Trust	3 December 2019	10	6
Southwest Yorkshire Partnership NHS Foundation Trust	11 November 2021	0	0
Southwest London and St George's Mental Health NHS Trust	6 January 2020	0	0
Tees, Esk and Wear Valleys NHS Foundation Trust	18 February 2020	3	2

TABLE 26 Schedule of events

					Treatment week (post randomisation)																												Tapering[a–d]	
	Screening	Pre-randomisation	Screening/randomisation	Baseline	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[e]		X[f]																															
Demographics	X																																	
Medical history	X		X																															
Eligibility assessment[g]	X		X																															
BDTQ	X																																	
MINI	X																																	
QIDS-SR (paper)	X		X																															
Pregnancy test	X		X																															X
Antipsychotic and mood stabiliser adjustment if required		X																																
Randomisation			X																															
Dispensing's			X					X						X				X				X				X				X				
IMP/placebo admin					Titration phase. 0.25 mg OD ↑ by 0.25 mg every 3 days to 2.5 mg OD or max. tolerated				Fixed dose phase. 2.5 mg OD or max. tolerated from titration.						Flexible dose phase between 0.25 and 2.5 mg/day.																		Tapering phase ↓ by 0.25 mg every 3 days	
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	X	X[h]	X
CSO[i] contact						X				X				X						X						X						X		X
Unblinding																																X[l]		

				Treatment week (post randomisation)																														Tapering[a–d]	
	Screening	Pre-randomisation	Screening/randomisation	Baseline	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)
End of study info sheet					X The End of Study Information Sheet needs to be given out at an appropriate time, that is 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																																
Participant Questionnaires to be completed on TrueColours[j]																																			
Self-reported demographics		X[k]																																	
QIDS-SR[m]		X[n]		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	X[h]	X	
ASRM[m]		X[n]		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	X[h]	X	
GAD-7		X[n]		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	X[h]	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	
EQ-5D-5L		X[k]		X										X						X						X						X			
ICECAP-A		X[k]		X										X						X						X						X			
OxCAP-MH		X[k]		X										X						X						X						X			
HEQ				X										X						X						X						X			
Central Research Assistant Activities																																			
RA contact		X[n]		X	X	X	X	X	X	X	X	X	X	X		X		X		X		X		X		X		X		X		X		X[h]	X	
Safety SOPs[m]					X	X	X	X	X	X	X	X	X	X		X		X		X		X		X		X		X		X		X		X[h]	X	
Concomitant medications		X[n]		X	X	X	X	X	X	X	X	X	X	X		X		X		X		X		X		X		X		X		X		X[h]	X	
DAWS screening																																		X[h]	X
YMRS				X										X																					
QIDS-C				X										X																					
MADRS				X										X																					

continued

TABLE 26 Schedule of events (*continued*)

	Screening	Pre-randomisation	Screening/randomisation	Baseline	Treatment week (post randomisation)																													Tapering[a–d]	
					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)
AE reporting		X[o]		X	X	X	X	X	X	X	X	X	X	X		X		X		X		X		X		X		X		X		X[h]	X
Flexible dosing reports														X																		X		X
Qualitative interviews (pilot phase only)		X												X																				
Participant Gift vouchers														X											X									X

a If a participant stops taking medication for any reason during the trial, RA contacts including dopamine agonist withdrawal syndrome (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.
b Final safety assessments will take place at week 52 or when participant has been drug-free for 2 weeks (whichever is later).
c 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 contact following unblinding medication. No further safety assessments, including pregnancy test, will be undertaken for these participants.
d Where we reference 52 + 2 weeks, the + 2 weeks refers to patients who may require a longer taper – please see section 8.4.2 for full details.
e Consent is received to enter the pre-randomisation stage.
f To be randomised to trial medication.
g See eligibility section in Chapter 2 for inclusion and exclusion criteria.
h Weekly through tapering phase.
i 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).
j If entering on TrueColours is not an option, paper alternatives are available.
k Completed at the beginning of the pre-randomisation stage.
l 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. Following the decision by the funders to close the study early this may happen earlier than 48 weeks but should still happen after the final assessments have been completed for the participant.
m 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.
n Weekly through pre-randomisation stage and until participant begins trial medication.
o Four weekly through pre randomisation.

TABLE 27 Research Ethics Committee-approved amendments that included changes to the PAX-BD protocol

Amendment 1 (submitted as part of SA4)	Updates made to some eligibility criteria. These updates were made for clarification purposes only and did not change the eligibility criteria itself. This impacted Pre-Randomisation Inclusion Criteria number 5, Pre-Randomisation Exclusion Criteria numbers 5, 10 and 11 and Randomisation Exclusion Criteria number 8 and 9. Full stability data for pramipexole were also available at this stage and this section of the protocol was therefore updated to reflect that there were no specific storage requirements for the trial medication.
Amendment 2 (submitted as part of SA7)	Protocol updated in response to COVID-19 to allow delivery to continue during government and local restrictions, without compromising participant safety or trial primary outcomes. This included removal of blood pressure and pulse measurements (as agreed by the DMC); allowing for pre-randomisation and randomisation screening activities to also be carried out remotely; ability for pre-randomisation and randomisation stage consent discussions to be conducted via telephone/teleconference or videoconference before the patient attends a shorter face-to-face clinic visit to complete the consent form; more options regarding collection of urine samples and returning of unused IMP. Pre-randomisation inclusion criterion number 5 was also updated for clarification purposes only.
Amendment 3 (submitted as part of SA9)	Updates to allow further flexibility regarding how the participant can initially be approached and to provide sites and participants with a further option regarding collection of unused IMP/empty bottles.
Amendment 4 (submitted as part of SA10)	Inclusion criteria added to state that participants should be in the pre-randomisation stage for a minimum of 23 days to increase flexibility for those participants who already met the remaining inclusion criteria allowing them to progress to the randomisation stage promptly and not delay their treatment.
Amendment 5 (submitted as part of SA11)	This amendment included an update to the inclusion and exclusion criteria to allow participants to enter the trial while taking certain antipsychotics, which could be adjusted during the pre-randomisation stage to meet the eligibility criteria for randomisation. This update was made following a meeting with the funder and had the full support of both the PPI group and TSC. The update was approved by the HTA funder committee and their scientific advisers following submission of a written proposal which demonstrated that the coadministration of pramipexole in combination with a limited number of antipsychotics would allow increased recruitment and retention to the trial without comprising clinical effectiveness or safety.
Amendment 6 (submitted as part of NSA6)	Protocol updated to correct the dose of an antipsychotic that can be used in the trial; to allow researchers to use a wider range of communication methods and to provide greater clarification around the timing and nature of trial procedures. As the trial was paused from March to September 2020 (reducing the amount of time available for the trial to complete the pilot phase), this amendment also outlined that, with the agreement of the funder, the pilot could start again in October 2020 with an end date of October 2021.
Amendment 7 (submitted as part of SA12)	This amendment related to the early closure of the PAX-BD trial. The protocol was amended to reflect this change and confirmed that all participants would have the opportunity to be followed up to treatment week 12, including those currently in the pre-randomisation stage of the trial. As well as this there were updates to the inclusion and exclusion criteria to aid sites when randomising the remaining participants to the randomisation stage.

Appendix 3 Additional data relating to main results

Additional figures

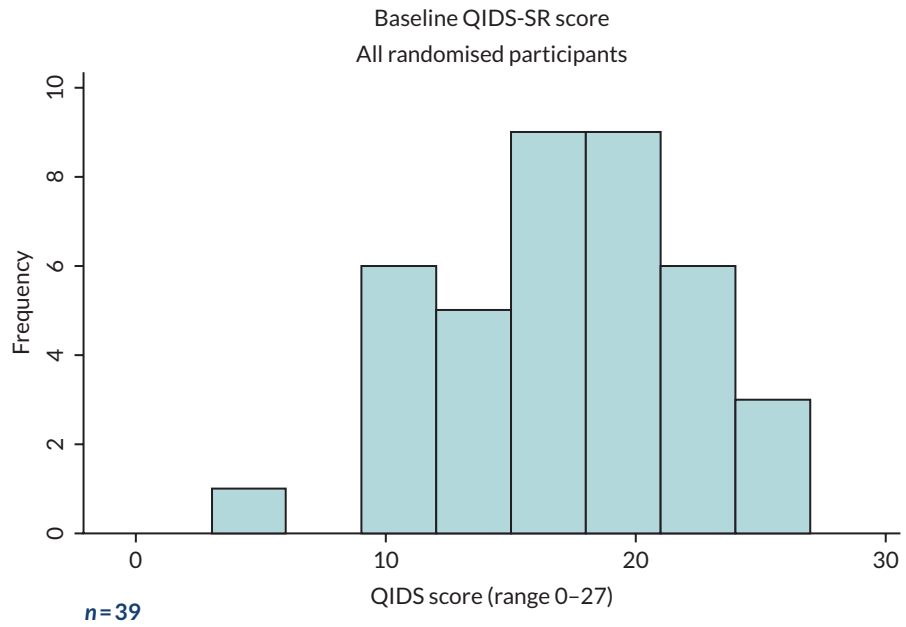

FIGURE 26 Distribution of baseline QIDS-SR scores (*n* = 39).

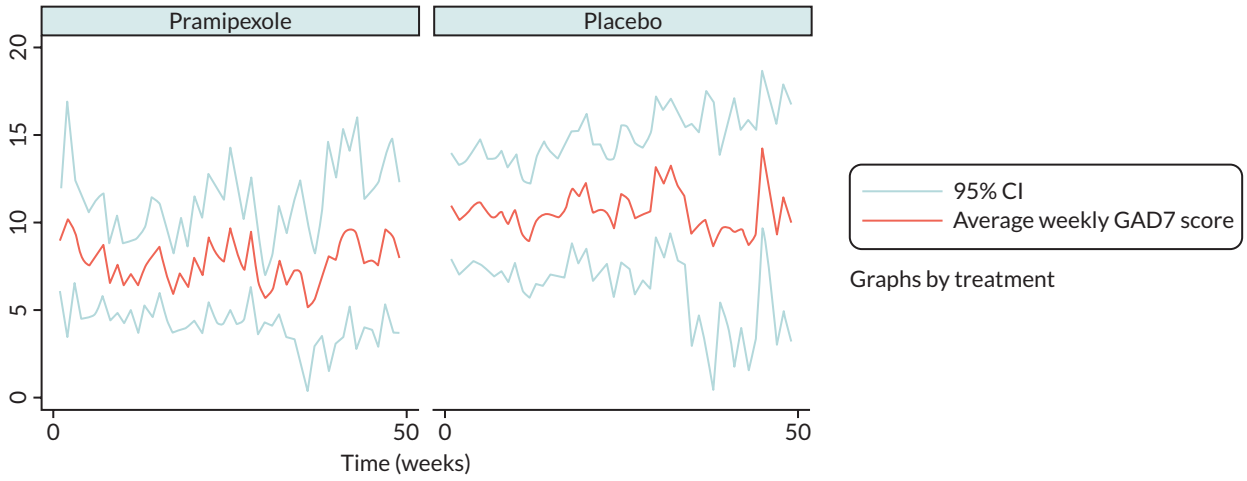

FIGURE 27 Weekly GAD-7 scores from randomisation to a maximum of 48 weeks.

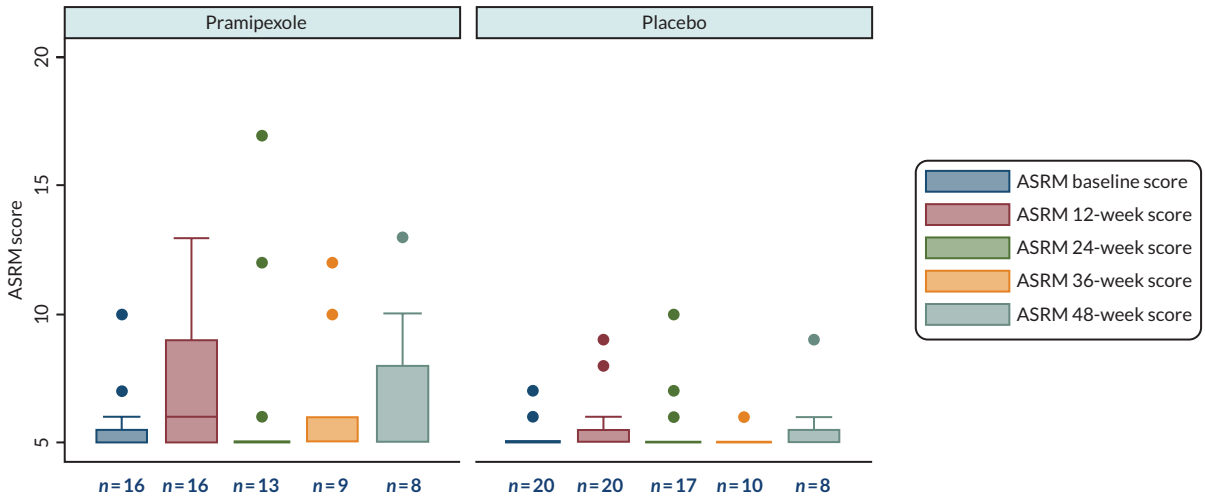

FIGURE 28 Box plot of ASRM scores for baseline, 12, 24, 36 and 48 weeks (n = 36). Reproduced with permission from McAllister-Williams *et al.*[84] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, in any medium and for any purpose, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original text.

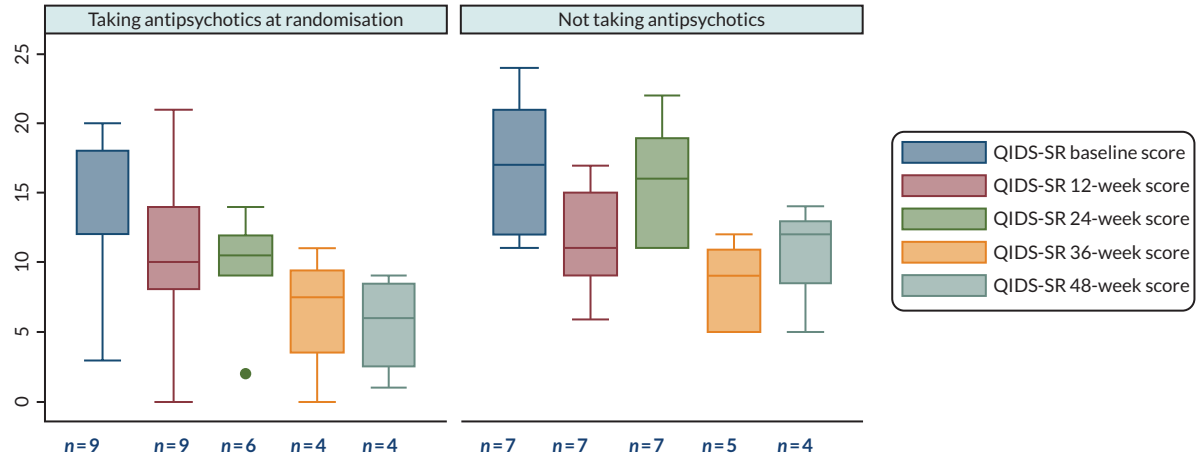

FIGURE 29 Box plot for QIDS-SR baseline, 12, 24, 36 and 48 weeks, for participants on and not on antipsychotics in the pramipexole arm.

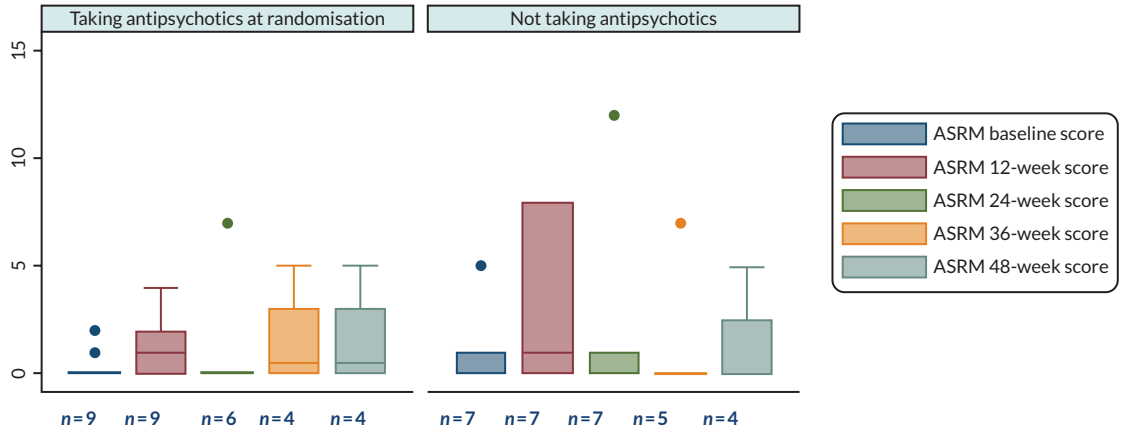

FIGURE 30 Box plot for ASRM baseline, 12, 24, 36 and 48 weeks, for participants on and not on antipsychotics in the pramipexole arm. Reproduced with permission from McAllister-Williams *et al.*[84] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, in any medium and for any purpose, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original text.

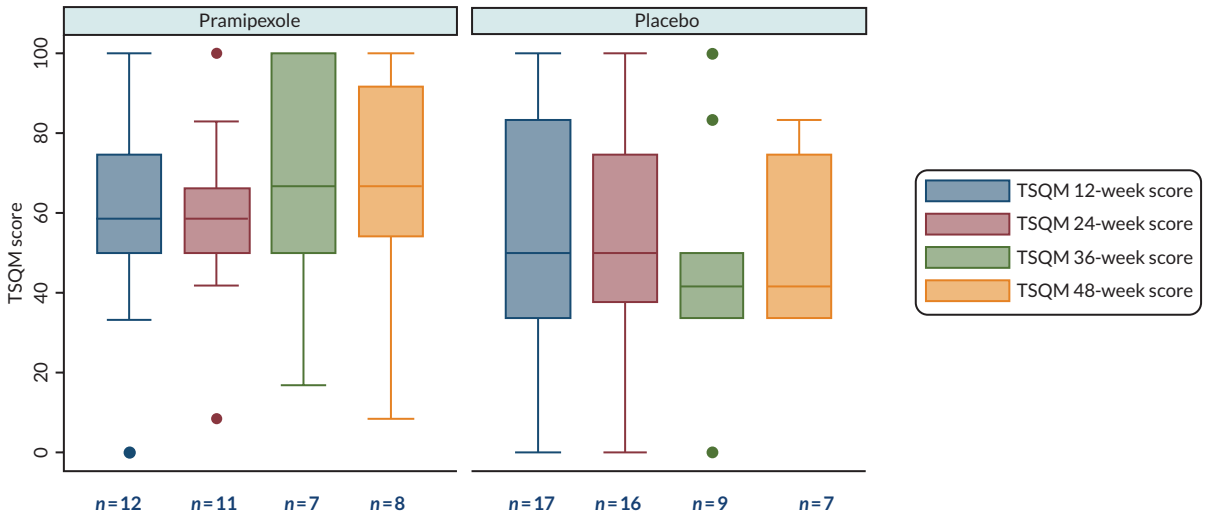

FIGURE 31 Box plot for TSQM scores at weeks 12, 24, 36 and 48 weeks (*n* = 36).

Additional tables

TABLE 28 Participant demographics in the various stages of the trial

Demographics		Pre randomisation: did not progress (*n* = 12)	Pramipexole arm (*n* = 16)	Placebo arm (*n* = 20)
Gender	Male	3 (25%)	9 (56%)	10 (50%)
	Female	9 (75%)	7 (44%)	10 (50%)
Age (years)	Median (IQR)	45 (41–56)	47.5 (40–51)	50 (35.5–58.5)
	Mean (SD)	47.5 (12.2)	46.0 (9.0)	48.0 (12.8)
	Range (min–max)	(25–66)	(30–60)	(26–68)
Body mass index	Median (IQR)	*N* = 8 of 12 31.4 (24.8–44.3)	27.1 (24.1–37.8)	28.4 (24.9–32.2)
	Mean (SD)	34.6 (12.3)	33.2 (14.4)	30.3 (9.3)
	Range (min–max)	(20.3–55.4)	(20.0–78.0)	(21.2–63.3)
Current smoker	Yes	*N* = 8 of 12 2 (25%)	3 (19%)	4 (20%)
	No	6 (75%)	13 (81%)	16 (80%)
Education level	1–4 GCSE passes	2 (25%)	2 (13%)	2 (10%)
	O level 2 ≥ 5 passes at GCSE	0 (0%)	1 (6%)	0 (0%)
	O level 3 = A levels or equivalent	0 (0%)	2 (13%)	6 (30%)
	University (undergraduate) degree	1 (13%)	5 (31%)	3 (15%)
	Postgraduate degree	2 (25%)	4 (25%)	3 (15%)
	Other	2 (25%)	1[a] (6%)	2[a] (10%)

TABLE 28 Participant demographics in the various stages of the trial (*continued*)

Demographics		Pre randomisation: did not progress (*n* = 12)	Pramipexole arm (*n* = 16)	Placebo arm (*n* = 20)
	Prefer not to answer	1 (13%)	0 (0%)	1 (5%)
	Not applicable	0 (0%)	0 (0%)	1 (5%)
	Don't know	0 (0%)	1 (6%)	0 (0%)
	None	0 (0%)	0 (0%)	2 (10%)

GCSE, General Certificate of Secondary Education; IQR, Intequartile range; max, maximum; min, minimum.
a Three specified 'other' for their education level. These are further specified as 'city and guild 4' (equivalent to the first year of an undergraduate degree), 'RMN' (mental health nurse qualification) and 'Level 3 diploma' (BTEC qualification equivalent to 3 A-levels).

TABLE 29 Illness characteristics of participants in the various stages of the trial

	Pre randomisation: did not progress (*n* = 12)	Pramipexole arm (*n* = 18)	Placebo arm (*n* = 21)
Bipolar type (I or II)			
I	9 (75%)	13 (72%)	15 (71%)
II	3 (25%)	5 (28%)	6 (29%)
Age at 1st onset (years)			
n (%)	11 (92%)	18 (100%)	21 (100%)
Median (IQR)	34 (18–48)	27 (21–33)	23 (17–31)
Mean (SD)	33.9 (15.0)	27.7 (9.9)	25.8 (12.4)
Range (min–max)	(13–61)	(14–48)	(9–59)
Missing (from completed BDTQ)	1 (8%)	0 (0%)	0 (0%)
Duration of current depressive episode (months)			
N (%)	12 (100%)	16 (89%)	21 (100%)
Median (IQR)	16.0 (7.2–20.0)	7.9 (3.1–42.2)	18.3 (6.7–41.3)
Mean (SD)	17.7 (14.9)	25.3 (33.1)	35.0 (47.3)
Range (min–max)	(1.9–49)	(1.2–111.6)	(2–178.7)
Missing	0 (0%)	2 (11%)	0 (0%)
Number of mood episodes in last 12 months			
No episodes	1 (8%)	1 (6%)	1 (5%)
1 episode	6 (50%)	8 (44%)	12 (57%)
2 episodes	2 (17%)	6 (33%)	0 (0%)
3 episodes	2 (17%)	0 (0%)	4 (19%)
4 episodes	0 (0%)	1 (6%)	1 (5%)

continued

TABLE 29 Illness characteristics of participants in the various stages of the trial (*continued*)

	Pre randomisation: did not progress (*n* = 12)	Pramipexole arm (*n* = 18)	Placebo arm (*n* = 21)
5 episodes	0 (0%)	2 (11%)	2 (5%)
More than 12 episodes	1 (8%)	0 (0%)	1 (5%)

IQR, interquartile range; max, maximum; min, minimum.

Note

TABLE 30 Medication history of participants in the various stages of the trial

	Mean daily dose (range) in mg unless otherwise stated	Pre randomisation: did not progress (*N* = 12)	Pramipexole arm (*n* = 18)	Placebo arm (*n* = 21)
Currently taking an antipsychotics				
Yes		9 (75%)	10 (56%)	10 (48%)
No		3 (25%)	8 (44%)	11 (52%)
Antipsychotics taken[a]		***N* = 10 (9 unique)**	***N* = 7 (7 unique)**	***N* = 11 (10 unique)**
Aripiprazole	18.8 (10–30)	2	1	1
Flupenthixol	50 (50)	0	1	0
Haloperidol	2 (2)	1	0	0
Lurasidone	78.5 (55.5–110)	1	1	2
Olanzapine	11.8 (2.5–20)	3	1	2
Paliperidone	350 (175–525)[b]	1	0	1
Quetiapine	281 (100–600)	2	3	5
Risperidone	1 (1)	0	0	0
Currently taking mood stabilisers				
Yes		5 (42%)	17 (94%)	20 (95%)
No		7 (58%)	1 (6%)	1 (5%)
Mood stabilisers taken[c]		***N* = 5 (5 unique)**	***N* = 20 (17 unique)**	***N* = 26 (20 unique)**
Lamotrigine	241 (25–400)	1	10	11
Lithium	760 (400–1600)	1	7	10
Oxcarbamazepine	600 (600)	0	0	1
Valproate	1060 (500–1500)	3	3	4
Currently taking antidepressants				
Yes		7 (58%)	11 (61%)	11 (52%)
No		5 (42%)	7 (49%)	10 (48%)
Antidepressants taken[d]		***N* = 8 (7 unique)**	***N* = 12 (11 unique)**	***N* = 15 (11 unique)**
Selective serotonin reuptake inhibitors				
Citalopram	10 (10)	1	0	0
Escitalopram	3.8 (2.5–5)	0	0	2

TABLE 30 Medication history of participants in the various stages of the trial (*continued*)

	Mean daily dose (range) in mg unless otherwise stated	Pre randomisation: did not progress (*N* = 12)	Pramipexole arm (*n* = 18)	Placebo arm (*n* = 21)
Fluoxetine	42.5 (20–60)	1	2	5
Paroxetine	25 (10–50)	0	1	1
Sertraline	150 (100–200)	2	0	0
Serotonin–norepinephrine reuptake inhibitor				
Venlafaxine	225 (75–375)	2	4	2
Tricyclic antidepressants				
Amitriptyline	100 (50–150)	0	1	1
Dosulepin	75 (75)	0	1	0
Lofepramine	210 (210)	0	1	0
Others				
Mirtazapine	33 (15–45)	1	1	3
Trazodone	50 (50)	1	0	0
Vortioxetine	15 (10–20)	0	1	1
Anxiolytics/hypnotics				
Yes		7 (58%)	8 (44%)	10 (48%)
No		5 (42%)	10 (56%)	11 (52%)
Anxiolytics/hypnotics taken[e]		***N* = 9 (7 unique)**	***N* = 8 (8 unique)**	***N* = 14 (10 unique)**
Benzodiazepines				
Clonazepam	2 (2)	0	0	1
Diazepam	5.7 (2–11)	1	1	4
Lorazepam	1.4 (1–2)	2	1	2
Temazepam	10 (10)	0	1	0
Z drugs				
Zolpidem	5 (5)	0	0	1
Zopiclone	7.5 (7.5)	3	2	1
Others				
Buspirone	15 (15)	0	1	0
Gabapentin	900 (900)	0	1	0
Pregabalin	367 (150–600)	2	1	3
Melatonin	2 (2)	0	0	1
Promethazine	25 (25)	1	0	1
Currently taking other psychotropics[f]				
Yes		2 (17%)	4 (19%)	4 (19%)
No		10 (83%)	14 (81%)	17 (81%)

continued

TABLE 30 Medication history of participants in the various stages of the trial (*continued*)

	Mean daily dose (range) in mg unless otherwise stated	Pre randomisation: did not progress (*N* = 12)	Pramipexole arm (*n* = 18)	Placebo arm (*n* = 21)
Currently taking non-psychotropic medication				
Yes		7 (58%)	13 (72%)	13 (62%)
No		5 (42%)	5 (28%)	8 (38%)

a One participant was on a combination of lurasidone + quetiapine and another on paliperidone depot injection + oral haloperidol.
b Monthly depot injection.
c Four participants were taking lithium + lamotrigine, three lamotrigine + valproate; two lithium + valproate and one lithium + oxcarbazepine.
d Five participants were taking mirtazapine + another antidepressant: two on venlafaxine and one each on dosulepine, vortioxetine and fluoxetine.
e Two participants were on combinations of three anxiolytics/hypnotics.
f 'Other' psychotropics included two participants on modafinil and one each on methylphenidate, pregabalin, procyclidine and promethazine.

Note
Note that statements regarding whether medication was taken relates to entry to the pre-randomisation stage. All participants were taking a mood stabiliser at the point of entry to the randomisation stage.

TABLE 31 Rating scale baseline scores for participants randomised and those contributing data to the primary outcome

Rating scale		Randomised participants	Participants contributing to primary outcome
QIDS-SR		*n* = 39	*n* = 36
	Median (IQR)	17 (12–20)	17 (12–20)
	Mean (SD)	16.5 (4.9)	16.3 (5.0)
	95% CI about mean	14.9 to 18.1	14.6 to 18.0
	Range (min–max)	(3–25)	(3–25)
MADRS		*n* = 39	*n* = 35
	Median (IQR)	30 (26–35)	30 (26–33)
	Mean (SD)	30.8 (7.7)	30.3 (7.5)
	95% CI about mean	28.3 to 33.3	27.0 to 32.9
	Range (min–max)	(11–48)	(11–47)
QIDS-C		*n* = 39	*n* = 35
	Median (IQR)	18 (15–20)	18 (15–19)
	Mean (SD)	17.1 (3.8)	16.9 (3.8)
	95% CI about mean	15.9 to 18.3	15.6 to 18.2
	Range (min–max)	(6–24)	(6–24)
GAD-7		*n* = 39	*n* = 36
	Median (IQR)	9 (5–14)	9 (5–13.5)
	Mean (SD)	10.4 (6.1)	10.1 (6.1)
	95% CI about mean	8.4 to 12.4	8.0 to 12.1
	Range (min–max)	(0–21)	(0–21)
SHAPS		*n* = 37	*n* = 34
	Median (IQR)	6 (4–10)	6 (4–10)
	Mean (SD)	7.0 (4.0)	6.7 (3.8)

TABLE 31 Rating scale baseline scores for participants randomised and those contributing data to the primary outcome (*continued*)

Rating scale		Randomised participants	Participants contributing to primary outcome
	95% CI about mean	5.7 to 8.3	5.4 to 8.1
	Range (min–max)	(0–14)	(0–13)
WSAS		*n* = 36	*n* = 34
	Median (IQR)	31 (24.5–35)	31 (25–35)
	Mean (SD)	29.7 (6.9)	29.6 (6.9)
	95% CI about mean	27.3 to 32.0	27.2 to 32.0
	Range (min–max)	(15–40)	(15–40)
ASRM		*n* = 39	*n* = 36
	Median (IQR)	0 (0–0)	0 (0–0)
	Mean (SD)	0.3 (0.9)	0.4 (1.0)
	95% CI about mean	0.0 to 0.6	0.0 to 0.7
	Range (min–max)	(0–5)	(0–5)
YMRS		*n* = 39	*n* = 35
	Median (IQR)	1 (0–3)	2 (1–3)
	Mean (SD)	1.9 (2.1)	1.9 (1.7)
	95% CI about mean	1.3 to 2.6	1.3 to 2.5
	Range (min–max)	(0–9)	(0–7)
QUIP-RS		*n* = 32	*n* = 31
	Median (IQR)	19 (9–33.5)	19 (8–34)
	Mean (SD)	21.6 (14.2)	21.6 (14.5)
	95% CI about mean	16.5 to 26.8	16.3 to 26.9
	Range (min–max)	(2–57)	(2–57)

max, maximum; min, minimum.

Note
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TABLE 32 Assessment of criteria for TRBD: rates of positive responses to 'inadequate response', 'intolerance' and 'declined/clinically inappropriate'

Medication	Inadequate response (%)	Intolerance (%)	Declined/clinically inappropriate (%)
Full pre-randomisation sample (n = 51)			
Olanzapine	12 (25)	10 (20)	26 (51)
Quetiapine	20 (39)	16 (31)	26 (51
Lurasidone	7 (14)	3 (6)	13 (25)
Lamotrigine	21 (41)	5 (10)	14 (27)

continued

TABLE 32 Assessment of criteria for TRBD: rates of positive responses to 'inadequate response', 'intolerance' and 'declined/clinically inappropriate' (*continued*)

Medication	Inadequate response (%)	Intolerance (%)	Declined/clinically inappropriate (%)
Randomised (n = 39)			
Olanzapine	9 (23)	8 (21)	19 (49)
Quetiapine	16 (41)	14 (36)	19 (49)
Lurasidone	5 (13)	3 (8)	9 (23)
Lamotrigine	19 (49)	5 (13)	9 (23)
Not randomised (n = 12)			
Olanzapine	3 (25)	2 (17)	7 (58)
Quetiapine	4 (33)	2 (17)	7 (58)
Lurasidone	2 (17)	0 (0)	4 (33)
Lamotrigine	3 (25)	0 (0)	5 (42)

Note

Note that these criteria were judged clinically with regard to the current episode of BD. If a medication had been trialled in a previous episode and either there had been a non-response or intolerance, this would be grounds for indicating it to be 'clinically inappropriate' in the current episode. For an 'inadequate response' there needed to have been a minimum of an 8-week trial of olanzapine at a minimum dose of 5 mg/day, quetiapine 300 mg/day or lurasidone 55.5 mg/day, or a trial of lamotrigine at a minimum of 200 mg for at least 12 weeks. If these doses or duration were not tolerated, this would be grounds for a positive response to 'intolerance'.

TABLE 33 Rates of multiple 'inadequate' responses when assessing TRBD criteria

Number of inadequate responses	Full pre-randomisation sample (*n* = 51) (%)	Randomised (*n* = 39) (%)	Not randomised (*n* = 12) (%)
0	12 (24)	8 (21)	4 (33)
1	21 (41)	17 (44)	4 (33)
2	15 (29)	11 (28)	4 (33)
3	2 (4)	2 (5)	0 (0)
4	1 (2)	1 (3)	0 (0)
Total	51 (100)	39 (100)	12 (100)

Note

TABLE 34 Summary statistics of time (weeks) in pre randomisation for participants who progressed to the randomisation stage, by treatment arm

Time in pre randomisation (weeks)	Pramipexole (*N* = 18)	Placebo (*N* = 21)	Total (*N* = 39)
Median (IQR)	8 (5–10)	8 (6–10 weeks + 1 day)	8 (5 weeks + 5 days– 10 weeks + 1 day)
Mean (SD)	9.6 (6.8)	10.2 (8.7)	9.9 (7.8)
Range (min–max)	(3 weeks + 6 days–28 weeks + 1 day)	(4–43 weeks + 6 days)	(3 weeks + 6 days– 43 weeks + 6 days)

IQR, interquartile range; max, maximum; min, minimum.

TABLE 35 Quick Inventory of Depressive Symptoms, Self-Rated scores before and after randomisation eligibility check and baseline assessment for three participants scoring < 10 at baseline

Participant ID	Last pre-randomisation QIDS-SR score		Randomisation eligibility check confirming QIDS-SR 10 +	Baseline QIDS-SR score		Next recorded QIDS-SR score	
	Score	Timing		Score	Timing	Score	Timing
1013	8	10 days before start medication	Yes	9	5 days before start medication	10	5 days after start medication
23004	6	31 days before start medication	Yes	3	4 days before start medication	3	14 days after start medication
28002	6	10 days before start medication	Yes	9	0 days before start medication	10	4 days after start medication

TABLE 36 Randomisation minimisation factors by treatment allocation

Minimisation factor		Pramipexole (*N* = 16) (%)	Placebo (*N* = 20) (%)
Bipolar type	Bipolar I	12 (75)	13 (65)
	Bipolar II	4 (25)	7 (35)
Severity of depression at randomisation (QIDS-SR)	Moderate (11–15)	5 (31)	7 (35)
	Severe (16–20)	8 (50)	10 (50)
	Very severe (> 20)	3 (19)	3 (15)
Age group	18–50	11 (69)	10 (50)
	> 50	5 (31)	10 (50)
Biological sex	Male	9 (56)	10 (50)
	Female	7 (44)	10 (50)
Site (region)	North	9 (56)	7 (35)
	Midlands and East	3 (19)	5 (25)
	London	0 (0)	2 (10)
	South East	4 (25)	5 (25)
	South West	0 (0)	1 (5)
Concurrent mood stabiliser	Lithium	7 (44)	7 (35)
	Valproate	2 (13)	1 (5)
	Lamotrigine	7 (44)	9 (45)
	Carbamazepine	0 (0)	0 (0)
	Multiple mood stabilisers	0 (0)	3 (15)

continued

TABLE 36 Randomisation minimisation factors by treatment allocation (*continued*)

Minimisation factor		Pramipexole (*N* = 16) (%)	Placebo (*N* = 20) (%)
Concurrent antidepressant	Yes	6 (38)	9 (45)
	No	10 (63)	11 (55)
Taking an antipsychotic at randomisation	Yes	9 (56)	10 (50)
	No	7 (44)	10 (50)
Number of mood episodes in the past year	< 4	14 (88)	16 (80)
	≥ 4	2 (13)	4 (20)

TABLE 37 Summary statistics of rates of missed doses of study medication

	Pramipexole (*n* = 18)	Placebo (*n* = 21)	Combined (*n* = 39)
Median (IQR)	5 (2–31)	72.5 (28–120)	28 (4–88)
Mean (SD)	27.1 (44.8)	83.8 (69.4)	49.8 (60.8)
Range (min–max)	(1–141)	(10–200)	(1–200)

IQR, interquartile range; max, maximum; min, minimum.

TABLE 38 Summary statistics of duration of follow-up post starting trial medication in the two treatment arms

	Pramipexole (*N* = 18)	Placebo (*N* = 21)	Total (*N* = 39)
Median (IQR)	38 weeks + 3 days (23 weeks + 6 days–48 weeks + 0 days)	33 weeks + 6 days (28 weeks + 4 days–48 weeks + 0 days)	35 weeks + 0 days (23 weeks + 6 days–48 weeks + 0 days)
Mean (SD)	35.1 (14.9)	34.8 (13.1)	34.9 (13.8)
Range (min–max)	(3 weeks + 0 days–48 weeks + 0 days)	(6 weeks + 4 days–48 weeks + 0 days)	(3 weeks + 0 days–48 weeks + 0 days)

IQR, interquartile range; max, maximum; min, minimum.

TABLE 39 Completion rates for the 3 weekly participant rated scales (*n* = 39)

Questionnaire weekly	Pramipexole (*N* = 18)	Placebo (*N* = 21)
QIDS-SR		
Median (IQR)	75% (51–95%)	91% (74–98%)
Mean (SD)	73% (0.2)	83% (0.2)
Range (min–max)	(40–100%)	(25–100%)
GAD-7		
Median (IQR)	79% (61–98%)	94% (74–100%)
Mean (SD)	77% (0.2)	85% (0.2)
Range (min–max)	(45–100%)	(25–100%)
ASRM		
Median (IQR)	75% (53–98%)	92% (74–100%)
Mean (SD)	75% (0.2)	84% (0.2)
Range (min–max)	(46–100%)	(25–100%)

IQR, interquartile range; max, maximum; min, minimum.

TABLE 40 Completion rates for other scales

Questionnaires	Pramipexole (*N* = 18)	Placebo (*N* = 21)
QIDS-C (baseline and 12 weeks)		
Median (IQR)	100% (100–100%)	100% (100–100%)
Mean (SD)	100% (0)	98% (10.9)
Range (min–max)	(100–100%)	(50–100%)
MADRS (baseline and 12 weeks)		
Median (IQR)	100% (100–100%)	100% (100–100%)
Mean (SD)	100% (0)	98% (10.9)
Range (min–max)	(100–100%)	(50–100%)
YSRM (baseline and 12 weeks)		
Median (IQR)	100% (100–100%)	100% (100–100%)
Mean (SD)	100% (0)	98% (10.9)
Range (min–max)	(100–100%)	(50–100%)
***SHAP* (baseline, 6 and 12 weeks)**	Pramipexole (*N* = 18)	Placebo (*N* = 21)
Median (IQR)	100% (100–100%)	100% (100–100%)
Mean (SD)	86% (29.3)	91% (19.5)
Range (min–max)	(0–100%)	(33–100%)
***WSAS* (baseline, 6, 12, 24, 36 and 48 weeks)**	Pramipexole (*N* = 18)	Placebo (*N* = 21)
Median (IQR)	73% (50–100%)	80% (67–100%)
Mean (SD)	68% (32.6)	79% (21.1)
Range (min–max)	(0–100%)	(25–100%)
TSQM (6 and 12 weeks, then every 4 weeks to 48 weeks)	Pramipexole (*N* = 18)	Placebo (*N* = 21)
Median (IQR)	89% (73–100%)	91% (73–100%)
Mean (SD)	78% (29.5)	82% (26.2)
Range (min–max)	(0–100%)	(0–100%)
QUIP-RS (baseline, *6 and 12 weeks, then every 4 weeks to 48 weeks*)	Pramipexole (*N* = 18)	Placebo (*N* = 21)
Median (IQR)	92% (71–100%)	92% (75–100%)
Mean (SD)	81% (27.4)	85% (19.9)
Range (min–max)	(0–100%)	(25–100%)

IQR, interquartile range; max, maximum; min, minimum;

Note that the baseline for these weekly questionnaires were sometimes completed after the participant started taking trial medication. After consultation with the clinical team, it was decided that any questionnaires completed up to 3 days after start of trial medication could be used. (This translates into between 4 and 6 of the 7 affected participants been included for particular questionnaires.)

TABLE 41 Time from start of medication that 12-week primary outcome measure was completed (*n* = 36)

Time to 12 weeks	Pramipexole (*N* = 16)	Placebo (*N* = 20)
Median (IQR)	11 weeks + 6 days (11 weeks + 6 days–12 weeks + 0 days)	12 weeks + 0.5 days (11 weeks + 2.5 days–12 weeks + 2 days)
Mean (SD)	11.8 (0.4)	11.7 (0.8)
Range (min–max)	(10 weeks + 5 days–12 weeks + 3 days)	(9 weeks + 4 days–12 weeks + 3 days)

IQR, interquartile range; max, maximum; min, minimum.

TABLE 42 Assessment of effect of minimisation factors and baseline GAD-7 scores on the primary outcome measure (QIDS-SR @ 12 weeks), with and without treatment arm included in model and adjusted for baseline QIDS-SR. Twelve-week complete population

			95% CI	
Minimisation factor (reference value)	*N*	Coefficient	Lower	Upper
Bipolar type (type I)	36			
Type II		1.958	−1.715	5.631
With treatment arm	36			
		1.683	−1.914	5.280
Severity at randomisation (moderate)	36			
Severe		0.793	−3.762	5.348
Very severe		−0.739	−7.443	5.965
With treatment arm	36			
		1.598	−2.916	6.112
		0.790	−5.946	7.527
Age (19–50)	36			
> 50		−0.105	−3.586	3.377
With treatment arm	36			
		−0.691	−4.130	2.749
Biological sex (male) female	36			
		−2.810	−6.333	0.714
With treatment arm	36			
		−2.766	−6.182	0.650
Site region (North)	35			
Midlands and East		−0.569	−5.189	4.052
London		4.859	−3.085	12.802
South East		0.144	−4.137	4.426
With treatment arm	35			
		−0.957	−5.414	3.501
		3.362	−4.435	11.159
		−0.194	−4.322	3.935

TABLE 42 Assessment of effect of minimisation factors and baseline GAD-7 scores on the primary outcome measure (QIDS-SR @ 12 weeks), with and without treatment arm included in model and adjusted for baseline QIDS-SR. Twelve-week complete population (*continued*)

			95% CI	
Minimisation factor (reference value)	***N***	**Coefficient**	**Lower**	**Upper**
Concurrent mood stabilisers (lithium)	36			
Valproate		3.634	−3.007	10.275
Lamotrigine		1.073	−2.798	4.943
Multiple mood stabilisers		1.505	−5.225	8.235
With treatment arm	36			
		4.226	−2.210	10.662
		0.977	−2.756	4.711
		0.062	−6.619	6.742
Concurrent antidepressant (yes) no	36			
		0.102	−3.590	3.794
With treatment arm	36			
		0.110	−3.478	3.697
Antipsychotic at randomisation (yes) no	31			
		1.256	−2.221	4.734
With treatment arm	31			
		1.009	−2.397	4.416
Number of mood episodes in past year (< 4)	36			
4 +		4.001	−0.395	8.397
With treatment arm	36			
		3.700	−0.604	8.004
GAD-7 baseline score (continuous)	36			
		0.380	0.077	0.683
With treatment arm	36			
		0.366	0.071	0.660

TABLE 43 Pearson correlations between QIDS-SR and GAD-7 scores

	Baseline QIDS	**QIDS week 12**	**QIDS week 24**	**QIDS week 36**	**QIDS week 48**
Baseline GAD	*N* = 36				
Correlation coefficient	0.4988				
GAD week 12		*N* = 36			
Correlation coefficient		0.7045			
GAD week 24			*N* = 30		
Correlation coefficient			0.7031		

continued

TABLE 43 Pearson correlations between QIDS-SR and GAD-7 scores (*continued*)

	Baseline QIDS	QIDS week 12	QIDS week 24	QIDS week 36	QIDS week 48
GAD week 36				*N* = 19	
Correlation coefficient				0.6773	
GAD week 48					*N* = 16
Correlation coefficient					0.4427

TABLE 44 Assessment of effect of baseline demographic factors on the primary outcome measure (QIDS-SR @ 12 weeks), with and without treatment arm included in model and adjusted for baseline QIDS-SR

			95% CI	
Baseline factor (reference value)	*N*	Coefficient	Lower	Upper
Age (continuous)	36	−0.038	−0.193	0.117
With treatment arm	36	−0.052	−0.203	0.099
Smoking (yes)	36	1.529	−3.015	6.074
No				
With treatment arm	36	1.899	−2.515	6.313
Education level (none)	36			
1–4 GCSE passes at GSE, GCSE		1.262	−7.587	10.111
O level 2 ≥ 5 passes at GSE, GCSE		2.64	−10.11	15.392
O level 3 = A levels or equivalent		5.448	−2.73	13.625
Undergraduate degree		−0.221	−8.313	7.871
Postgraduate degree		−2.138	−10.41	6.136
Other		3.578	−5.848	13.003
Prefer not to answer		−1.663	−14.5	11.176
Not applicable		4.477	−8.041	16.994
Don't know		1.477	−11.04	13.994
With treatment arm	36			
		2.032	−7.128	11.192
		3.927	−9.384	17.238
		5.687	−2.594	13.968
		0.71	−7.817	9.237
		−1.084	−9.883	7.716
		3.939	−5.626	13.504
		−1.308	−14.3	11.69
		4.527	−8.113	17.168
		3.119	−10.23	16.47
Body mass index (continuous)	36	−0.088	−0.235	0.059
With treatment arm	36	−0.077	−0.221	0.067

GCSE, General Certificate of Secondary Education.

TABLE 45 Analysis of QIDS-SR scores from ad hoc per-protocol cohort with baseline QIDS-SR score of 10+

Primary outcome measure QIDS-SR at 12 weeks	Coeff[a]	SE of coeff	*P* value	95% confidence interval coefficient	
				Lower	Upper
Difference between treatment arms	2.395	1.764	0.185	−1.214	6.003
Baseline QIDS-SR	0.717	0.211	0.002	0.285	1.148
Constant	−0.023	3.580	0.995	−7.344	7.298

a Adjusted for baseline QIDS-SR score. Reference category is pramipexole.

TABLE 46 Summary statistics of MADRS scores at baseline and 12 weeks (*n* = 36)

MADRS	Pramipexole (*N* = 16)		Placebo (*N* = 19)[a]	
	Baseline	12 weeks	Baseline	12 weeks
Median (IQR)	27 (23–32.5)	15.5 (12–30.5)	32 (29–35)	30 (16–34)
Mean (SD)	27.4 (8.4)	18.4 (11.4)	32.7 (5.8)	26.2 (11.6)
Range (min–max)	(11–47)	(0–36)	(24–47)	(0–44)

IQR, interquartile range; max, maximum; min, minimum.
a One participant is missing follow-up data so removed from table.

TABLE 47 Summary statistics of QIDS-C-scores at baseline and 12 weeks (*n* = 36)

QIDS-C	Pramipexole (*N* = 16)		Placebo (*N* = 19)[a]	
	Baseline	12 weeks	Baseline	12 weeks
Median (IQR)	18 (14–19)	10 (7–17)	17 (15–20)	15 (8–18)
Mean (SD)	16.3 (4.6)	11.0 (6.6)	17.5 (2.9)	12.9 (6.3)
Range (min–max)	(6–23)	(0–21)	(12–24)	(0–22)

IQR, interquartile r max, maximum; min, minimum; UQ, upper quartile.
a One participant is missing follow-up data so removed from table.

TABLE 48 Response rates at 12 weeks and exit from trial (*n* = 36)

Response	Pramipexole (*N* = 16)		Placebo (*N* = 20)	
	12 weeks	Exit from trial	12 weeks	Exit from trial
In response	4 (22%)	6 (33%)	3 (14%)	1 (5%)
Not in response	12 (67%)	7 (39%)	17 (81%)	15 (71%)
Missing data		3 (17%)		4 (19%)

TABLE 49 Remission rates at 12 weeks and at exit from trial (*n* = 36)

	Pramipexole (*N* = 16)		Placebo (*N* = 20)	
Remission	**12 weeks**	**Exit from trial**	**12 weeks**	**Exit from trial**
In remission	2 (11%)	4 (25%)	3 (14%)	0 (0%)
Not in remission	14 (78%)	9 (56%)	17 (81%)	16 (80%)
Missing data		3 (19%)		4 (20%)

TABLE 50 Proportion of weeks free of depressive symptoms reported

	Pramipexole (*N* = 16)	Placebo (*N* = 20)
Percentage depressive free weeks		
Median (IQR)	0% (0–13%)	0% (0–0%)
Mean (SD)	15.4% (28.4)	7.1% (0.16)
Range (min–max)	(0–94%)	(0–54%)

IQR, interquartile range; max, maximum; min, minimum.

TABLE 51 Summary statistics of GAD-7 data at baseline, 12, 24, 36 and 48 weeks

	Baseline		12 weeks		24 weeks		36 weeks		48 weeks	
GAD-7	**PAX**	**Plac**	**PAX**	**Plac**	**PAX**	**Plac**	**PAX**	**Plac**	**PAX**	**Plac**
n	16	20	16	20	13	17	9	10	8	8
Median (IQR)	9 (5.5–11.5)	10 (4.5–18)	7 (5–9.5)	10 (4–18)	8 (4–10)	10 (6–17)	5 (3–7)	9.5 (4–14)	7 (4–13.5)	6.5 (6–15)
Mean (SD)	9.0 (5.5)	10.9 (6.5)	7.6 (4.2)	10.5 (7.2)	8.9 (6.0)	10.9 (6.9)	5.8 (4.1)	9.8 (7.0)	8.0 (5.2)	9.5 (6.9)
Range (min–max)	(0–21)	(3–21)	(2–17)	(0–21)	(2–20)	(0–21)	(0–13)	(0–21)	(1–14)	(0–21)

IQR, interquartile range; max, maximum; min, minimum; PAX, pramipexole; Plac, placebo.

TABLE 52 Summary statistics of SHAPS data at baseline, 6 and 12 weeks

SHAPS	Baseline		6 weeks		12 weeks	
	Pramipexole	**Placebo**	**Pramipexole**	**Placebo**	**Pramipexole**	**Placebo**
n	15	19	14	18	15	19
Median (IQR)	6 (2–10)	7 (5-10)	3.5 (2–7)	7 (5–10)	3 (1–8)	7 (4–9)
Mean (SD)	5.9 (4.2)	7.4 (3.4)	4.6 (3.4)	7.3 (3.2)	5.0 (4.1)	6.6 (4.1)
Range (min–max)	(0–13)	(1–13)	(0–11)	(1–13)	(0–14)	(0–14)

IQR, interquartile range; max, maximum; min, minimum.

TABLE 53 Summary statistics of WSAS data at baseline, 12, 24, 36 and 48 weeks

	Baseline		12 weeks		24 weeks		36 weeks		48 weeks	
WSAS	PAX	Plac	PAX	Plac	PAX	Plac	PAX	Plac	PAX	Plac
n	15	19	15	17	10	15	8	9	7	5
Median (IQR)	31 (27–35)	31 (24–35)	28 (20–34)	30 (20–33)	29.5 (20–33)	30 (22–34)	25.5 (20–29)	30 (27–31)	21 (11–28)	30 (21–37)
Mean (SD)	29.7 (6.9)	29.5 (7.0)	26.7 (7.3)	26.9 (8.1)	27.2 (6.8)	28.6 (7.9)	24.0 (6.9)	28.7 (3.7)	20.6 (7.6)	29.2 (8.5)
Range (min–max)	(15–38)	(17–40)	(14–37)	(11–40)	(15–33)	(9–40)	(11–32)	(21–34)	(10–28)	(20–38)

IQR, interquartile range; max, maximum; min, minimum; PAX, pramipexole; Plac, placebo.

TABLE 54 Proportion of weeks free of manic symptoms

Percentage of weeks free of manic symptoms	Pramipexole (*N* = 16)	Placebo (*N* = 20)
Proportion free of manic weeks		
Median (IQR)	97% (81–100%)	100% (96–100%)
Mean (SD)	87.6% (20.7)	95.8 (8.3)
Range (min–max)	(21–100%)	(68–100%)

IQR, interquartile range; max, maximum; min, minimum.

TABLE 55 Summary statistics of ASRM data at baseline, 12, 24, 36 and 48 weeks

	Baseline		12 weeks		24 weeks		36 weeks		48 weeks	
ASRM	PAX	Plac	PAX	Plac	PAX	Plac	PAX	Plac	PAX	Plac
n	16	20	16	20	13	17	9	10	8	8
Median (IQR)	0 (0–0.5)	0 (0–0)	1 (0–4)	0 (0–0.5)	0 (0–0)	0 (0–0)	0 (0–1)	0 (0–0)	0 (0–3)	0 (0–0.5)
Mean (SD)	0.6 (1.3)	0.2 (0.5)	2.1 (2.8)	0.5 (1.1)	1.5 (3.7)	0.5 (1.3)	1.4 (2.7)	0.1 (0.3)	1.8 (3.1)	0.6 (1.4)
Range (min–max)	(0–5)	(0–2)	(0–8)	(0–4)	(0–12)	(0–5)	(0–7)	(0–1)	(0–8)	(0–4)

IQR, interquartile range; max, maximum; min, minimum; PAX, pramipexole; Plac, placebo.

TABLE 56 Summary statistics for YMRS at baseline and 12 weeks

	Pramipexole (*N* = 16)		Placebo (*N* = 19[a])	
YMRS baseline	Baseline	12 weeks	Baseline	12 weeks
Median (IQR)	2 (0.5–3)	1 (0–5)	1 (1–2)	1 (0–4)
Mean (SD)	2.0 (1.6)	3.0 (4.1)	1.8 (1.8)	1.8 (2.3)
Range (min–max)	(0–5)	(0–15)	(0–7)	(0–7)

IQR, interquartile range; max, maximum; min, minimum.
a One participant is missing follow-up data so removed from baseline table.

TABLE 57 Summary statistics of QUIP-RS scores at weeks 0, 6, 12 and then at 4-week intervals to week 48

	Pramipexole (*n* = 16)											
QUIP-RS	**Base**	**6 weeks**	**12 weeks**	**16 weeks**	**20 weeks**	**24 weeks**	**28 weeks**	**32 weeks**	**36 weeks**	**40 weeks**	**44 weeks**	**48 weeks**
n	15	13	13	14	14	12	10	11	8	8	8	8
Median	19	15	13	18	12.5	10	7.5	12	2	0.5	5	3
Lower quartile	11	3	7	3	1	0.5	0	0	0	0	0	0
Upper quartile	33	24	27	27	21	19	21	27	8	9	11.5	9.5
Mean (SD)	21.9 (14.9)	16.0 (13.8)	16.2 (13.4)	16.0 (13.0)	14.2 (13.3)	11.9 (11.6)	11.6 (13.5)	12.4 (13.4)	7.1 (12.6)	6.9 (12.4)	8.6 (12.3)	7.8 (12.6)
Minimum	2	0	0	0	0	0	0	0	0	0	0	0
Maximum	57	44	38	40	37	34	38	37	37	36	36	37
Placebo (n = 20)												
n	17	20	18	15	16	16	14	9	9	8	8	6
Median	19	12	12	5	5.5	7	6	6	5	14.5	9	3
Lower quartile	8	4.5	2	0	0	0	2	4	0	2.5	0	2
Upper quartile	34	26.5	20	11	13.5	18.5	19	12	23	26.5	18.5	8
Mean (SD)	21.4 (14.0)	15.4 (13.0)	15.4 (16.3)	8.4 (10.6)	9.1 (11.3)	10.1 (11.6)	9.3 (9.4)	9.4 (9.2)	13.1 (14.2)	15.5 (14.2)	10.6 (11.5)	5.2 (5.5)
Minimum	4	0	0	0	0	0	0	0	0	0	0	0
Maximum	45	40	59	39	43	33	29	28	35	37	30	15

TABLE 58 Summary statistics of QIDS-SR scores for participants in the pramipexole arm who were taking (on), and not taking (not on), antipsychotic when randomised

QIDS-SR	**Baseline**		**12 weeks**		**24 weeks**		**36 weeks**		**48 weeks**	
Antipsychotic	**On**	**Not on**	**On**	**Not on**	**On**	**Not on**	**On**	**Not on**	**On**	**Not on**
n	9	7	9	7	6	7	4	5	4	4
Median (IQR)	12 (12–18)	17 (12–21)	10 (8–14)	11 (9–15)	10.5 (9–12)	16 (11–19)	7.5 (3.5–9.5)	9 (5–11)	6 (2.5–8.5)	12 (8.5–13)
Mean (SD)	13.7 (5.4)	17.0 (4.6)	10.0 (6.5)	11.6 (3.7)	9.7 (4.1)	15.9 (4.0)	6.4 (4.7)	8.4 (3.3)	5.5 (3.7)	10.8 (3.9)
Range (min–max)	(3–20)	(11–24)	(0–21)	(6–17)	(2–14)	(11–22)	(0–11)	(5–12)	(1–9)	(5–14)

IQR, interquartile range; max, maximum; min, minimum.

TABLE 59 Summary statistics of ASRM scores for participants in the pramipexole arm who were taking (on), and not taking (not on), antipsychotic when randomised

ASRM	**Baseline**		**12 weeks**		**24 weeks**		**36 weeks**		**48 weeks**	
Antipsychotic	**On**	**Not on**	**On**	**Not on**	**On**	**Not on**	**On**	**Not on**	**On**	**Not on**
n	9	7	9	7	6	7	4	5	4	4
Median (IQR)	0 (0–0)	0 (0–1)	1 (0–2)	1 (0–8)	0 (0–0)	0 (0–1)	0.5 (0–3)	0 (0–0)	0.5 (0–3)	0 (0–2.5)
Mean (SD)	0.3 (0.7)	0.9 (1.9)	1.4 (1.7)	3.0 (3.7)	1.2 (2.9)	1.9 (4.5)	1.5 (2.4)	1.4 (3.1)	1.5 (2.4)	1.3 (2.5)
Range (min–max)	(0–2)	(0–5)	(0–4)	(0–8)	(0–7)	(0–12)	(0–5)	(0–7)	(0–5)	(0–5)

IQR, interquartile range; max, maximum; min, minimum.

TABLE 60 Summary statistics of TSQM scores at weeks 6, and 4 weekly thereafter to 48 weeks

	Pramipexole (*n* = 16)										
TSQM	**6 weeks**	**12 weeks**	**16 weeks**	**20 weeks**	**24 weeks**	**28 weeks**	**32 weeks**	**36 weeks**	**40 weeks**	**44 weeks**	**48 weeks**
n	14	12	14	14	11	11	10	7	6	8	8
Median	66.7	58.3	66.7	66.7	58.3	66.7	66.7	66.7	58.3	66.7	66.7
Lower quartile	50	50	50	50	50	50	50	50	33.3	45.8	54.2
Upper quartile	83.3	75	75	75	66.7	83.3	83.3	100	83.3	70.8	91.7
Mean (SD)	66.7 (22.6)	57.6 (25.2)	63.1 (21.1)	60.7 (23.7)	58.3 (23.6)	61.4 (23.1)	63.3 (24.9)	69.0 (30.7)	58.3 (31.2)	60.4 (24.7)	66.7 (29.9)
Minimum	33.3	0	16.7	0	8.3	16.7	16.7	16.7	16.7	16.7	8.3
Maximum	100	100	100	100	100	100	100	100	100	100	100
Placebo (n = 20)											
n	20	17	15	17	16	14	8	9	8	8	7
Median	50	50	50	50	50	37.5	33.3	41.7	33.3	41.7	41.7
Lower quartile	33.3	33.3	33.3	41.7	37.5	33.3	33.3	33.3	29.2	29.2	33.3
Upper quartile	58.3	83.3	83.3	83.3	75	83.3	58.3	50	75	70.8	75
Mean (SD)	47.5 (17.3)	51.5 (28.4)	55.6 (26.5)	58.8 (26.4)	52.6 (27.2)	51.2 (28.1)	44.8 (19.9)	47.2 (29.2)	50.0 (29.2)	47.9 (25.5)	51.2 (21.2)
Minimum	16.7	0	16.7	16.7	0	25	25	0	25	16.7	33.3
Maximum	83.3	100	100	100	100	100	83	100	100	83.3	83.3

TABLE 61 Severity of AEs reported in pre-randomisation stage of trial

Severity	Never randomised (%)	Later randomised (%)
Mild	24 (69)	28 (78)
Moderate	10 (29)	7 (19)
Severe	1 (3)	1 (3)
Total	35 (100)	36 (100)

TABLE 62 Line listing of AEs reported in pre-randomisation stage (*n* = 71)

AE description	Severity	Start date	Resolution date	Outcome AE
AE reported in participants who did not progress to randomised phase of trial (n = 35)				
Facial swelling and soreness after starting her sodium valproate. Ceased taking it but some swelling remains. To be monitored	Moderate	18 July 2021	9 August 2021	Recovered
Dizziness after taking a dose of sumatriptan for a migraine	Moderate	16 August 2021	16 August 2021	Recovered
Received a diagnosis of myalgic encephalomyelitis	Moderate	18 August 2021		Condition unchanged

continued

TABLE 62 Line listing of AEs reported in pre-randomisation stage (*n* = 71) (*continued*)

AE description	Severity	Start date	Resolution date	Outcome AE
Burning rash on her face, neck and arms after taking her sodium valproate	Moderate	20 August 2021	24 August 2021	Recovered
Participant diagnosed with GAD	Moderate	29 September 2021		Condition unchanged
Hypomania	Moderate	1 January 2022	14 January 2022	Participant died
COVID-19	Moderate	24 April 2022		Condition unchanged
COVID-19 – Patient recovered but felt too unwell to continue	Moderate	4 May 2022	11 May 2022	Recovered
Manic and psychotic symptoms. Believes she is a star seed sent to earth to spread happiness and peace. Care coordinator at site aware	Moderate	24 June 2022		Condition unchanged
Manic and psychotic symptoms noted by participant and in her TrueColours score	Moderate	1 July 2022		Condition unchanged
Participant started on lamotrigine on Saturday this week. Awoke yesterday morning with a swollen face and rash, quite painful. She wonders if it is anything to do with her new meds. Discussed with CI who advised me to inform the local PI	Mild	19 January 2021	24 February 2021	Condition improved
Chest infection reported by participant. Doxycycline prescribed by GP	Mild	1 February 2021	15 February 2021	Recovered
Participant broke her upper right molar. Attended dentist for fixation. Completed	Mild	15 March 2021	18 March 2021	Recovered
Participant started carbamazepine on Saturday night as her new mood stabiliser. Began having a painful rash across her eyebrows, neck, shoulders and arms. Has ceased taking carbamazepine. Until advice received from clinician	Mild	3 April 2021	28 April 2021	Recovered
Participant has had her tooth chipped. Upper right molar has been repaired previously but has fallen out. Due to speak to dentist for repair (13 July 2021)	Mild	17 June 2021	13 July 2021	Recovered
Participant has noticed dry skin around her eyes. She thinks it may be the valproate	Mild	31 July 2021		Recovered
Sedation	Mild	2 September 2021	9 October 2021	Condition improved
Participant has complained of tremors since 3 September 2021 that is obvious to others. They have contacted her GP and is expecting a call back	Mild	3 September 2021		Condition improved
Participant experienced a panic attack yesterday while out in public	Mild	5 September 2021	5 September 2021	Recovered
Hypomania, felt impulsive, described silly heightened mood	Mild	24 September 2021	25 September 2021	Recovered
Feeling zombie like due to tramazole reduction	Mild	25 September 2021	9 October 2021	Recovered
Participant reports feeling numbness to her legs when taking the full dose of her promethazine. Will be speaking to her GP about this as to why this is happening. Has been advised to stop this medication and start another	Mild	12 October 2021	12 October 2021	Recovered
Headaches	Mild	28 October 2021	14 November 2021	Recovered

TABLE 62 Line listing of AEs reported in pre-randomisation stage (*n* = 71) (*continued*)

AE description	Severity	Start date	Resolution date	Outcome AE
Participant complains of cold symptoms, which are getting them down this week	Mild	28 October 2021	2 November 2021	Recovered
Dulled emotions	Mild	8 November 2021	19 November 2021	Recovered
Acid reflux	Mild	8 November 2021	14 November 2021	Recovered
Nausea	Mild	22 November 2021	2 December 2021	Recovered
Increased suicidal ideation	Mild	19 December 2021	1 January 2022	Condition improved
Chest infection	Mild	30 December 2021	5 January 2022	Recovered
Metallic taste (pt. associates it with zopiclone)	Mild	5 January 2022	14 January 2022	Condition stable and no change anticipated
Participant complains of a cough and sore throat. She believes it is COVID-19 as her daughter tested positive yesterday (18 January 2022)	Mild	18 January 2022		Recovered
Sore throat, swollen glands. Will be seeing her GP to get it sorted. No idea what it is	Mild	23 January 2022		Recovered
Participant reported manic and psychotic symptoms. Site made aware. Participant contacting her treatment team	Mild	1 March 2022		Condition improved
Lying in bed alone and heard her name whispered several times over the course of a few seconds. Isolated incident ASRM completed scoring 9	Mild	8 April 2022	8 April 2022	Recovered
AE reported in participants who went on to progress to randomised phase of trial (n = 36)				
AE description	Severity	Start date	Resolution date	Outcome AE
Participant had an abnormal electrocardiogram result with a QTC at 519. Clinicians and study staff aware	Severe	24 May 2021		Condition unchanged
Sleeplessness from escitalopram commenced before trial	Moderate	20 December 2019		Recovered
Participant broke his toe while decorating his son's house. Has not attended hospital but is taking painkillers to manage pain	Moderate	9 May 2021	28 May 2021	Recovered
On 20 June 2021, participant reported that she had palpitations since 30 May 2021. These were ongoing but not perpetual	Moderate	30 May 2021		Condition improved
Episode of nausea after taking her up-titrated study medication. Participant described it as mild. Resolved after 1 hour	Moderate	4 June 2021	4 June 2021	Recovered
Participant describes manic symptoms while stating she does not think she is manic. Describes increased spending, reduced sleep, loss of appetite, racing thoughts and has been described by her partner as jumping between conversations.	Moderate	21 June 2021		Condition improved
Participant complained of an episode of tunnel vision and feeling like she was going to faint. This is in the context of her tapering down from 2.5 to 2.25 mg IMP. This has not reoccurred, but it is planned for her to have an urgent cardiology appointment.	Moderate	27 June 2021	27 June 2021	Recovered

continued

TABLE 62 Line listing of AEs reported in pre-randomisation stage (*n* = 71) (*continued*)

AE description	Severity	Start date	Resolution date	Outcome AE
Participant describes some manic symptoms. Mania and psychosis SOP delivered. Site made aware of symptoms	Moderate	5 March 2022	9 March 2022	Condition improved
Nausea from escitalopram commenced before trial	Mild	20 December 2019		Recovered
Flu	Mild	14 January 2020	21 January 2020	Recovered
Headache	Mild	8 November 2020	17 December 2020	Recovered
Back pain	Mild	17 November 2020	17 December 2020	Recovered
Nausea	Mild	6 December 2020	13 December 2020	Recovered
Vomiting	Mild	8 December 2020	13 December 2020	Recovered
Hypomania	Mild	13 December 2020	2 January 2021	Condition improved
Two episodes of vomiting reported. Participant has just increased her dose to 0.75 mg. Participant will monitor her situation and report any further episodes	Mild	23 May 2021	23 May 2021	Recovered
Since tapering down from 2.5 mg to 2.25 mg of IMP, the participant has described the return of her lithium tremor	Mild	27 June 2021		Condition unchanged
Walked into something, grazing his lower leg leading to an infection. Antibiotics prescribed, 14 July 2021	Mild	1 July 2021	8 August 2021	Recovered
Twisted his back causing pain Tramadol prescribed	Mild	9 July 2021	5 August 2021	Recovered
Twisted groin, tramadol given	Mild	29 July 2021	5 August 2021	Recovered
Sleeplessness	Mild	14 September 2021	30 September 2021	Condition improved
Increased anxiety	Mild	20 September 2021		Condition improved
Tenderness in upper left arm due to COVID-19 and flu jabs	Mild	28 October 2021	29 October 2021	Recovered
Fuzzy headedness. Participant believes it is due to the flu and COVID-19 jabs	Mild	28 October 2021	29 October 2021	Recovered
Dizziness, unknown cause	Mild	6 November 2021	16 November 2021	Recovered
Nausea, unknown reason	Mild	6 November 2021	16 November 2021	Recovered
Diarrhoea, unknown cause	Mild	6 November 2021	16 November 2021	Recovered
Participant reports seeing movement and shadows at the periphery of her vision. She explained that she had this before when she was put on lamotrigine and wasn't concerned by it. Mania and psychosis SOP delivered but no reported symptoms	Mild	16 November 2021	22 November 2021	Recovered
Indistinct shadows in her peripheral vision, could be due to her not sleeping well. Mania and psychosis SOP delivered; no symptoms reported	Mild	18 December 2021	5 January 2022	Condition stable and no change anticipated
Nausea, participant believes this is due to the change in quetiapine dose	Mild	20 December 2021	22 December 2021	Recovered

TABLE 62 Line listing of AEs reported in pre-randomisation stage (*n* = 71) (*continued*)

AE description	Severity	Start date	Resolution date	Outcome AE
Chest and throat infection	Mild	28 December 2021		Condition stable and no change anticipated
Nausea	Mild	8 January 2022	10 January 2022	Recovered
Constipation	Mild	9 January 2022	11 January 2022	Recovered
Participant reports seeing fleeting figures out of the corner of his eye	Mild	20 February 2022		Condition improved
Tooth abscess	Mild	18 March 2022	23 March 2022	Recovered
Nausea	Mild	26 March 2022	30 March 2022	Recovered

Note
Shaded grey are AEs for active pramipexole treatment arm (*n* = 128), unshaded placebo arm (*n* = 162).

TABLE 63 Line listing of AEs reported in randomised phase of the trial (*n* = 290)

AE description	Severity	Causality	Start date	Resolution date	Outcome AE
AEs reported in the pramipexole arm (n = 128)					
Hair picking	Severe	Related	25 August 2021	24 October 2021	Recovered
Disoriented on waking	Severe	Unable to determine	30 June 2021	4 July 2021	Recovered
Participant attended emergency department by ambulance for hip pain (unknown cause) at 3 a.m. on Saturday morning.	Severe	Unrelated	23 October 2021	23 October 2021	Condition unchanged
Death of a relative	Severe	Unrelated	15 April 2021		Condition unchanged
Manic symptoms. Elation	Moderate	Related	19 August 2022		Condition unchanged
Participant reports manic and psychotic symptoms of buying to excess: Mania and psychosis, and impulse control behaviours SOPs delivered. Reports spending money both in shops and online	Moderate	Related	3 April 2022		Condition unchanged
Sleep disturbance	Moderate	Related	28 July 2021	6 August 2021	Recovered
Participant reports impulse control behaviours in gambling and has lost over £2000 on the grand national and on the slots over the weekend	Moderate	Related	8 April 2022	11 April 2022	Recovered
Continues to have impulse control behaviours, especially around gaming and buying	Moderate	Related	1 November 2021		Condition improved
Constipation. Started when he was taking 2.25 mg. Very painful. RA advised he speak to his GP	Moderate	Related	28 October 2021		Condition improved
Participant reports that she has had chest pain since early June. She believed it was due to her overexerting herself during a house move so didn't report it at the time. Electrocardiogram clear (she reports). Blood test for heart failure done with results due.	Moderate	Related	17 June 2021		Condition improved

continued

TABLE 63 Line listing of AEs reported in randomised phase of the trial (*n* = 290) (*continued*)

AE description	Severity	Causality	Start date	Resolution date	Outcome AE
Participant had been feeling sick and unwell for some time. Agreed to reduce her dose of the IMP to 2 mg	Moderate	Related	1 July 2021	26 July 2021	Condition improved
Pins and needles	Moderate	Related	27 July 2021	6 November 2021	Recovered
Insomnia	Moderate	Related	23 December 2021		Condition improved
Sweating	Moderate	Related	25 June 2021	6 November 2021	Recovered
Retching	Moderate	Related	26 December 2021	9 May 2022	Recovered
Fall	Moderate	Related	10 August 2021	10 August 2021	Recovered
Participant's gambling remains an issue for him causing him to go into his overdraft on several occasions	Moderate	Related	21 April 2022		Condition unchanged
Dizziness	Moderate	Related	12 August 2022	17 August 2022	Condition improved
Diarrhoea	Moderate	Related	28 July 2021	10 August 2021	Recovered
Nausea	Moderate	Related	28 July 2021	7 August 2021	Recovered
Racing thoughts	Moderate	Related	3 April 2022		Condition improved
Constipation	Moderate	Related	9 May 2022		Condition unchanged
Prolonged masturbation	Moderate	Related	9 August 2022	9 August 2022	Condition improved
Restlessness	Moderate	Related	3 April 2022		Condition improved
Hypomanic symptoms	Moderate	Unable to determine	23 April 2021	10 May 2021	Recovered
Fuzzy headedness. Staying on 0.5 mg until spoken to PI	Moderate	Unable to determine	10 May 2022	19 May 2022	Condition improved
Participant reports he has manic symptoms	Moderate	Unable to determine	13 June 2022		Condition unchanged
Disturbing thoughts, visuals since titrating to 1.75 mg. Dose reduced to 1 mg	Moderate	Unable to determine	27 April 2022		Condition improved
Manic symptoms	Moderate	Unable to determine	21 April 2022		Condition unchanged
Hypomania	Moderate	Unable to determine	4 April 2022	20 June 2022	Condition improved
Participant diagnosed with diabetes	Moderate	Unable to determine	13 July 2021		Condition unchanged
Impulse control – eating	Moderate	Unable to determine	23 June 2021	5 October 2021	Condition improved
Balance issues	Moderate	Unable to determine	25 July 2021	21 October 2021	Condition unchanged

TABLE 63 Line listing of AEs reported in randomised phase of the trial (*n* = 290) (*continued*)

AE description	Severity	Causality	Start date	Resolution date	Outcome AE
Inappropriate humour, staying on 0.5 until spoken to PI	Moderate	Unable to determine	10 May 2022	19 May 2022	Condition improved
Worsening of his depression	Moderate	Unable to determine	13 June 2022		Condition unchanged
Reports manic symptoms this week (ASRM = 5).Needing less sleep this week, thoughts racing through his head, having trouble staying on one track with his thoughts and having longer periods of activity late at night.	Moderate	Unable to determine	8 April 2022	11 April 2022	Condition improved
Tardive dyskinesia in arm staying on 0.5 mg until spoken to PI	Moderate	Unable to determine	10 May 2022	19 May 2022	Condition improved
Hypomanic symptoms	Moderate	Unrelated	15 July 2022		Condition unchanged
Incorrect dose	Moderate	Unrelated	24 July 2021	2 August 2021	Condition stable and no change anticipated
Shingles	Moderate	Unrelated	15 December 2021		Condition unchanged
Chest infection	Moderate	Unrelated	25 January 2022	22 February 2022	Recovered
Death of friend	Moderate	Unrelated	20 December 2021		Condition stable and no change anticipated
Viral chest infection confirmed by GP	Moderate	Unrelated	4 April 2021	11 April 2021	Recovered
Dry mouth	Moderate	Unrelated	29 June 2021	19 August 2021	Recovered
Participant continues to have sleep issues despite reducing his IMP dose to 2 mg	Moderate	Unrelated	21 April 2022		Condition unchanged
Increased suicidal ideations	Moderate	Unrelated	6 September 2021	20 September 2021	Condition improved
Participant stopped taking his IMP without tapering. Denies any symptom of DAWS	Moderate	Unrelated	2 July 2022		Condition improved
COVID-19	Moderate	Unrelated	4 November 2021	24 November 2021	Condition stable and no change anticipated
Rash on legs	Moderate	Unrelated	2 February 2022	7 February 2022	Recovered
Impulse control symptoms, spending, has been secretive about his spending, how much it cost. Doesn't think this is due to study medication. Admits to not saving money for solicitor's fees (moving house at the moment). Admits to being quite anxious about these issues	Moderate	Unrelated	13 May 2022		Condition unchanged
COVID-19	Moderate	Unrelated	18 February 2022	28 February 2022	Recovered
Itchy scalp	Mild	Related	23 December 2021	30 March 2022	Condition unchanged

continued

TABLE 63 Line listing of AEs reported in randomised phase of the trial (*n* = 290) (*continued*)

AE description	Severity	Causality	Start date	Resolution date	Outcome AE
Constipation, but participant states that it is not too bad	Mild	Related	12 November 2021		Condition improved
Nausea on the morning of 17 December 2020. Resolved within 2 hours. Not repeated since	Mild	Related	17 December 2020	17 December 2020	Recovered
Dry mouth	Mild	Related	10 May 2022	10 June 2022	Recovered
Participant experienced nausea. Equates this with having stress due to securing a new job and concerns about the new role	Mild	Related	8 October 2021	10 October 2021	Condition improved
Nausea	Mild	Related	3 April 2021	3 April 2021	Recovered
Nausea	Mild	Related	12 May 2022		Condition stable and no change anticipated
Nausea when taking IMP. Tried taking it with a snack, which eases it, but still present	Mild	Related	26 November 2021		Condition improved
Has reported that she is not sleeping well, noticeably over the last 2 weeks. Advised to contact her clinical team that it is becoming a problem for her	Mild	Related	1 January 2021		Condition stable and no change anticipated
Nausea	Mild	Related	23 April 2021	7 May 2021	Recovered
Sedation	Mild	Related	12 June 2021	13 October 2021	Recovered
Impulse control issues (gambling and spending)	Mild	Related	1 November 2021	9 February 2022	Condition unchanged
Sleep disturbance	Mild	Related	5 August 2021	25 September 2021	Recovered
Sleep disturbance	Mild	Related	11 May 2022		Condition unchanged
Itching skin	Mild	Related	31 March 2021	5 April 2021	Recovered
Insomnia	Mild	Related	23 April 2021	10 May 2021	Recovered
Experienced nausea when up-titrating from 1.75 to 2 mg. Reduced in subsequent days, felt it again when up-titrating from 2 to 2.25. Takes them in the evening with no food. Study team notified	Mild	Related	22 October 2021	25 October 2021	Recovered
Nausea	Mild	Related	28 May 2022	28 May 2022	Recovered
Hypomanic symptoms	Mild	Related	10 January 2022	21 January 2022	Recovered
Retching	Mild	Related	25 June 2021	15 July 2021	Recovered
Rapid weight loss	Mild	Related	19 August 2021	17 October 2021	Condition stable and no change anticipated
Sedation	Mild	Related	26 May 2021	5 June 2021	Recovered
Insomnia	Mild	Related	1 April 2021	8 April 2021	Condition improved
Nausea	Mild	Related	6 May 2022	7 May 2022	Recovered

TABLE 63 Line listing of AEs reported in randomised phase of the trial (*n* = 290) (*continued*)

AE description	Severity	Causality	Start date	Resolution date	Outcome AE
Hair loss	Mild	Related	2 January 2022	30 March 2022	Condition improved
Nausea after taking tablets. This is an ongoing problem, but transient after taking IMP	Mild	Related	5 November 2021		Condition improved
Increased anxiety	Mild	Unable to determine	7 June 2022		Condition improved
Daytime drowsiness	Mild	Unable to determine	25 December 2021	8 January 2022	Recovered
Sedation	Mild	Unable to determine	22 May 2021	29 May 2021	Condition improved
Blurred vision when he is playing for long periods on computer games. Participant has reported that they have ongoing issues with muscles in his eyes	Mild	Unable to determine	26 December 2021	1 February 2022	Condition improved
Rosacea	Mild	Unable to determine	10 February 2022	25 June 2022	Condition improved
Dry mouth	Mild	Unable to determine	15 January 2022		Condition improved
Increased levels of anxiety	Mild	Unable to determine	10 September 2021	12 September 2021	Condition improved
Drowsiness potentially due to olanzapine increase to 5 mg	Mild	Unable to determine	10 January 2022		Condition unchanged
Blurred vision	Mild	Unable to determine	25 June 2021	28 June 2021	Recovered
Participant describes feeling hypersexual in their head, since taking their IMP. Has decided to withdraw from both the IMP and the study as a whole	Mild	Unable to determine	10 September 2021	12 September 2021	Condition improved
Manic symptoms reported this week, but participant puts this down to feeling a bit more normal again	Mild	Unable to determine	14 June 2022		Condition improved
Tremor	Mild	Unable to determine	3 December 2021		Condition unchanged
Visual disturbances in the form of focusing issues and black flashes. Transient	Mild	Unable to determine	5 November 2021	16 November 2021	Condition improved
Missed dose	Mild	Unrelated	7 September 2021	7 September 2021	Condition stable and no change anticipated
Tested positive for COVID-19	Mild	Unrelated	1 May 2022	8 May 2022	Recovered
Contracted COVID-19	Mild	Unrelated	9 March 2022	16 March 2022	Recovered
Diarrhoea and sickness	Mild	Unrelated	25 July 2022	26 July 2022	Recovered
Participant reported feelings of being high, especially with buying. reported to treatment team who increased lithium dose and reduced fluoxetine	Mild	Unrelated	24 March 2022	8 April 2022	Recovered
Stomach bug	Mild	Unrelated	21 January 2022	24 January 2022	Recovered
Participant reports having cold-like symptoms.	Mild	Unrelated	17 October 2021	21 October 2021	Recovered

continued

TABLE 63 Line listing of AEs reported in randomised phase of the trial (*n* = 290) (*continued*)

AE description	Severity	Causality	Start date	Resolution date	Outcome AE
Oral thrush	Mild	Unrelated	11 October 2021	28 January 2022	Recovered
Participant reports feeling increased clumsiness. Attributes this to anxiety	Mild	Unrelated	11 December 2021		Condition improved
Fatigue	Mild	Unrelated	7 August 2021	8 August 2021	Condition improved
Features of hypotension (dizzy and nauseous on standing; tingling in right arm)	Mild	Unrelated	16 March 2022	13 April 2022	Condition stable and no change anticipated
Sinusitis	Mild	Unrelated	8 August 2022	26 August 2022	Recovered
Memory issues	Mild	Unrelated	13 June 2021		Condition unchanged
Symptoms of hypomania	Mild	Unrelated	19 January 2022		Condition stable and no change anticipated
Increased libido over the past week	Mild	Unrelated	10 October 2021	26 October 2021	Condition improved
Shaking	Mild	Unrelated	26 May 2021	30 May 2021	Recovered
Cold-like symptoms	Mild	Unrelated	18 January 2022	23 January 2022	Recovered
Dry mouth	Mild	Unrelated	13 August 2021	4 September 2021	Recovered
Cyst on tongue	Mild	Unrelated	18 August 2021	22 August 2021	Recovered
Episodes of dizziness this week. Has had them before	Mild	Unrelated	18 July 2022	19 July 2022	Recovered
Dry mouth pretty much constantly, especially at night, also has this with olanzapine at 5 mg	Mild	Unrelated	10 May 2022		Condition unchanged
Complains of a tremor in her right hand, similar to what she got with her lithium. Was very bad today but has abated but wants to see if it goes away	Mild	Unrelated	7 May 2021		Condition improved
Fatigue	Mild	Unrelated	25 April 2021	28 April 2021	Recovered
Fatigue	Mild	Unrelated	1 March 2022	3 March 2022	Recovered
Strained calf	Mild	Unrelated	2 July 2022	5 August 2022	Recovered
Urinary tract infection	Mild	Unrelated	24 November 2021	14 December 2021	Condition stable and no change anticipated
Constipation	Mild	Unrelated	12 August 2021	21 August 2021	Recovered
Feeling really rough after the COVID-19 booster jab. Cold-like symptoms	Mild	Unrelated	5 December 2021	9 December 2021	Recovered
Water infection	Mild	Unrelated	29 July 2021	26 August 2021	Recovered

TABLE 63 Line listing of AEs reported in randomised phase of the trial (*n* = 290) (*continued*)

AE description	Severity	Causality	Start date	Resolution date	Outcome AE
Participant suffered a burn to herself due to tremor. No further details available	Mild	Unrelated	24 February 2022	24 February 2022	Recovered
Dizziness. This occurs periodically but is transient	Mild	Unrelated	5 November 2021		Condition improved
Participant has trouble with racing thoughts and staying on one track	Mild	Unrelated	12 October 2021	26 October 2021	Condition improved
Participant complains of brain fog and forgetfulness. This he attributes to the increase in olanzapine on the 23 November 2021	Mild	Unrelated	23 November 2021		Condition unchanged
Shakiness. Attributes this to anxiety	Mild	Unrelated	11 December 2021		Condition improved
Participant has been diagnosed with laryngitis	Mild	Unrelated	9 March 2022		Condition improved
Participant had a fall due to dizziness, injured her hand and knee. She was taken to hospital by ambulance, although not admitted to hospital.	Mild	Unrelated	19 November 2021	24 November 2021	Recovered
Missed dose	Mild	Unrelated	10 July 2021	11 July 2021	Condition stable and no change anticipated
AEs reported in the placebo arm (n = 162)					
Participant reports feeling extremely tired, dizzy, nauseous, shivery and not able to concentrate. Does not know whether this is a side effect of the IMP or if she is physically unwell	Severe	Unable to determine	25 March 2022	28 March 2022	Recovered
Fidgety legs. All day but becomes worse at night. Site aware	Severe	Unable to determine	9 March 2022		Condition unchanged
Drowsiness	Severe	Unable to determine	11 October 2020	20 November 2020	Recovered
Participant took an overdose of paracetamol and is being treated at a medical assessment unit. Participant has not yet started his IMP	Severe	Unrelated	9 November 2021	12 November 2021	Recovered
Participant reports raised blood pressure	Severe	Unrelated	21 June 2022	15 July 2022	Recovered
Cold sore outbreak after COVID	Severe	Unrelated	23 April 2022	2 May 2022	Recovered
Death in family	Severe	Unrelated	29 July 2022		Condition unchanged
Nose bleeds	Severe	Unrelated	7 June 2022	15 July 2022	Recovered
Participant incorrectly believed that the blue tablets were 0.5 mg doses and took this with her 0.25 mg dose. Titrating herself from 0.5 mg to 1.25 mg overnight. Study team contacted by phone and e-mail. Participant awaiting contact	Moderate	Related	28 August 2021	1 September 2021	Recovered
Exhausted since titrating to 2 mg	Moderate	Related	26 March 2022	1 April 2022	Recovered
QUIP-RS increased from 21 at baseline to 31 at 6 weeks, with increases in gambling, sex, buying, eating, performing simple tasks, and taking medications. Flagged to site.	Moderate	Related	8 April 2022		Condition improved
Participant feels exhausted, fuzzy headed since titrating to 2 mg. Has asked to remain on 2 mg for another 3 days. PI agreed	Moderate	Related	26 March 2022	1 April 2022	Recovered

continued

TABLE 63 Line listing of AEs reported in randomised phase of the trial (*n* = 290) (*continued*)

AE description	Severity	Causality	Start date	Resolution date	Outcome AE
Complained of having restless legs after up-titrating to 1 mg	Moderate	Related	5 January 2022	6 January 2022	Recovered
Impulse control behaviours. Vaping, smoking, and buying things online leading to being £250 overdrawn	Moderate	Related	31 January 2022		Condition unchanged
Headache all day after titrating to 0.75 mg	Moderate	Related	11 March 2022	11 March 2022	Recovered
Headaches all day after titrating to 0.5 mg	Moderate	Related	9 March 2022	9 March 2022	Recovered
Impulse control symptoms	Moderate	Related	25 January 2022	30 January 2022	Condition improved
Participant describes having had hypomanic symptoms with impulse control symptoms. Local site made aware of participant's IMP dose reduced to 1.5 mg	Moderate	Related	25 January 2022	30 January 2022	Condition improved
Participant states that his vaping and smoking behaviour continues. Also states that this behaviour may be a hangover from the hypomanic episode	Moderate	Related	31 January 2022		Condition unchanged
Extreme restless legs after reducing IMP to 1 mg	Moderate	Related	29 January 2022	30 January 2022	Recovered
Acid reflux. Cannot swallow tablets	Moderate	Unable to determine	16 October 2021	10 November 2021	Condition improved
Irritability	Moderate	Unable to determine	25 February 2022	28 March 2022	Condition improved
Paranoia	Moderate	Unable to determine	25 February 2022	28 March 2022	Condition improved
Participant self-harmed. They reported to the initial response service that they had cut their legs superficially which did not require treatment	Moderate	Unable to determine	27 February 2022	27 February 2022	Recovered
Nausea after titrating up from 2.25 to 2.5 mg	Moderate	Unable to determine	29 September 2021	30 September 2021	Recovered
Headache. More painful and lasting than usual	Moderate	Unable to determine	21 August 2021	22 August 2021	Condition improved
Fluctuations in mood	Moderate	Unable to determine	12 December 2021		Condition unchanged
Participant reports drinking a bottle of wine a night for the past week due to a decline in her mental health	Moderate	Unable to determine	27 February 2022	13 March 2022	Condition improved
Participant reports both manic and psychotic symptoms including paranoia about her colleagues at work and being a lot more snappy than usual	Moderate	Unable to determine	25 February 2022	28 March 2022	Condition improved
Participant complains of vomiting	Moderate	Unable to determine	16 October 2021	10 November 2021	Recovered
Vertigo	Moderate	Unable to determine	12 September 2020	20 November 2020	Recovered
Participant has been severely sleepless for the past week with the last 24 hours having had only 4 hours sleep. Remains very sleepless as of 13 September 2021	Moderate	Unable to determine	25 August 2021		Condition improved
Nausea. Patient usually has this in the morning but has suffered with this well into the afternoon	Moderate	Unable to determine	20 August 2021	22 August 2021	Recovered
Fidgety arms and legs	Moderate	Unable to determine	27 June 2022		Condition unchanged

TABLE 63 Line listing of AEs reported in randomised phase of the trial (*n* = 290) (*continued*)

AE description	Severity	Causality	Start date	Resolution date	Outcome AE
Reduced sleep with daytime tiredness after starting IMP	Moderate	Unable to determine	20 August 2021	22 August 2021	Condition improved
Self-harm reported by participant. Delivered several hammer blows to her right hand. Subsequent X-ray. Results TBC	Moderate	Unable to determine	30 May 2022	30 May 2022	Condition improved
Participant reports wheeziness for the last 4 weeks. Participant has asthma and has inhalers to support this	Moderate	Unrelated	25 March 2022		Condition improved
Endoscopy	Moderate	Unrelated	19 March 2022	19 March 2022	Recovered
Torn rotator cuff	Moderate	Unrelated	5 August 2022		Condition improved
Unsteady on her feet at the moment which is getting worse. Jerky movements and losing balance at home. Started since she went on lithium	Moderate	Unrelated	1 March 2021		Condition unchanged
Burnt herself deliberately by putting her hand under a stream of boiling water. Superficial damage	Moderate	Unrelated	29 June 2022	29 June 2022	Recovered
Participant has been placed in a witness protection programme after having her details released to the public. She is currently in a hotel. Site made aware	Moderate	Unrelated	28 February 2022		Condition unchanged
Tested positive for COVID	Moderate	Unrelated	1 July 2022	15 July 2022	Condition improved
Suicidal ideation identified on QUIP-RS. Site informed. Participant in contact with care coordinator and psychiatrist	Moderate	Unrelated	14 August 2022		Condition improved
Tested positive for COVID	Moderate	Unrelated	10 April 2022	18 April 2022	Recovered
Urinary tract infection	Moderate	Unrelated	29 October 2021	6 November 2021	Recovered
Tooth ache from abscess. Had this removed 25 January 2022	Moderate	Unrelated	14 January 2022	25 January 2022	Recovered
Suicidal ideation	Moderate	Unrelated	23 August 2022		Condition improved
Participant reports impulse control behaviours. As she couldn't sleep (and her thoughts were racing), she went for a drive at 3 a.m. She does not know if this is the study medication as lamotrigine does this to her sometimes	Moderate	Unrelated	27 February 2022	27 February 2022	Recovered
Hypomania	Moderate	Unrelated	15 September 2020	8 October 2020	Recovered
Describes some manic symptoms during her house move. Needing less sleep, being more talkative (changing subjects a lot), more sociable, more fidgety, pacing a lot. Unable to prioritise her work despite meticulous planning.	Moderate	Unrelated	9 April 2022		Condition unchanged
Suicidal ideation Item 12 score = 2. CC and crisis team are aware. Suicidality SOP delivered and site made aware	Moderate	Unrelated	5 August 2022	8 August 2022	Condition improved
Tooth ache – for future root canal work.	Moderate	Unrelated	7 May 2022		Condition unchanged
Bereavement of family member. Organisation of funeral	Moderate	Unrelated	23 March 2022		Condition unchanged
Lethargy	Moderate	Unrelated	20 October 2020	21 December 2020	Condition unchanged

continued

TABLE 63 Line listing of AEs reported in randomised phase of the trial (*n* = 290) (*continued*)

AE description	Severity	Causality	Start date	Resolution date	Outcome AE
Abnormal LFT results from this participant, GGT 900*H, ALT 82*H, ALB 51*H	Moderate	Unrelated	11 March 2022		Condition unchanged
Increased anxiety	Moderate	Unrelated	2 September 2021	15 October 2021	Condition stable and no change anticipated
Vomiting	Mild	Related	25 April 2021	25 April 2021	Condition improved
Nausea	Mild	Related	31 May 2022	3 June 2022	Recovered
Hand tremors	Mild	Related	15 September 2020	8 October 2020	Recovered
Participant reports having an episode of diarrhoea every morning. She has discussed this with her care worker but is not sure of the cause	Mild	Related	20 July 2021	1 August 2021	Recovered
Participant took 2.75 mg instead of 1.75 mg during her taper down. PI and CI informed, advised to continue taper from 1.75 mg	Mild	Related	12 May 2022	12 May 2022	Recovered
Nausea	Mild	Related	7 May 2021	10 May 2021	Recovered
Fuzzy head, feeling tired since going up to 2.5 mg. Participant is unconcerned by this at the moment	Mild	Related	5 December 2021	8 December 2021	Recovered
Insomnia	Mild	Related	14 February 2021		Condition unchanged
Persistent headache	Mild	Related	18 December 2021	18 December 2021	Condition improved
Evidence of hypotension	Mild	Related	20 February 2020	20 February 2020	Recovered
Constipation, although the participant states this could be due to irritable bowel syndrome	Mild	Related	12 March 2022		Condition unchanged
Nausea	Mild	Related	15 February 2021	17 February 2021	Condition improved
Nausea (mornings and sometimes evenings) and occasional sickness	Mild	Related	1 March 2022		Condition improved
Reports her eyes feeling funny when she's blinking like they go out of focus, just after she titrates up	Mild	Related	1 December 2021	1 December 2021	Recovered
Participant reported that after he had woken up from a doze, he believed he saw that his wife's hair had turned blue. This did not last long, and the participant describes it as an isolated incident	Mild	Related	8 December 2021	8 December 2021	Recovered
Reports her eyes are feeling funny when she's blinking, like they go out of focus. Occurred just after titrating up	Mild	Related	25 November 2021	25 November 2021	Recovered
Insomnia	Mild	Related	10 January 2022	11 January 2022	Recovered
Believes he has put on weight due to eating more. Believes this is due to the medication	Mild	Related	1 March 2022		Condition improved
Getting a headache at night. Participant states he gets headaches usually during the day and is now getting them at night. Takes IMP at 10.30 at night	Mild	Related	28 December 2021		Condition unchanged

TABLE 63 Line listing of AEs reported in randomised phase of the trial (*n* = 290) (*continued*)

AE description	Severity	Causality	Start date	Resolution date	Outcome AE
Has had some sleep disturbance over the past week, since starting IMP. Ongoing at present	Mild	Related	7 December 2021		Condition unchanged
Nausea after up-titrating to 1 mg	Mild	Related	5 January 2022	5 January 2022	Recovered
Participant feels she is sleeping less. Waking up earlier. Does not see this as an issue, believes it is a benefit	Mild	Related	13 November 2021		Condition unchanged
Nausea when titrating to 0.5 and 0.75 mg	Mild	Related	30 December 2021		Condition unchanged
Restlessness	Mild	Related	10 January 2022	11 January 2022	Recovered
Participant has had diarrhoea every morning since Tuesday and does not know the cause. RA advised speaking to her care worker and seek advice	Mild	Related	20 July 2021	9 August 2021	Recovered
Compromised vision. Seeing movements out of the corner of right eye, which was not present when checked. Pt. has not experienced before. Has happened at least dozen times	Mild	Related	28 September 2020	20 October 2020	Recovered
Participant reports he walked out of his job as a nursing home support worker last week and that he has felt happier since he left his job	Mild	Related	4 January 2022		Condition unchanged
Participant complains of continuing headaches this week. Taking paracetamol and co-codamol, but they make it bearable, rather than stopping the pain	Mild	Related	7 February 2022		Condition unchanged
Balance issues when going from sitting to standing	Mild	Related	17 July 2020	10 August 2020	Recovered
Nausea and vomiting, occurred hours after taking study medication. Participant does not believe it was the medication that caused it. Participant reassures that he had not had a drink	Mild	Related	1 January 2022	2 January 2022	Recovered
Has had some strange dreams this week since starting IMP	Mild	Related	7 December 2021		Condition unchanged
Sickness	Mild	Unable to determine	6 June 2022	13 June 2022	Recovered
Vomiting	Mild	Unable to determine	13 February 2021	14 February 2021	Condition improved
Describes some psychotic symptoms. M&P SOP delivered; participant reports that she feels that people have been speaking about her and that they have been negative. Has been more social this week	Mild	Unable to determine	15 April 2022		Condition unchanged
Reports feeling pin pricks randomly across his body and head	Mild	Unable to determine	21 March 2022	23 March 2022	Recovered
Possible manic symptoms	Mild	Unable to determine	19 March 2020	6 April 2020	Recovered
Diarrhoea	Mild	Unable to determine	12 January 2022	13 January 2022	Recovered
Possible impulse control behaviours	Mild	Unable to determine	19 March 2020	6 April 2020	Recovered
Short-term memory issues	Mild	Unable to determine	20 September 2020	20 November 2020	Recovered

continued

TABLE 63 Line listing of AEs reported in randomised phase of the trial (*n* = 290) (*continued*)

AE description	Severity	Causality	Start date	Resolution date	Outcome AE
Manic symptoms	Mild	Unable to determine	3 March 2021	11 April 2021	Condition improved
Sleeplessness – difficulty getting to sleep	Mild	Unable to determine	2 September 2021	20 October 2021	Condition improved
Constipation	Mild	Unable to determine	13 February 2021	19 February 2021	Condition improved
Symptoms of hypotension	Mild	Unable to determine	7 May 2021	10 May 2021	Recovered
Impulse control behaviours	Mild	Unable to determine	17 September 2020	12 November 2020	Recovered
Hypomanic symptoms	Mild	Unable to determine	23 May 2021		Condition unchanged
Fuzzy headedness which participant puts down to getting her COVID jab	Mild	Unable to determine	19 December 2021	20 December 2021	Recovered
Paranoia; believes people have been talking about them	Mild	Unable to determine	15 April 2022		Condition unchanged
Symptoms of hypotension when going from sitting to standing	Mild	Unable to determine	16 February 2021	11 March 2021	Condition unchanged
Dizziness	Mild	Unable to determine	28 February 2020	5 April 2020	Recovered
Sleeplessness	Mild	Unrelated	27 April 2022	8 August 2022	Condition improved
Missed dose	Mild	Unrelated	11 June 2021	12 June 2021	Condition stable and no change anticipated
Cold-like symptoms. after the Xmas period	Mild	Unrelated	25 December 2021	8 January 2022	Recovered
Trial medication was expected to start on 11 February 2021 but was not started until 13 February 2021, in part due to package arriving on 12 February 2021 and participant's low mood	Mild	Unrelated	11 February 2021	13 February 2021	Condition stable and no change anticipated
Participant complained of being irritable angry and ridiculously busy since starting on 0.75. RA advised that if symptoms worsen, they should contact their treatment team	Mild	Unrelated	18 February 2022		Condition improved
Cold-like symptoms	Mild	Unrelated	25 March 2022	1 April 2022	Recovered
Complained of stomach upset with diarrhoea and some nausea	Mild	Unrelated	13 January 2022	15 January 2022	Recovered
Concomitant postural dizziness, likely related to a recent hypertensive (lying 121/76 P 54: stand 112/72, P 66 no symptoms)	Mild	Unrelated	22 June 2022		Condition unchanged
Flu symptoms	Mild	Unrelated	1 June 2021	6 June 2021	Recovered
Suicidal ideation	Mild	Unrelated	20 June 2022	22 July 2022	Condition improved
Cold-like symptoms	Mild	Unrelated	15 January 2022	19 January 2022	Recovered

TABLE 63 Line listing of AEs reported in randomised phase of the trial (*n* = 290) (*continued*)

AE description	Severity	Causality	Start date	Resolution date	Outcome AE
Diarrhoea	Mild	Unrelated	27 July 2022	29 August 2022	Recovered
Thrush	Mild	Unrelated	3 June 2022		Recovered
Missed dose	Mild	Unrelated	24 April 2021	25 April 2021	Condition stable and no change anticipated
Missed dose ×1	Mild	Unrelated	10 May 2021	11 May 2021	Condition stable and no change anticipated
Impaired urination	Mild	Unrelated	17 January 2022		Condition improved
Flu	Mild	Unrelated	21 December 2021	27 December 2021	Recovered
One missed dose due to nausea	Mild	Unrelated	26 July 2020	26 July 2020	Recovered
Flu	Mild	Unrelated	14 January 2022	19 January 2022	Recovered
Anxiety-related movement disorder	Mild	Unrelated	22 June 2022		Condition unchanged
Missed dose ×2	Mild	Unrelated	26 May 2021	28 May 2021	Condition stable and no change anticipated
Nausea	Mild	Unrelated	3 July 2022	16 July 2022	Condition improved
Participant complained of a severe cold last week. Tired all the time and couldn't get anything done	Mild	Unrelated	19 November 2021	28 November 2021	Recovered
Insomnia	Mild	Unrelated	1 July 2022	4 July 2022	Recovered
Due to suspected tummy bug has been sick and vomited	Mild	Unrelated	19 July 2022	20 July 2022	Recovered
Reduced appetite	Mild	Unrelated	26 November 2021	2 December 2021	Recovered
Participant described a rapid cycle depressive to manic switch. Partner present. No negative consequences reported	Mild	Unrelated	26 April 2022	27 April 2022	Recovered
Suspected 1 mg overdose	Mild	Unrelated	19 September 2020	20 September 2020	Condition stable and no change anticipated
Missed dose	Mild	Unrelated	3 April 2021	3 April 2021	Condition stable and no change anticipated
Has a gastrointestinal complaint that is flaring up at the moment. Participant doesn't believe it is the IMP. Due for colorectal scan in near future	Mild	Unrelated	22 April 2022		Recovered

continued

TABLE 63 Line listing of AEs reported in randomised phase of the trial (*n* = 290) (*continued*)

AE description	Severity	Causality	Start date	Resolution date	Outcome AE
Missed dose	Mild	Unrelated	24 April 2020	25 April 2020	Condition stable and no change anticipated
Suicidal ideation. Has discussed this with her CPN	Mild	Unrelated	1 July 2022	10 August 2022	Condition improved
Migraine	Mild	Unrelated	9 January 2022	10 January 2022	Recovered
Parkinsonian disorder, ongoing tremor in hands and legs	Mild	Unrelated	22 June 2022		Condition unchanged
Nonspecific movement disorder secondary to medication	Mild	Unrelated	22 June 2022		Condition unchanged
Elated mood lasting few days described. Believed to be due to stressful external circumstances – elderly friend tested positive for COVID-19. Subsided after weekend	Mild	Unrelated	3 April 2020	6 April 2020	Recovered
Hypomanic symptoms	Mild	Unrelated	25 April 2022	5 July 2022	Condition improved
Constipation	Mild	Unrelated	5 October 2020	27 October 2020	Recovered
Participant reports lowered mood due to having lost his job last week, 5 July 2022	Mild	Unrelated	5 July 2022		Condition unchanged
Missed dose	Mild	Unrelated	22 July 2021	23 July 2021	Condition stable and no change anticipated
Participant complains of lethargy which she attributes to having a virus recently	Mild	Unrelated	1 February 2022		Condition improved
Twisted the middle finger of her right hand after falling in the garden. Doesn't think this was to do with the IMP. Still painful	Mild	Unrelated	13 June 2022		Condition improved
Participant reports the need to urinate more frequently	Mild	Unrelated	17 January 2022		Condition unchanged
Cold-like symptoms, after Christmas day. COVID test taken, negative	Mild	Unrelated	25 December 2021	28 December 2021	Recovered
Diarrhoea	Mild	Unrelated	26 November 2021	2 December 2021	Recovered
Vomited prior to CSO visit. Participant stated it was associated with escitalopram	Mild	Unrelated	20 February 2020	20 February 2020	Recovered
Dog bite on middle finger of left hand	Mild	Unrelated	26 April 2022	26 April 2022	Recovered
Participant has become low in mood	Mild	Unrelated	26 August 2022		Condition unchanged
Nausea	Mild	Unrelated	26 July 2020	26 July 2020	Recovered
Participant reports that she has had no sense of taste for quite sometime	Mild	Unrelated	8 March 2022		Condition unchanged
Missed dose	Mild	Unrelated	15 September 2020	16 September 2020	Condition stable and no change anticipated

TABLE 63 Line listing of AEs reported in randomised phase of the trial (*n* = 290) (*continued*)

AE description	Severity	Causality	Start date	Resolution date	Outcome AE
Missed dose	Mild	Unrelated	2 January 2021	3 January 2021	Recovered
Self-harm	Mild	Unrelated	2 April 2021	3 April 2021	Condition stable and no change anticipated
Asthma flare-up	Mild	Unrelated	12 September 2020	27 October 2020	Recovered
Anxiety	Mild	Unrelated	20 September 2020	26 September 2020	Recovered
Missed dose	Mild	Unrelated	14 May 2020	15 May 2020	Condition stable and no change anticipated

TABLE 64 MEDRA categories of AEs occurring during the randomisation stage

MEDRA classifications		Pramipexole (*n* = 48)			Placebo (*n* = 43)		
		Severe (%)	Moderate (%)	Mild (%)	Severe (%)	Moderate (%)	Mild (%)
Definitely related to IMP	Psychiatric disorders	1 (2)	10 (21)	7 (15)	0 (0)	5 (12)	8 (19)
	Gastrointestinal disorders	0 (0)	6 (13)	13 (27)	0 (0)	0 (0)	11 (26)
	Nervous system disorders	0 (0)	2 (4)	2 (4)	0 (0)	4 (9)	6 (14)
	Injury, poisoning and procedural complications	0 (0)	1 (2)	0 (0)	0 (0)	1 (2)	1 (2)
	General disorders and administration site conditions	0 (0)	1 (2)	0 (0)	0 (0)	2 (5)	2 (5)
	Skin and subcutaneous tissue disorders	0 (0)	1 (2)	3 (6)	0 (0)	0 (0)	0 (0)
	Social circumstances	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)
	Investigations	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	Vascular disorders	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)
	Metabolism and nutrition disorders	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)
		Pramipexole (*n* = 27)			Placebo (*n* = 39)		
		Severe	Moderate	Mild	Severe	Moderate	Mild
Unable to determine if related	Psychiatric disorders	1 (4)	9 (33)	4 (15)	0 (0)	10 (27)	8 (22)
	Gastrointestinal disorders	0 (0)	0 (0)	1 (4)	0 (0)	4 (11)	3 (8)
	Nervous system disorders	0 (0)	1 (4)	4 (15)	2 (5)	1 (3)	3 (8)

continued

TABLE 64 MEDRA categories of AEs occurring during the randomisation stage (*continued*)

		Pramipexole (*n* = 27)			Placebo (*n* = 39)		
		Severe	Moderate	Mild	Severe	Moderate	Mild
	General disorders and administration site conditions	0 (0)	2 (7)	0 (0)	1 (3)	0 (0)	2 (5)
	Skin and subcutaneous tissue disorders	0 (0)	0 (0)	1 (4)	0 (0)	0 (0)	0 (0)
	Eye disorders	0 (0)	0 (0)	3 (11)	0 (0)	0 (0)	0 (0)
	Vascular disorders	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (5)
	Metabolism and nutrition disorders	0 (0)	1 (4)	0 (0)	0 (0)	0 (0)	0 (0)
	Ear and labyrinth disorders	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)
Unrelated to IMP		Pramipexole (*n* = 53)			Placebo (*n* = 82)		
		Severe	**Moderate**	**Mild**	**Severe**	**Moderate**	**Mild**
	Psychiatric disorders	0 (0)	4 (8)	5 (9)	0 (0)	8 (10)	14 (17)
	Gastrointestinal disorders	0 (0)	1 (2)	4 (8)	0 (0)	1 (1)	9 (11)
	Nervous system disorders	0 (0)	0 (0)	8 (15)	0 (0)	1 (1)	5 (6)
Unrelated to IMP		Pramipexole (*n* = 53)			Placebo (*n* = 82)		
		Severe	**Moderate**	**Mild**	**Severe**	**Moderate**	**Mild**
	Infections and infestations	0 (0)	4 (8)	10 (19)	1 (1)	4 (5)	9 (11)
	Injury, poisoning and procedural complications	0 (0)	2 (4)	3 (6)	1 (1)	1 (1)	15 (18)
	General disorders and administration site conditions	0 (0)	0 (0)	4 (8)	0 (0)	1 (1)	0 (0)
	Skin and subcutaneous tissue disorders	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)
	Social circumstances	1 (2)	1 (2)	0 (0)	1 (1)	2 (2)	0 (0)
	Investigations	0 (0)	0 (0)	0 (0)	1 (1)	2 (2)	0 (0)
	Vascular disorders	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	Musculoskeletal and connective tissue disorders	1 (2)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	Respiratory, thoracic and mediastinal disorders	0 (0)	1 (2)	0 (0)	1 (1)	1 (1)	0 (0)
	Metabolism and nutrition disorders	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
	Renal and urinary disorders	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (2)
	Neoplasms benign, malignant and unspecified (including cysts and polyps)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
	Immune system disorders	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
	Total (% is out of pramipexole = 128, placebo = 162)	4 (3)	48 (38)	76 (59)	8 (5)	49 (30)	105 (65)

TABLE 65 Details of SAEs reported for participants who were randomised (*n* = 5)

Treatment	Event	Hospital	Severity	Medication commenced	SAE start	SAE stop	Important medical event?	Outcome	Related?
Pramipexole	Colitis	Yes	Moderate	25 May 2021	7 September 2021	8 September 2021	Yes	Condition stable and no change anticipated	No
Pramipexole	Mania and BAPD relapse with psychotic symptoms	Yes	Severe	25 November 2021	24 January 2022	9 March 2022	No	Recovered	Yes
Placebo	Severe depressive episode with suicidality	No	Severe	6 November 2021	16 February 2022	30 March 2022	Yes	Recovered	No
Placebo	Foot surgery with overnight stay in hospital	Yes	Mild	6 December 2021	4 March 2022	5 March 2022	No	Recovered	No
Placebo	Death, likely by suicide	No	Severe	14 November 2021	30 December 2021	31 December 2021	No	Death – pending coroner's inquest. Likely suicide	Unable to determine

Appendix 4 Additional data relating to the health economic analysis

Additional figures

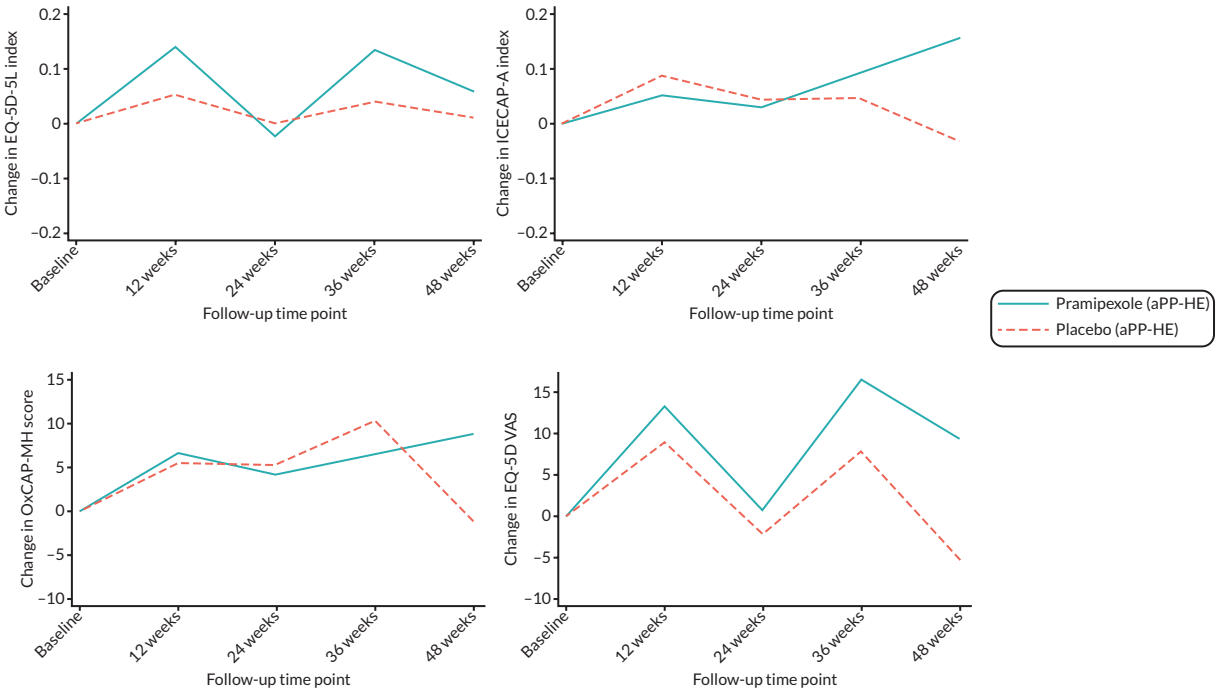

FIGURE 32 Development of the main health economic outcomes. (a) EQ-5D-5L (NW); (b) ICECAP-A (NE); (c) OxCAP-MH (SW); and (d) EQ-5D VAS (SE) for the PP-HE sample.

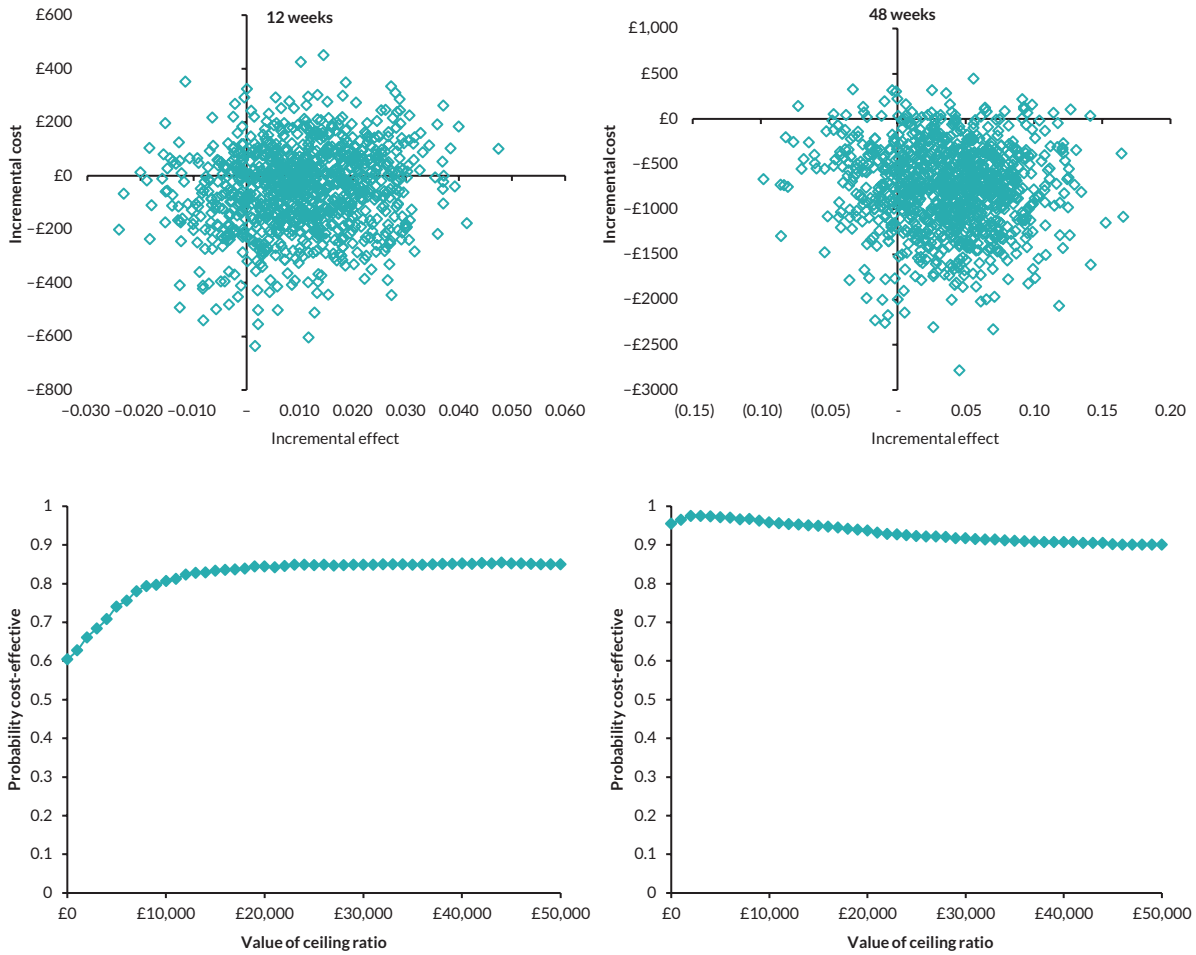

FIGURE 33 Uncertainty in the cost-effectiveness results (NHS + PSS perspective) over 12 weeks and 48 weeks follow-up sample with quality-of-life changes at the beginning of each period. Cost-effectiveness plane with bootstrapped ICERs for pramipexole versus placebo treatment (left: 12 weeks, right: 48 weeks); CEAC showing the probability of pramipexole being cost-effective in comparison to placebo treatment at different WTP thresholds for QALY gained (left: 12 weeks, right: 48 weeks).

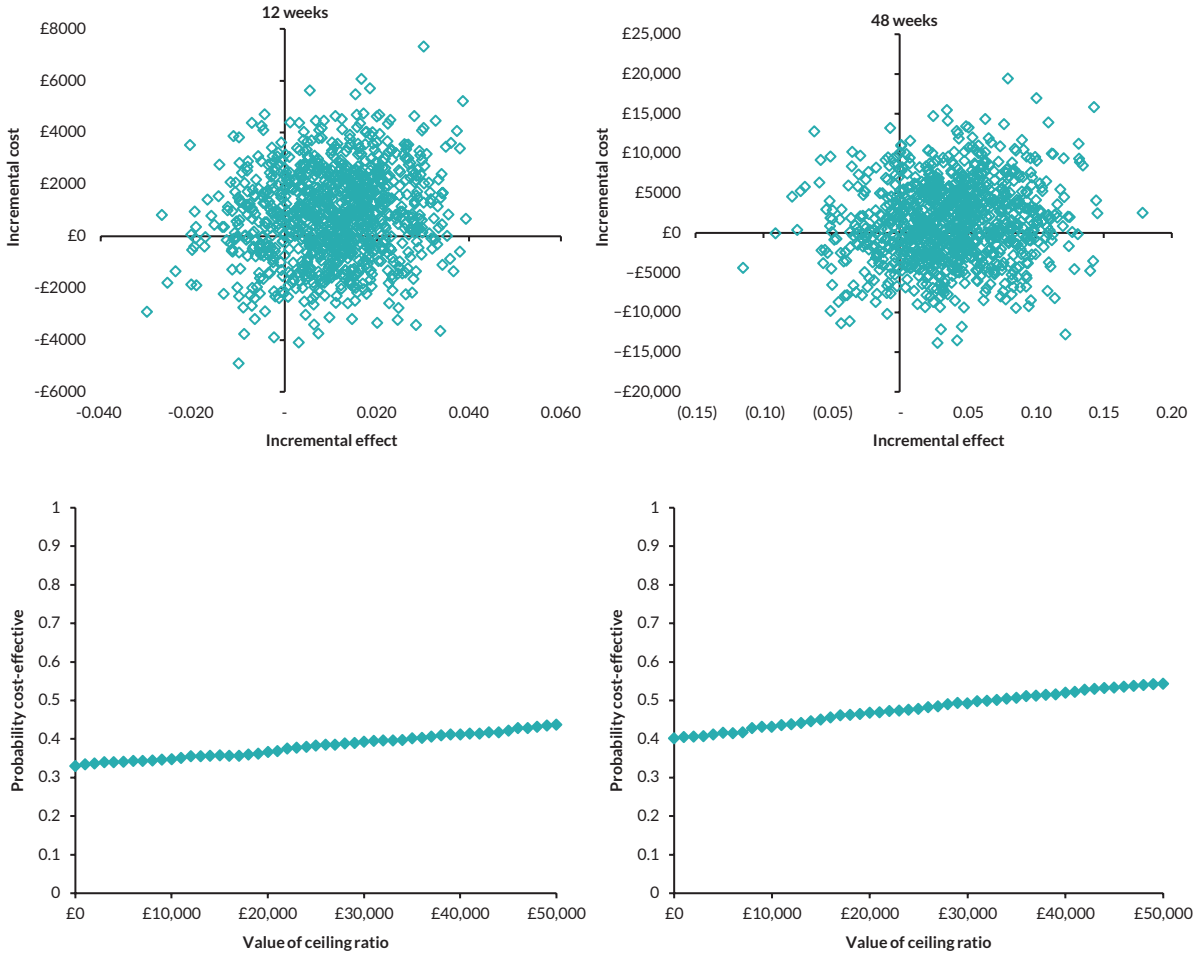

FIGURE 34 Uncertainty in the cost-effectiveness results (societal perspective) over 12 weeks and 48 weeks follow-up with quality-of-life changes at the beginning of each period. Cost-effectiveness plane with bootstrapped ICERs for pramipexole versus placebo treatment (left: 12 weeks, right: 48 weeks); CEAC showing the probability of pramipexole being cost-effective in comparison to placebo treatment at different WTP thresholds for QALY gained (left: 12 weeks, right: 48 weeks).

Additional tables

TABLE 66 Resource use categories and their unit costs (in £ for year 2020–1)

Resource use	Unit cost (£)	Unit of measurement	Source of estimate
Study costs			
Pramipexole	£0.06–0.36	Per prescribed daily dose	Prescription Cost Analysis – England 2021–2
Additional treatment cost (clinical care)	£41.00	Per hour	PSSRU Unit Cost of Health and Social Care 2021
Administrative tasks – psychiatrist	£123.00	Per hour	PSSRU Unit Cost of Health and Social Care 2021
MH medication			
Medication: antipsychotics	£0.50–314.07	Per prescribed dose	Prescription Cost Analysis – England 2021–2
Medication: mood stabilisers	£0.60–0.76	Per prescribed dose	Prescription Cost Analysis – England 2021–2
Medication: antidepressants	£0.30–1.82	Per prescribed dose	Prescription Cost Analysis – England 2021–2
Medication: hypnotics	£0.20–1.23	Per prescribed dose	Prescription Cost Analysis – England 2021–2
Medication: other mental health-related	£0.60	Per prescribed dose	Prescription Cost Analysis – England 2021–2
MH inpatient care	n/a	n/a	n/a

TABLE 66 Resource use categories and their unit costs (in £ for year 2020–1) (*continued*)

Resource use	Unit cost (£)	Unit of measurement	Source of estimate
MH community care			
Community mental health centre	£197.00	Per contact	PSSRU Unit Cost of Health and Social Care 2021
Community psychiatric nurse/case manager	£55.00	Per hour	PSSRU Unit Cost of Health and Social Care 2021
Specialist education	£18.10	Per client contact	PSSRU Unit Cost of Health and Social Care 2021
Self-help/support group	£97.00	Per contact	National Schedule of Reference Costs, 2020–1
MH outpatient care			
Psychiatric outpatient (department) contact (face-to-face, telephone)	£74.56–323.50	Per contact	National Schedule of Reference Costs, 2020–1
Psychologist outpatient contact	£184.69	Per contact	National Schedule of Reference Costs, 2020–1
NMH primary care			
GP	£217.00	Per hour	PSSRU Unit Cost of Health and Social Care 2021
Primary care practice nurse	£42.00	Per hour	PSSRU Unit Cost of Health and Social Care 2021
NMH community care			
Community/district nurse	£44.00	Per hour	PSSRU Unit Cost of Health and Social Care 2021
NMH outpatient care			
Other hospital outpatient visits	£117.47 – 181.55	Per face-to-face contact, non-face-to-face contact	National Schedule of Reference Costs, 2020–1
Accident and emergency visit	£170.46	Per contact	National Schedule of Reference Costs, 2020–1
NMH inpatient care			
Medical ward	£275.92	Per day	Based on Ride *et al.* (2020)
Surgical ward	£1061.58	Per day	Scottish Costs Book 2019–20
Social care			
Social worker	£46.00	Per hour	PSSRU Unit Cost of Health and Social Care 2021
Informal care			
Informal care	£25.00	Per hour	PSSRU Unit Cost of Health and Social Care 2021
Lost productivity			
Absenteeism	£29.03	Per working hour	Based on PECUNIA Group (2021): PECUNIA Reference Unit Cost Compendium (PECUNIA RUC Compendium) (Version 1.0/2021)

MH, mental health; NMH, non-mental health.

Note
All unit costs are expressed as £ for year 2020–1 and were inflated using the NHSCII as reported in the PSSRU Unit Cost of Health and Social care 2021 report[104] if the relevant unit cost was not available for 2020–1.

TABLE 67 Participant socioeconomic characteristics at baseline (*n* = 36)

Participant characteristics at baseline	Pramipexole (*n* = 16)		Placebo (*n* = 20)		*p*-value
	n	% or mean (SD)	*n*	% or mean (SD)	
Biological sex					0.719
Female	7	44%	10	50%	
Male	9	56%	10	50%	
Age	16	46.9 (9.198)	20	48.7 (12.828)	0.642
Bipolar disorder					0.748
Type 1	12	75%	14	70%	
Type 2	4	25%	6	30%	
Higher education					0.119
Yes	9	56%	6	30%	
No	7	44%	14	70%	
Depression severity (QIDS-SR)					0.246
Mild (< 11)	1	6%	2	10%	
Moderate (11–15)	8	50%	4	20%	
Severe (16–20)	5	31%	9	45%	
Very severe (> 20)	2	13%	5	25%	
Accommodation					0.544
Missing information	1	6%	3	15%	
Owner occupied/privately rented accommodation	9	56%	12	60%	
Housing association/local authority accommodation	6	38%	5	25%	
Residential facilities	0	.	0	.	
Living situation					0.555
Missing information	1	6%	3	15%	
Living alone	3	19%	5	25%	
Living with others	12	75%	12	60%	
Employment					0.224
Missing information	1	6%	3	15%	
Employed, self-employed or voluntary employed	4	25%	4	20%	
Unemployed	7	44%	5	25%	
Student	1	6%	0	.	
Retired/medically retired	2	13%	5	25%	
Long-term sick leave	1	6%	3	15%	

TABLE 68 Participant socioeconomic characteristics of the PP-HE sample (*n* = 32)

	Pramipexole (*n* = 15)		Placebo (*n* = 17)		
Baseline characteristics at randomisation	***n***	**% or mean (SD)**	***n***	**% or mean (SD)**	***p*-value**
Biological sex					0.734
Female	8	53%	8	47%	
Male	9	47%	9	52%	
Age					
Bipolar disorder type					0.613
Bipolar disorder type 1	11	73%	11	65%	
Bipolar disorder type 2	4	27%	6	35%	
Higher education					0.173
Yes	9	60%	6	35%	
No	6	40%	11	65%	
Depression severity (QIDS-SR)					0.050
Mild (< 11)	0	0%	0	0%	
Moderate (11–15)	8	53%	3	18%	
Severe (16–20)	5	33%	9	53%	
Very severe (> 20)	2	13%	5	29%	
Accommodation					0.699
Missing information	1	7%	3	18%	
Owner occupied/privately rented accommodation	9	60%	10	59%	
Housing association/local authority accommodation	5	33%	4	24%	
Residential facilities	0	.	0	.	
Living situation					0.677
Missing information	1	7%	3	18%	
Living alone	3	20%	4	24%	
Living with others	11	73%	10	59%	
Employment					0.240
Missing information	1	7%	3	18%	
Employed, self-employed or voluntary employed	4	27%	4	24%	
Unemployed	7	47%	4	24%	
Student	1	7%	0	.	
Retired/medically retired	1	7%	3	18%	
Long-term sick leave	1	7%	3	18%	

TABLE 69 Number and proportion of study participants with available data by treatment arm (*n* = 36)

	Baseline *n* (%) complete		12 weeks *n* (%) complete		24 weeks *n* (%) complete		36 weeks *n* (%) complete		48 weeks *n* (%) complete		All follow-up time points *n* (%) complete	
	Pramipexole (*n* = 16)	Placebo (*n* = 20)	Pramipexole (*n* = 16)	Placebo (*n* = 20)	Pramipexole (*n* = 16)	Placebo (*n* = 20)	Pramipexole (*n* = 16)	Placebo (*n* = 20)	Pramipexole (*n* = 16)	Placebo (*n* = 20)	Pramipexole (*n* = 80)	Placebo (*n* = 100)
EQ-5D-5L	16 (100%)	20 (100%)	16 (100%)	19 (95%)	12 (75%)	17 (85%)	9 (56%)	11 (55%)	7 (44%)	8 (40%)	60 (75%)	75 (75%)
EQ VAS	16 (100%)	20 (100%)	16 (100%)	19 (95%)	12 (75%)	17 (85%)	9 (56%)	11 (55%)	7 (44%)	8 (40%)	60 (75%)	75 (75%)
ICECAP-A	16 (100%)	20 (100%)	16 (100%)	19 (95%)	12 (75%)	17 (85%)	9 (56%)	12 (60%)	8 (50%)	8 (40%)	61 (76%)	76 (76%)
OxCAP-MH	16 (100%)	20 (100%)	16 (100%)	19 (95%)	12 (75%)	17 (85%)	9 (56%)	12 (60%)	8 (50%)	8 (40%)	61 (76%)	76 (76%)
Resource use (HEQ)	15 (94%)	18 (90%)	16 (100%)	19 (95%)	12 (75%)	17 (85%)	8 (50%)	11 (55%)	8 (50%)	8 (40%)	59 (74%)	73 (73%)
Pramipexole	36 (100%)	36 (100%)	36 (100%)	36 (100%)	36 (100%)	36 (100%)	36 (100%)	36 (100%)	36 (100%)	36 (100%)	36 (100%)	36 (100%)

TABLE 70 Observed HRQoL (EQ-5D-5L, EQ VAS) and capability well-being results (ICECAP-A, OxCAP-MH), (*n* = 36)

Outcome measure	Baseline Mean (SD) (*n*)	Trial week 12 Mean (SD) (*n*)	Trial week 24 Mean (SD) (*n*)	Trial week 36 Mean (SD) (*n*)	Trial week 48 Mean (SD) (*n*)
EQ-5D-5L index (0–1)					
Pramipexole	0.502 (0.195) (*n* = 16)	0.610 (0.189) (*n* = 16)	0.455 (0.188) (*n* = 12)	0.600 (0.200) (*n* = 9)	0.564 (0.176) (*n* = 7)
Placebo	0.408 (0.143) (*n* = 20)	0.463 (0.149) (*n* = 19)	0.415 (0.196) (*n* = 17)	0.437 (0.145) (*n* = 11)	0.407 (0.136) (*n* = 8)
EQ VAS (0–100)					
Pramipexole	45.38 (24.15) (*n* = 16)	58.50 (23.80) (*n* = 16)	46.67 (23.57) (*n* = 12)	54.11 (30.07) (*n* = 9)	58.57 (19.83) (*n* = 7)
Placebo	38.45 (19.37) (*n* = 20)	50.74 (22.53) (*n* = 19)	38.59 (23.82) (*n* = 17)	48.64 (17.67) (*n* = 11)	35.63 (19.60) (*n* = 8)
ICECAP-A index (0–1)					
Pramipexole	0.488 (0.178) (*n* = 16)	0.514 (0.174) (*n* = 16)	0.509 (0.094) (*n* = 12)	0.577 (0.135) (*n* = 9)	0.646 (0.188) (*n* = 8)
Placebo	0.380 (0.141) (*n* = 20)	0.456 (0.240) (*n* = 19)	0.436 (0.199) (*n* = 17)	0.414 (0.165) (*n* = 12)	0.355 (0.196) (*n* = 8)
OxCAP-MH score (0–100)					
Pramipexole	52.83 (14.15) (*n* = 16)	57.91 (12.35) (*n* = 16)	55.730 (6.118) (*n* = 12)	59.722 (7.958) (*n* = 9)	61.329 (8.751) (*n* = 8)
Placebo	48.83 (13.77) (*n* = 20)	52.63 (15.59) (*n* = 19)	52.391 (12.029) (*n* = 17)	56.383 (6.939) (*n* = 12)	45.118 (10.038) (*n* = 8)

TABLE 71 Resource use for all available cases (observations)

Resource use	Before trial (baseline)				During trial (weeks 1–12)				During trial (weeks 1–48)			
	Pramipexole (*n* = 16)		Placebo (*n* = 20)		Pramipexole (*n* = 16)		Placebo (*n* = 20)		Pramipexole (*n* = 16)		Placebo (*n* = 20)	
	Mean (SD)	*n* of users	Mean (SD)	*n* of users	Mean (SD)	*n* of users	Mean (SD)	*n* of users	Mean (SD)	*n* of users	Mean (SD)	*n* of users
MH inpatient care	–		–		–		–		–		–	
MH community care												
Community mental health centre[a]	0.27 (0.80)	2	0.28 (0.57)	4	0.13 (0.50)	1	0.05 (0.23)	1	0.19 (0.75)	1	0.21 (0.54)	3
Community psychiatric nurse/ case manager[b]	0.03 (0.13)	1	0.00 (0.00)	0	0.08 (0.33)	1	0.02 (0.10)	1	0.11 (0.34)	2	0.06 (0.15)	3
Specialist education[b]	0.53 (2.07)	1	0.00 (0.00)	0	0.00 (0.00)	0	0.00 (0.00)	0	0.00 (0.00)	0	0.00 (0.00)	0
Self-help/support group[a]	0.53 (1.60)	2	0.67 (2.59)	1	0.00 (0.00)	0	0.00 (0.00)	0	0.13 (0.50)	1	0.00 (0.00)	0
MH outpatient care												
Psychiatric outpatient (department) contact[a]	0.27 (0.59)	3	0.72 (1.45)	7	0.19 (0.54)	2	0.53 (1.87)	2	0.81 (1.87)	4	1.84 (4.54)	6
Psychologist outpatient contact[a]	0.00 (0.00)	0	0.00 (0.00)	0	0.00 (0.00)	0	0.00 (0.00)	0	0.13 (0.50)	1	0.00 (0.00)	0
Primary care												
GP[b]	0.00 (0.00)	0	0.15 (0.48)	3	0.01 (0.04)	1	0.00 (0.00)	0	0.18 (0.43)	3	0.14 (0.52)	2
Primary care practice nurse[b]	0.07 (0.26)	1	0.03 (0.12)	3	0.05 (0.21)	1	0.07 (0.29)	1	0.07 (0.27)	1	0.10 (0.32)	2
NMH community care												
Community/district nurse[b]	0.00 (0.00)	0	0.00 (0.00)	0	0.00 (0.00)	0	0.00 (0.00)	0	0.00 (0.00)	0	0.01 (0.04)	1
NMH outpatient care												
Other hospital outpatient visits[a]	0.00 (0.00)	0	0.11 (0.47)	1	0.19 (0.75)	1	0.00 (0.00)	0	0.31 (1.01)	2	0.05 (0.23)	1
Accident and emergency visit[a]	0.00 (0.00)	1	0.00 (0.00)	0	0.00 (0.00)	0	0.00 (0.00)	0	0.19 (0.54)	2	0.05 (0.23)	1
NMH inpatient care												
Medical wards[c]	0.07 (0.26)	0	0.00 (0.00)	0	0.06 (0.25)	1	0.00 (0.00)	0	0.06 (0.25)	1	0.00 (0.00)	0
Surgical wards[c]	0.13 (0.52)	0	0.00 (0.00)	0	0.00 (0.00)	0	0.00 (0.00)	0	0.00 (0.00)	0	0.11 (0.46)	1
Social care												
Social worker[b]	0.00 (0.00)	0	0.00 (0.00)	0	0.00 (0.00)	0	0.00 (0.00)	0	0.00 (0.00)	0	0.05 (0.23)	1
Medication												
Antipsychotics		4		3		2		1		2		3
Mood stabilisers		7		5		4		2		4		3
Antidepressants		2		3		0		1		1		2

continued

TABLE 71 Resource use for all available cases (observations) (*continued*)

	Before trial (baseline)				During trial (weeks 1–12)				During trial (weeks 1–48)			
	Pramipexole (*n* = 16)		Placebo (*n* = 20)		Pramipexole (*n* = 16)		Placebo (*n* = 20)		Pramipexole (*n* = 16)		Placebo (*n* = 20)	
Resource use	Mean (SD)	*n* of users	Mean (SD)	*n* of users	Mean (SD)	*n* of users	Mean (SD)	*n* of users	Mean (SD)	*n* of users	Mean (SD)	*n* of users
Hypnotics		1		2		1		0		1		2
Other mental health-related		1		0		0		0		0		0
Pramipexole		0		0		16		0		16		0
Informal care												
Hours of informal care received	20.20 (32.96)	7	5.72 (12.49)	8	16.31 (49.92)	5	2.05 (4.67)	7	36.69 (71.12)	9	19.11 (37.78)	15
Lost productivity												
Absenteeism (hours absent from work)	61.33 (130.32)	5	43.56 (117.17)	4	90.00 (193.49)	3	71.16 (154.78)	5	254.00 (489.57)	4	211.37 (368.72)	10

MH, mental health; NMH, non-mental health.
a Per contact.
b Per hour.
c Per day.

TABLE 72 Cost results, full imputed sample (in £, for year 2020–1)

	Before trial (weeks −4–0)			During trial (weeks 1–12)			During trial (weeks 1–48)		
	Pramipexole (*n* = 16)	Placebo (*n* = 20)	Δ costs	Pramipexole (*n* = 16)	Placebo (*n* = 20)	Δ costs	Pramipexole (*n* = 16)	Placebo (*n* = 20)	Δ costs
	Mean (SD)	Mean (SD)	Difference (95% CI)	Mean (SD)	Mean (SD)	Difference (95% CI)	Mean (SD)	Mean (SD)	Difference (95% CI)
Cost category									
Pramipexole	–	–	–	£18.97 (2.16)	–	£18.97 (£18.00 to £19.95)	£70.61 (30.95)	–	£70.61 (£56.60 to £84.62)
Clinical care: trial researchers	–	–	–	£276.75 (.)	£275.73 (4.58)	£1.03 (−£1.31 to £3.36)	£513.78 (122.59)	£513.01 (139.33)	£0.77 (−£89.35 to £90.89)
Clinical care: psychiatrists	–	–	–	£153.75 (.)	£153.75 (.)	0 (.)	£322.88 (76.15)	£330.05 (85.28)	−£7.18 (−£62.65 to £48.30)
Treatment costs	–	–	–	£449.47 (2.16)	£429.48 (4.58)	**£20.00 (£17.47 to £22.53)**	£907.26 (228.15)	£843.06 (223.28)	£64.20 (−£89.47 to £217.87)
Medication: antipsychotics	£1.27 (3.93)	£31.10 (108.70)	−£29.83 (−£85.25 to £25.59)	£0.35 (1.14)	£44.11 (167.50)	−£43.76 (−£129.11 to £41.59)	£1.53 (4.11)	£246.60 (660.15)	−£245.07 (−£581.46 to £91.32)
Medication: mood stabilisers	£3.95 (5.80)	£3.76 (8.79)	£0.19 (−£5.00 to £5.38)	£5.12 (11.52)	£3.69 (12.66)	£1.43 (−£6.86 to £9.73)	£24.63 (44.67)	£20.44 (49.48)	£4.19 (−£28.13 to £36.51)
Medication: antidepressants	£6.84 (26.85)	£0.75 (1.93)	£6.10 (−£6.10 to £18.29)	£0.00 (0.00)	£0.10 (0.44)	−£0.10 (−£0.32 to £0.12)	£0.06 (0.09)	£1.23 (3.12)	−£1.17 (−£2.76 to £0.42)

TABLE 72 Cost results, full imputed sample (in £, for year 2020–1) (*continued*)

	Before trial (weeks −4–0)			During trial (weeks 1–12)			During trial (weeks 1–48)		
	Pramipexole (*n* = 16)	Placebo (*n* = 20)	Δ costs	Pramipexole (*n* = 16)	Placebo (*n* = 20)	Δ costs	Pramipexole (*n* = 16)	Placebo (*n* = 20)	Δ costs
	Mean (SD)	Mean (SD)	Difference (95% CI)	Mean (SD)	Mean (SD)	Difference (95% CI)	Mean (SD)	Mean (SD)	Difference (95% CI)
Medication: hypnotics	£0.33 (1.10)	£2.36 (8.16)	−£2.03 (−£6.22 to £2.16)	£0.52 (2.08)	£0.02 (0.08)	£0.50 (−£0.44 to £1.44)	£2.43 (7.98)	£10.87 (31.38)	−£8.44 (−£24.83 to £7.96)
Medication: other MH-related	£0.12 (0.50)	£0.00 (0.00)	£0.12 (−£0.10 to £0.35)	£0.00 (0.00)	£0.00 (0.00)	–	£0.00 (0.00)	£0.00 (0.00)	–
MH medication	£12.51 (33.48)	£37.96 (116.33)	−£25.45 (−£86.63 to £35.74)	£5.99 (13.55)	£47.92 (180.08)	−£41.92 (−£133.89 to £50.04)	£28.65 (51.98)	£279.13 (706.92)	−£250.49 (−£611.47 to £110.49)
MH inpatient care	–	–	–	–	–	–	–	–	–
MH community care	£49.74 (152.44)	£50.43 (107.88)	−£0.69 (−£88.92 to £87.54)	£24.63 (98.50)	£9.85 (44.05)	£14.78 (−£35.15 to £64.70)	£71.91 (160.64)	£98.50 (178.51)	−£26.60 (−£143.06 to £89.87)
MH outpatient care	£84.11 (185.72)	£214.16 (446.93)	−£130.05 (−£372.81 to £112.71)	£60.66 (175.95)	£157.71 (579.79)	−£97.06 (−£403.04 to £208.93)	£350.43 (623.25)	£948.60 (1712.58)	−£598.17 (−£1515.31 to £318.97)
MH care cost	£133.85 (239.49)	£264.59 (518.88)	−£130.74 (−£416.50 to £155.03)	£85.28 (193.59)	£167.56 (585.73)	−£82.28 (−£393.35 to £228.78)	£422.33 (646.24)	£1047.10 (1853.91)	−£624.76 (−£1613.70 to £364.17)
Primary care	£3.33 (10.69)	£32.35 (102.88)	£29.02 (−£23.63 to £81.67)	£4.45 (17.79)	£2.85 (11.73)	−£1.60 (−£11.63 to £8.43)	£53.36 (101.29)	£60.70 (115.04)	−£7.34 (−£81.77 to £67.08)
NMH community care	£0.00 (0.00)	£0.0 (0.00)	–	£0.00 (0.00)	£0.00 (0.00)	–	£0.00 (0.00)	£0.82 (3.27)	−£0.82 (−£2.49 to £0.84)
NMH outpatient care	£0.00 (0.00)	£18.88 (81.09)	£18.88 (−£22.44 to £60.20)	£34.04 (136.16)	£1.07 (4.77)	−£32.97 (−£94.67 to £28.72)	£108.42 (197.54)	£32.18 (59.34)	£76.24 (−£18.17 to £170.65)
NMH inpatient care	£149.94 (599.77)	£0.00 (0.00)	−£149.94 (−£421.49 to £121.60)	£17.25 (68.98)	£0.00 (0.00)	−£17.25 (−£48.48 to £13.99)	£83.43 (93.41)	£135.88 (470.35)	−£52.45 (−£295.83 to £190.92)
NMH care costs	£153.27 (610.09)	£51.23 (126.02)	£102.04 (−£181.54 to £385.62)	£55.73 (164.45)	£3.91 (12.80)	£51.82 (−£22.92 to £126.56)	£245.20 (280.52)	£229.58 (511.51)	£15.62 (−£274.32 to £305.56)
Social care	£0.00 (0.00)	£0.18 (0.57)	−£0.18 (−£0.47 to £0.10)	£0.00 (0.00)	£0.09 (0.41)	−£0.09 (−£0.30 to £0.12)	£0.00 (0.00	£3.22 (10.56)	−£3.22 (−£8.60 to £2.16)
NHS + PSS perspective	£299.64 (705.10)	£353.97 (548.55)	−£54.33 (−£478.64 to £369.98)	£596.48 (322.62)	£648.96 (600.70)	−£52.48 (−£391.64 to £286.67)	£1603.44 (965.24)	£2402.09 (1945.78)	−£798.65 (−£1882.17 to £284.87)
Informal care	£539.44 (807.92)	£135.66 (296.28)	£403.78 (£8.06 to £799.49)	£407.81 (1248.12)	£57.40 (118.71)	£350.41 (−£217.90 to £918.73)	£1465.38 (1991.08)	£667.46 (908.30)	£797.91 (−£215.42 to £1811.25)
Lost productivity	£1738.90 (3658.81)	£1316.71 (3204.16)	£422.19 (−£1903.70 to £2748.08)	£2612.70 (5617.14)	£2115.90 (4379.15)	£496.80 (−£2886.52 to £3880.12)	£10,247.01 (13,743.14)	£9075.55 (12,601.54)	£1171.46 (−£7769.85 to £10,112.78)

continued

TABLE 72 Cost results, full imputed sample (in £, for year 2020–1) (*continued*)

	Before trial (weeks −4–0)			During trial (weeks 1–12)			During trial (weeks 1–48)		
	Pramipexole (*n* = 16)	Placebo (*n* = 20)	Δ costs	Pramipexole (*n* = 16)	Placebo (*n* = 20)	Δ costs	Pramipexole (*n* = 16)	Placebo (*n* = 20)	Δ costs
	Mean (SD)	Mean (SD)	Difference (95% CI)	Mean (SD)	Mean (SD)	Difference (95% CI)	Mean (SD)	Mean (SD)	Difference (95% CI)
Societal perspective	£2577.97 (3734.38)	£1806.34 (3458.63)	£771.64 (−£1670.60 to £3213.87)	£3616.99 (5926.54)	£2822.26 (4390.55)	£794.73 (−£2698.82 to £4288.29)	£13,315.83 (15,099.12)	£12,145.10 (14,624.59)	£1170.73 (−£8941.89 to £11,283.35)

MH, mental health; NMH, non-mental health.
"–" indicates that the value is not observed in the given period/group, "0 (.)" indicates that no patients incurred costs in this category.
The notation "(.)" indicates that the SD or CI cannot not be calculated, because the observed value is the same for all patients.

TABLE 73 Net monetary benefit results (pramipexole vs. placebo) with QALYs based on the primary EQ-5D-5L outcome

	WTP threshold £20,000		WTP threshold £30,000	
	ITT	PP-HE	ITT	PP-HE
Perspective	**NMB (95% CI)**	**NMB (95% CI)**	**NMB (95% CI)**	**NMB (95% CI)**
12 weeks				
NHS + PSS	£165.91 (−£177.08 to £536.21)	£239.62 (−£124.92 to £605.41)	£222.63 (−£205.54 to £672.53)	£329.22 (−£104.43 to £743.86)
Societal	−£681.30 (−£4235.59 to £2661.50)	−£1470.36 (−£5040.02 to £1802.05)	−£624.59 (−£4190.70 to £2,684,291.75)	−£1380.76 (−£4970.49 to £1923.31)
48 weeks				
NHS + PSS	£1448.15 (−£295.39 to £3057.81)	£2080.68 (£509.88 to £3494.22)	£1772.90 (−£542.81 to £3964.20)	£2675.83 (£650.07 to £4524.10)
Societal	−£521.23 (−£10,292.52 to £8793.74)	−£807.46 (−£10,512.68 to £9040.41)	−£196.48 (−£10,115.38 to £9076.27)	−£212.31 (−£9926.06 to £9440.27)

TABLE 74 Available HRQoL (EQ-5D-5L, EQ VAS) and capability well-being results (ICECAP-A, OxCAP-MH) in the PP-HE sample (*n* = 32)

	WTP threshold £20,000		WTP threshold £30,000	
	ITT	PP-HE	ITT	PP-HE
Perspective	**NHB (95% CI)**	**NHB (95% CI)**	**NHB (95% CI)**	**NHB (95% CI)**
12 weeks				
NHS + PSS	0.01 QALY (−0.01 QALY to 0.03 QALY)	0.01 QALY (−0.01 QALY to 0.03 QALY)	0.01 QALY (−0.01 QALY to 0.02 QALY)	0.01 QALY (0.00 QALY to 0.02 QALY)
Societal	−0.03 QALY (−0.21 QALY to 0.13 QALY)	−0.07 QALY (−0.25 QALY to 0.09 QALY)	−0.02 QALY (−0.14 QALY to 0.09 QALY)	−0.04 QALY (−0.17 QALY to 0.06 QALY)
48 weeks				
NHS + PSS	0.07 QALY (−0.01 QALY to 0.15 QALY)	0.10 QALY (0.03 QALY to 0.17 QALY)	0.06 QALY (−0.02 QALY to 0.13 QALY)	0.09 QALY (0.02 QALY to 0.15 QALY)
Societal	−0.03 QALY (−0.51 QALY to 0.44 QALY)	−0.05 QALY (−0.53 QALY to 0.45 QALY)	−0.01 QALY (−0.34 QALY to 0.30 QALY)	−0.01 QALY (−0.33 QALY to 0.31 QALY)

TABLE 75 Available HRQoL (EQ-5D-5L, EQ VAS) and capability well-being results (ICECAP-A, OxCAP-MH) in the PP-HE sample (*n* = 32)

Outcome measure	Baseline Mean (SD) (*n*)	Trial week 12 Mean (SD) (*n*)	Trial week 24 Mean (SD) (*n*)	Trial week 36 Mean (SD) (*n*)	Trial week 48 Mean (SD) (*n*)
EQ-5D-5L index (0–1)					
Pramipexole	0.469 (0.148) (*n* = 15)	0.609 (0.196) (*n* = 15)	0.447 (0.195) (*n* = 11)	0.603 (0.213) (*n* = 8)	0.528 (0.162) (*n* = 6)
Placebo	0.397 (0.147) (*n* = 17)	0.449 (0.149) (*n* = 17)	0.396 (0.186) (*n* = 15)	0.437 (0.145) (*n* = 11)	0.407 (0.136) (*n* = 8)
EQ VAS (0–100)					
Pramipexole	44.40 (24.67) (*n* = 15)	57.67 (24.39) (*n* = 15)	45.09 (24.05) (*n* = 11)	60.88 (23.73) (*n* = 8)	53.83 (16.83) (*n* = 6)
Placebo	40.76 (18.42) (*n* = 17)	49.76 (22.61) (*n* = 17)	38.47 (22.89) (*n* = 15)	48.64 (17.67) (*n* = 11)	35.63 (19.60) (*n* = 8)
ICECAP-A index (0–1)					
Pramipexole	0.458 (0.135) (*n* = 15)	0.510 (0.179) (*n* = 15)	0.487 (0.059) (*n* = 11)	0.552 (0.121) (*n* = 8)	0.613 (0.176) (*n* = 7)
Placebo	0.388 (0.129) (*n* = 17)	0.475 (0.235) (*n* = 17)	0.431 (0.186) (*n* = 15)	0.434 (0.157) (*n* = 11)	0.355 (0.196) (*n* = 8)
OxCAP-MH score (0–100)					
Pramipexole	50.94 (12.37) (*n* = 15)	57.50 (12.67) (*n* = 15)	55.11 (6.01) (*n* = 11)	57.62 (5.18) (*n* = 8)	59.82 (8.25) (*n* = 7)
Placebo	46.42 (12.28) (*n* = 17)	51.93 (16.38) (*n* = 17)	51.67 (12.17) (*n* = 15)	56.68 (7.20) (*n* = 11)	45.12 (10.04) (*n* = 8)

TABLE 76 Cost results (in £, for year 2020–1) for the PP-HE/MI sample

	Before trial (weeks −4 to 0)			During trial costs (weeks 1–12)			During trial costs (weeks 1–48)		
	Pramipexole (*n* = 15)	Placebo (*n* = 17)	Δ costs	Pramipexole (*n* = 15)	Placebo (*n* = 17)	Δ costs (95% CI)	Pramipexole (*n* = 15)	Placebo (*n* = 17)	Δ costs
	Mean (SD)	Mean (SD)	Difference (95% CI)	Mean (SD)	Mean (SD)	Difference (95% CI)	Mean (SD)	Mean (SD)	Difference (95% CI)
Cost category									
Pramipexole	–	–	–	£18.96 (2.23)	–	£18.96 (£17.86 to £20.07)	£68.04 (30.22)	–	£68.04 (£53.10 to £82.98)
Clinical care: RA	–	–	–	£276.75 (.)	£276.75 (.)	0 (.)	£504.98 (121.56)	£536.62 (132.21)	−£31.63 (−£123.77 to £60.50)
Clinical care: psychiatrists	–	–	–	£153.75 (0.00)	£153.75 (0.00)	0 (.)	£317.75 (75.92)	£346.69 (76.38)	−£28.94 (−£84.04 to £26.16)
Treatment costs	–	–	–	£449.46 (2.23)	£430.50 (0.00)	£18.96 (£17.86 to £20.07)	£890.77 (226.07)	£883.31 (207.24)	£7.46 (−£148.97 to £163.90)
Medication: antipsychotics	£1.39 (4.04)	£35.49 (117.02)	−£34.10 (−£95.96 to £27.76)	£0.38 (1.18)	£43.73 (180.31)	−£43.36 (−£138.62 to £51.91)	£1.75 (4.18)	£250.46 (713.08)	−£248.70 (−£625.46 to £128.06)

continued

TABLE 76 Cost results (in £, for year 2020–1) for the PP-HE/MI sample (*continued*)

	Before trial (weeks −4 to 0)			During trial costs (weeks 1–12)			During trial costs (weeks 1–48)		
	Pramipexole (*n* = 15)	Placebo (*n* = 17)	Δ costs	Pramipexole (*n* = 15)	Placebo (*n* = 17)	Δ costs (95% CI)	Pramipexole (*n* = 15)	Placebo (*n* = 17)	Δ costs
	Mean (SD)	Mean (SD)	Difference (95% CI)	Mean (SD)	Mean (SD)	Difference (95% CI)	Mean (SD)	Mean (SD)	Difference (95% CI)
Medication: mood stabilisers	£3.59 (5.84)	£3.36 (8.87)	£0.23 (−£5.27 to £5.73)	£4.01 (11.01)	£3.65 (13.59)	£0.36 (−£8.65 to £9.37)	£19.63 (41.27)	£20.59 (53.47)	−£0.96 (−£35.80 to £33.89)
Medication: antidepressants	£7.30 (27.73)	£0.42 (1.16)	£6.88 (−£6.84 to £20.60)	0 (.)	£0.11 (0.47)	−£0.11 (−£0.36 to £0.14)	£0.05 (0.08)	£1.17 (3.39)	−£1.12 (−£2.91 to £0.68)
Medication: hypnotics	£0.33 (1.12)	£2.61 (8.81)	−£2.28 (−£6.97 to £2.41)	£0.55 (2.14)	0 (.)	£0.55 (−£0.51 to £1.61)	£2.80 (8.21)	£12.92 (33.76)	−£10.12 (−£28.41 to £8.17)
Medication: other MH-related	£0.13 (0.51)	0 (.)	£0.13 (−£0.12 to £0.38)	0 (.)	0 (.)	0 (.)	0 (.)	0 (.)	0 (.)
MH medication	£12.74 (34.64)	£41.89 (125.30)	−£29.14 (−£97.52 to £39.24)	£4.94 (13.33)	£47.50 (193.80)	−£42.56 (−£145.16 to £60.05)	£24.24 (49.85)	£285.14 (763.84)	−£260.90 (−£665.22 to £143.42)
MH inpatient care	0 (.)	0 (.)	0 (.)	0 (.)	0 (.)	0 (.)	0 (.)	0 (.)	0 (.)
MH community care	£55.16 (156.75)	£66.75 (113.99)	−£11.59 (−£109.72 to £86.54)	£26.27 (101.73)	£11.59 (47.78)	£14.68 (−£41.58 to £70.94)	£69.34 (160.28)	£93.17 (188.47)	−£23.83 (−£151.07 to £103.42)
MH outpatient care	£91.44 (190.58)	£266.59 (474.88)	−£175.14 (−£443.14 to £92.85)	£64.70 (181.36)	£175.65 (629.07)	−£110.95 (−£455.19 to £233.29)	£295.82 (617.31)	£935.19 (1868.42)	−£639.36 (−£1672.61 to £393.88)
MH care cost	£146.60 (244.19)	£333.34 (549.95)	−£186.73 (−£501.36 to £127.89)	£90.97 (198.99)	£187.24 (635.21)	−£96.27 (−£445.99 to £253.45)	£365.17 (644.87)	£1028.36 (2020.17)	−£663.19 (−£1777.11 to £450.73)
NMH primary care	£2.80 (10.84)	£36.35 (111.63)	−£33.55 (−£92.78 to £25.67)	£4.74 (18.38)	0 (.)	£4.74 (−£4.34 to £13.83)	£37.26 (74.87)	£49.05 (124.56)	−£11.79 (−£87.28 to £63.71)
NMH community care	0 (.)	£0.03 (0.14)	−£0.03 (−£0.11 to £0.04)	0 (.)	0 (.)	0 (.)	0 (.)	£1.00 (3.54)	−£1.00 (−£2.87 to £0.87)
NMH outpatient care	£0.48 (1.88)	£22.61 (87.82)	−£22.13 (−£68.54 to £24.28)	£36.31 (140.63)	0 (.)	£36.31 (−£33.19 to £105.81)	£121.37 (207.23)	£20.07 (45.13)	£101.29 (−£3.86 to £206.45)
NMH inpatient care	£159.94 (619.44)	£5.00 (20.60)	£154.94 (−£151.39 to £461.28)	£18.39 (71.24)	0 (.)	£18.39 (−£16.81 to £53.60)	£82.59 (152.36)	£144.87 (512.00)	−£62.28 (−£343.08 to £218.52)
NMH care costs	£163.22 (630.15)	£64.00 (135.63)	£99.22 (−£220.35 to £418.80)	£59.45 (169.53)	0 (.)	£59.45 (−£24.33 to £143.23)	£241.22 (317.94)	£214.99 (555.46)	£26.23 (−£306.66 to £359.12)
Social Care	0 (.)	0 (.)	0 (.)	0 (.)	0 (.)	0 (.)	0 (.)	0 (.)	0 (.)

TABLE 76 Cost results (in £, for year 2020–1) for the PP-HE/MI sample (*continued*)

	Before trial (weeks −4 to 0)			During trial costs (weeks 1–12)			During trial costs (weeks 1–48)		
	Pramipexole (*n* = 15)	Placebo (*n* = 17)	Δ costs	Pramipexole (*n* = 15)	Placebo (*n* = 17)	Δ costs (95% CI)	Pramipexole (*n* = 15)	Placebo (*n* = 17)	Δ costs
	Mean (SD)	Mean (SD)	Difference (95% CI)	Mean (SD)	Mean (SD)	Difference (95% CI)	Mean (SD)	Mean (SD)	Difference (95% CI)
NHS + PSS perspective	£322.57 (724.29)	£439.22 (580.16)	−£116.65 (−£587.92 to £354.62)	£604.82 (332.16)	£665.24 (650.22)	−£60.42 (−£441.16 to £320.33)	£1521.40 (940.28)	£2411.79 (2136.76)	−£890.39 (−£2111.24 to £330.45)
Informal care	−£2176.19 (84.76)	£137.53 (308.81)	£426.73 (−£8.79 to £862.26)	£435.00 (1287.02)	£22.83 (42.02)	£412.17 (−£224.29 to £1048.63)	£1716.40 (2026.53)	£670.68 (992.28)	£1045.72 (−£84.76 to £2176.19)
Lost productivity	£1941.53 (3753.40)	£1507.65 (3454.57)	£433.88 (−£2168.51 to £3036.27)	£2786.88 (5769.39)	£1489.07 (3645.37)	£1297.81 (−£2143.09 to £4738.71)	£10,930.14 (13,828.08)	£9087.72 (13,542.34)	£1842.43 (−£8052.01 to £11,736.87)
Societal perspective	£2828.36 (3801.02)	£2084.40 (3723.79)	£743.96 (−£1976.29 to £3464.22)	£3826.70 (6072.80)	£2177.14 (3600.77)	£1649.56 (−£1903.91 to £5203.03)	£14,167.94 (15,187.91)	£12,170.19 (15,849.58)	£1997.75 (−£9248.04 to £13,243.54)

MH, mental health; NMH, non-mental health.
"–" indicates that the value is not observed in the given period/group, "0 (.)" indicates that no patients incurred costs in this category.
The notation "(.)" indicates that the SD or CI cannot not be calculated, because the observed value is the same for all patients.

TABLE 77 Cost-effectiveness results (pramipexole vs. placebo) with QALYs as outcome measure quality-of-life changes at the beginning of each period

Perspective	Cost difference (95% CI)	QALY difference (95% CI)	ICER (95% CI)	Interpretation
Weeks 1–12				
NHS + PSS	−£52.48 (−£393.94 to £238.56)	0.011 (−0.012 to 0.033)	−£4961.69/QALY (−£99,501.77/QALY to −£21,855.08/QALY)	Pramipexole on average saves costs and is more effective than placebo
Societal	£794.73 (−£2428.52 to £4181.67)	0.011 (−0.013 to 0.033)	£75,133.17/QALY (−£325,059.24/QALY to −£740,039.52/QALY)	Pramipexole on average is more expensive, but more effective than placebo
Weeks 1–48				
NHS + PSS	−£798.65 (−£1763.75 to £69.27)	0.035 (−0.042 to 0.117)	−£22,731/QALY (−£222,149.84/QALY to £6688.62/QALY)	Pramipexole on average saves costs and is more effective than placebo
Societal	£1170.73 (−£7989.04 to £10,871.54)	0.035 (−0.042 to 0.117)	£33,321.73/QALY (−£352,736.79/QALY to −£486,605.29/QALY)	Pramipexole on average is more expensive, but more effective than placebo

Appendix 5 Full qualitative investigation results

Subthemes are discussed within a narrative of HCP and patient experiences of barriers and facilitators to recruitment of participants and subsequent retention. This is closed with suggestions for future improvement which is expanded to encompass a reflective account of lessons learnt from the PAX-BD study. Augmented codes are provided within the subthemes.

Barriers

Expression of symptomatology

This subtheme considered the profile of TRBD, interplay from comorbid conditions and the clinical challenges these factors present in identifying eligible participants and engaging them.

Profile of bipolar depression

Healthcare professionals highlighted that BD has a complex profile with symptoms overlapping other disorders such as emotionally unstable personality disorder, and patient presentation can be compounded by lifestyle stressors. These nuances contribute to difficulties in identification of participants for the trial.

> *. . . the diagnosis of bipolar disorder which is not completely well established and in which case it would invariably affect the results of the study . . . historical diagnosis of bipolar disorder, but currently is presenting with features of an emotionally unstable personality disorder. There's often that overlap between certain conditions which blurs out the definite conviction that that particular patient definitely has bipolar disorder and therefore would be eligible for the study.*
>
> *HCP PI 2*

> *. . . a lot more going on than just depression. There are often psychological difficulties or interpersonal difficulties that are perpetuating the illness, making it trickier to treat. There can be social factors, poverty or other stressors or there's co-morbid substance misuse, etc that can make it more difficult to treat.*
>
> *HCP PI 0033*

Subsequent determination of treatment resistance poses further challenges in clinical practice. For instance, HCPs appeared to struggle with establishing TRBD when they felt patient refusal of psychotropics was not due to fundamental clinical intolerability.

> *. . . may be that it's a young girl and she's refused to try olanzapine because she doesn't want to gain weight . . . then she's tried one other one and it's not worked and therefore, you know, she's eligible but is she truly bipolar resistant depression?*
>
> *HCP Researcher 7*

The exclusion criteria included comorbid substance misuse and impulse control issues. HCPs highlighted that such comorbidities were prevalent among the bipolar patient group; they felt this narrowed the pool of eligible participants and decreased ecological validity.

> *I mean, most of our patients are on drugs and alcohol . . . cutting away huge swathes of potential patients to make it as clinically clean as possible. But in the end it doesn't reflect what is actually happening.*
>
> *HCP Researcher 8*

In PAX-BD, this multifaceted and complex profile of TRBD increased the burden on study PIs who acquired responsibility for patients they were not familiar with in clinical care.

> *[PI] didn't have a background knowledge of them, which made it a lot harder . . . it's very much on us to try to figure that out and figure out what they need . . . client group is a very complex client group.*
>
> *HCP Researcher 9*

Patient presentation at recruitment

Transcript analysis suggested an interplay between previous treatment failures and chronicity of BD, which appeared to yield a sense of desperation for active treatment. This made it difficult to accept the possibility of placebo, which was viewed as the antithesis to hope and recovery. The accounts were mainly reported by HCPs, given many of these patients did not consent to partake in the study.

> *. . . suffering so much from his mental illness that he couldn't bear the idea of being on a placebo, because he didn't feel it would give him enough hope.*
>
> *HCP PI 4*

> *'I just feel so awful. I couldn't bear the thought I get the placebo and then I'm not in- I feel this awful for this much longer'. It just wasn't worth the risk.*
>
> *HCP Researcher 6*

Participants were required to be in a current mood episode, contingent on the periodic nature of BD.

> *. . . sent an email to us being, like, 'Yes, I am bipolar, experiencing depression at the moment'. Then by the time we get back to them . . . weren't even in a mood episode anymore . . . their enthusiasm for interest had gone at that point.*
>
> *HCP Researcher 5*

There were instances in pre randomisation where participants became ineligible for progression to randomisation, perhaps due to the cyclical nature of bipolar disorder.

> *. . . cycling quite quickly between them and therefore not eligible.*
>
> *HCP Researcher 7*

> *. . . according to her scores she was doing better. So she wouldn't have made it on to Stage 2 (randomisation) . . .*
>
> *HCP Researcher 10*

The impact of depressive symptoms and side effects of medication were recognised as barriers to patients' capacity to process trial material. Digesting the vast amount of study information required a great deal of concentration and retaining this was demanding on impeded memory.

> *I was a bit overwhelmed, and it seemed to be involved a lot, but that's because of being depressed so everything does.*
>
> *Participant W12 < 1*

> *. . . really, really bad memory problems, since I started taking lithium mainly.*
>
> *Participant W12 > 2*

> *. . . given the nature of their diagnosis as well, it's hard if they're not stable or in a good place with their mental health to get them to sit down and actually take the information . . .*
>
> *HCP Researcher 10*

Similarly, poor motivation could also lead to difficulties completing study activities and engagement with HCPs.

> *. . . a couple of months in or so, as my motivation dipped, when my mood went low, I did struggle a bit with the motivation.*
>
> *Participant W12 > 6*

> *A couple of our participants don't engage well with the RAs or myself, and that is just a part of their presentation, low mood, potentially quite a chaotic lifestyle . . . another participant who just, their mood was so low it was just really, really difficult, again, to get much engagement from them.*
>
> *HCP Researcher 4*

Overall, recruiting patients from the TRBD cohort posed complex clinical challenges in considerations of eligibility and ability to safely participate in the PAX-BD trial.

> *A good example being on paper it might seem that they would be eligible based on their symptoms and their actual history, treatment [regimes 0:06:31] . . . but in practice there is a big difference . . . so the diagnostic clarity, engagement and then also perhaps unwillingness from certain service users, or maybe comorbid drugs and alcohol, or even risk because they would be expected to manage medication on their own for quite some time. All of these would be mitigating factors, so I think as a recruiter I would have to bear in mind all of those limitations to people suggesting somebody to the study . . . we're looking at a 52-week period. It's a very long time . . .*
>
> *HCP PI 2*

Determining causality of adverse events

During the randomisation stage, it was difficult to ascertain the causality of AEs due to similarities between common side effects of pramipexole and psychotropic concomitant medications, as well as bipolar symptoms of hypomania, mania and impulse control. The subsequent management of AEs was thereby also challenging, as it was unclear which medication doses should be adjusted.

> *I had quite a bad tremor, which I sometimes get with my lithium, so I did not know whether that was one or the other.*
>
> *Participant W12 > 2*

> *. . . quite problematic because they are on a lot of medication anyway, and it is just aggregating what might be the study medication.*
>
> *HCP Researcher 3*

> *. . . a very long list of the possible side effects. The problem is, most of them are things that I would normally experience as part of bipolar without medication. So it is hard to say, 'Well, is it the medication that is doing that or is it just the bipolar?'*
>
> *Participant W12 > 7*

Presenting the trial to participants

This subtheme presents an account of the barriers to trial promotion, as well as site factors impacting availability of resources for recruitment and retention of study participants.

Impact of COVID-19 on services

COVID-19 posed significant challenges to the PAX-BD trial whereby sites paused for recruitment until suitable amendments were approved. Although many trial activities were conducted remotely, sites were required to obtain consent in-person while adhering to strict guidelines around face-to-face contact.

> *It was just an extra barrier when we did that at their baseline consent, because obviously, we were in full PPE. They were limited, in our hospital, that you were only allowed two per room, which meant I was just having to wait in a waiting area for [PI] to do his part, for me to then conduct the pregnancy test, in another area.*
>
> *HCP Researcher 9*

It was particularly difficult to access teams and patients for opportunistic promotion and networking; research staff were actively advised against contacting clinical services.

> *It's like a research clinic or just things where you're there and you're speaking to patients and you're speaking to consultants. You're going to meetings. You're having that opportunity to talk to people rather than just relying on emails all the time . . . Just something that makes it more clinical in forefront of clinical practice rather than sat at the back of an email . . . we were told to, unless you really needed to contact clinical teams, to leave them alone.*
>
> *HCP Researcher 6*

> *COVID has changed everything, you don't do anything face-to-face. So, even MDT meetings were still done over Teams, and remotely, and stuff like that. Otherwise, you could pop over to the team and say, 'Hello, and everything'. But I feel like there's nothing else that you could have done because it's to do with networking.*
>
> *HCP Researcher 11*

After restrictions became more lenient, there was a lengthy adjustment period post pandemic; research prioritisation was even lower due to greater clinical responsibilities, redeployed staff, service pressures and ongoing local restrictions on building capacity. Overall, HCPs widely expressed the view that recruitment would have been more successful if not for the COVID-19 pandemic.

> *It's been very disruptive . . . during the real height of it there was really no ability to make any headway with any of the clinicians in our team . . . we've had- well, to roll back a step . . .*
>
> *HCP Researcher 5*

> *I think it's harder because of COVID and stuff, I think that probably impacted things. I get this feeling that staff want to help, but they're so busy that it's too hard for them to commit and to hold it in mind all the time . . . if we took the pandemic out of it, I think it could have gone better.*
>
> *HCP Researcher 6*

Some HCPs felt they would have benefited from in-person training, and others struggled to fulfil trial-related administrative duties due to restricted office access.

> *There is something about a practical application of learning or a face, which obviously we couldn't do because of COVID. There is something around that and a bit more of an interactive way of learning that, I think, would have helped me.*
>
> *HCP Researcher 6*

> *. . . we had limited access to our office, where our site files are kept. Keeping on top of that was quite difficult . . . just myself and another researcher, and we were, basically, allowed one hour in the office – that was it . . . really trying to keep sure that we're updating all of our study documents, and that they're the right versions, and that we're filing them, and that everything's where it should be. That became quite hard to manage with just an hour's slot.*
>
> *HCP Researcher 9*

Considering the wider impact of COVID-19 on mental health, staff observed that patients had become solitary and resistant to engagement, reducing scope for trial promotion. Additionally, patients referred to secondary care were described as more severe and therefore ineligible for the study.

> *. . . post COVID, I think everyone's outlook has changed. They are very much more recluse and don't want to come out or speak to people.*
>
> *HCP Researcher 10*

> *. . . threshold of who they're accepting onto the caseload [in NHS services is 00:06:11] is higher so therefore not necessarily suitable for the study.*
>
> *HCP Researcher 7*

Research prioritisation

Some PIs reported use of personal time for conducting research suggesting a workplace ethos that research is not a routine activity integrated into clinical care.

> *. . . only time I've got to do research is within my spare time, which is also taken up with other things such as training, teaching and personal development . . . doesn't leave out much time really for me to dedicate to research, which I think does take a fair bit of time . . .*
>
> *HCP PI 2*

Healthcare professionals employed at these sites reported limited recruitment and research experience, citing lack of staff capacity, resources and networks with clinical services as barriers to research involvement. They described PAX-BD as a sharp learning curve. Compared to research-active sites, they were not primed for trial promotion and had the added burden of establishing links with care services, and subsequently endorsing the study to clinical teams who were not inclined to accommodate research.

> *. . . everybody across the NHS is so busy and so stretched, and to ask anybody else, any other professionals, to stop and think about a study for which they are not invested in, and to hold that in their mind when they are thinking about their patients and talking to their patients, is very difficult.*
>
> *HCP PI 1*

> *. . . having to go through pre-screening and then going through care coordinators who are extremely busy . . . it's just because they're so busy and research isn't the forefront of what they're trying to do . . .*
>
> *HCP Researcher 10*

Overall, PIs reported that involvement in PAX-BD required consistent clinical input, which was challenging to provide without protected time and adequate research infrastructure. Reflecting on the trial, they stated they would reconsider involvement in research, particularly later in their careers due to mounting clinical pressures.

> *. . . adjusting to my new role itself has been rather challenging. I think freeing up some time to be fully engaged in the research is rather limited and sometimes even is opportunistic given the other commitments that I'm actually partaking into. I would say, yes, it's been a bit difficult with regards to availability. I think in the future, unless I'm actually able to have a bit more time, I perhaps wouldn't be able to take part in any further studies because of that . . .*
>
> *HCP PI 2*

> *. . . helpful research development unit is essential . . . later on in my career, if I wanted to do clinical research, I would need to get funding for a programmed activity as part of my job plan, and I know that could be a difficulty.*
>
> *HCP PI 4*

Trial promotion strategies

Non-medical staff across sites emphasised the importance of engaging clinicians to gain access to eligible participants. This was challenging due to the limited availability of PIs, which shifted the burden of marketing and recruitment to CSOs. They reported that clinicians were less receptive to promotion from non-clinical colleagues; therefore, peer-to-peer trial endorsement was critical in imbuing credibility, especially in relation to a CTIMP.

> *Trying to promote a medication trial when you are not a doctor is really challenging, and not necessarily appropriate . . . that promotion of the study shouldn't be left with the CSOs.*
>
> *HCP Researcher 4*

Overall, HCPs described the approach to recruitment as proactive and were perplexed when these attempts did not produce more referrals. The trial protocol was amended frequently to provide greater flexibility and sites indicated that strategies for trial promotion and patient screening had been exhausted. For instance, some sites took the initiative to organise presentations for colleagues, scoured patient databases and utilised patient groups such as Bipolar UK to access large cohorts; all were left uncertain about why such strategies were unsuccessful.

> *. . . we've had 2 or 3 people who presented the research at postgraduate meetings and such like, that hasn't translated into recruits as far as we know . . .*
>
> *HCP PI 1*

> *. . . change in the protocol to include people who are on antipsychotic medication . . . I'm not sure it has made a difference to recruitment . . .*
>
> *HCP Researcher 3*

> *Difficult to say exactly why some people might not be interested in research . . . many don't reply at all . . . enthusiasm for interest had gone at that point, for whatever reason . . . if they're not engaging at all, we've not really got any knowledge as to why . . . somewhere the size of London, and the Trust is, not blowing our own trumpets, but our Trust is well-established . . . no good reason that we would struggle to recruit at all. It's just been bafflingly thin on the ground . . . I'm at a bit of a loss.*
>
> *HCP Researcher 5*

> *I think we've screened and reviewed case notes for probably 400 people, if not more . . . lots of layers of barriers . . .*
>
> *HCP Researcher 7*

Access to eligible patients

Logistical issues in the care pathway structure were widely noted by HCPs who believed that patients with BD were largely under primary care, despite the nature of treatment resistance necessitating management under a community mental health team.

> *. . . one always senses that there are lots of patients who meet criteria but for whom we don't engage, and who never know about or think about taking part in a study . . . are in primary rather than secondary care . . . that would be interested in being part of the study, and who benefit from being in the study, that we just simply don't have access to . . .*
>
> *HCP PI 1*

Healthcare professionals stated this may be due to higher thresholds for referral in secondary care, whereby patients are often referred for manic or psychotic symptoms rather than mood episodes which have relatively less visibility. This also meant many patients on their caseloads did not meet the eligibility requirements for a current episode of depression and absence of mania and/or psychosis.

> *When people with bipolar come in contact with mental health services they are, more often than not, in a manic or mixed phase of their illness . . . depressive phase of the illness often happens in the background and patients don't cause as many difficulties for others, so therefore don't come to the attention of services.*
>
> *HCP PI 4*

> *I suspect a lot of people with that, the bipolar disorder, depression who, maybe their symptoms aren't as active, they are more settled and in remission, I suspect a lot of those people are actually in primary care rather than within a community mental health team.*
>
> *HCP Researcher 3*

> *. . . they're sitting quietly with their depression, it's not urgent that they need secondary care support . . . people that are in that limbo where they are really, in terms of their depression, too unwell to be in primary care but because our threshold, unfortunately, is so high because of all the pressures . . .*
>
> *HCP Researcher 7*

Healthcare professionals used patient databases and case notes for pre-screening but noted a lack of informative detail which did not confirm or refute eligibility criteria. This may have resulted in excluding patients who were eligible.

> *I think that there are lots of people that we just don't know meet inclusion criteria because they are- and we don't know that because our searches of the notes are blunt and don't tell us, and our relationships with clinicians looking after people don't always reveal the answers, and we don't have sufficient direct contact with those patients who might be eligible.*
>
> *HCP PI 1*

Clinical Studies Officers additionally encountered gatekeeping of clinical caseloads; clinicians and care co-ordinators were found to lack the availability to engage, be sceptical of research with the view of involvement as time consuming and burdensome, and/or non-responsive all together. At times, research staff would be redirected to multiple personnel due to high staff turnover within clinical services. There was a sense that research teams had utilised all resources within secondary care and the onus was also on clinical teams to engage. Ultimately, CSOs focused screening to the

caseloads of PIs who were already involved in the trial and with whom they had an existing working relationship. The pool of prospective patients was consequently narrowed, and the scope for professional development across the site was also limited.

> *. . . some clinicians are a little bit more protective over their patients than others . . . 'This person is not suitable. This person is not suitable'. . . . others would just not get back to you until like, I think, a month afterwards . . . I just left it. I got the message.*
>
> *HCP Researcher 11*

> *The barriers really were from staff . . . you wouldn't get any replies . . . a lot of psychiatric staff are still quite kind of suspicious of research.*
>
> *HCP Researcher 8*

> *. . . we can't just contact patients directly . . . Obviously because they're kind of linked in, they could maybe speak to the patients themselves, but that just wasn't really happening . . . we just were not getting any replies . . . barrier of the care coordinators, them not responding . . . left to the research team to push . . . at the end of the day . . . it lies with the clinic team.*
>
> *HCP Researcher 10*

Some sites reported failure to re-screen/re-promote the trial to patients who had previously been excluded/refused based on protocol guidelines that had since been amended. For instance, a participant withdrew in pre randomisation due to challenges commencing mood stabilisers and other patients cited medication adjustments as reason for refusal. These patients were not reapproached after revisions to the eligibility criteria, despite otherwise expressing interest in participation.

> *We didn't want to go back to them, because they'd already refused the study, even though the protocol had changed towards the end . . .*
>
> *HCP Researcher 9*

> *PI has decided that wouldn't really be in her best interest, because it was so difficult for her on stage one . . . were we to invite her back and it again not be successful, that would be upsetting for her . . .*
>
> *HCP Researcher 4*

The term 'Treatment resistance'

One patient stated that learning about the 'treatment-resistant' label was surprising, indicating this may have been a somewhat confronting experience. Given the nihilistic overtones of the term and potential stigmatic connotations, there are grounds for rethinking use of the label in patient-facing documents and clinic discussions, for example to 'difficult to treat bipolar depression', mirroring the use of this phraseology in major depressive disorder.[110]

> *. . . happy to be put forward, but it was a bit of a surprise that she felt that I was treatment resistant, I think she said . . . because no one had said it before. Although, I say it came as a surprise. It just confirmed what I felt I already knew.*
>
> *Participant W12 > 5*

Treatment failures prior to the trial appeared to contribute to scepticism about the efficacy of pramipexole, which may have impacted the time taken to consider the trial, particularly given the high level of engagement required from participants. During the trial, a lack of treatment response may have been taken as confirmation and exacerbated hopelessness.

> *. . . nothing worked, to be honest, I did not think that anything would.*
>
> *Participant W12 > 7*

> *I was a bit sceptical to start with . . . I did not know whether it would do any good. At the moment I am still not sure . . .*
>
> *Participant W12 > 8*

Conversely, one HCP believed patient cost–benefit appraisals did not swing in favour of participation for those who did not concretely identify with the perception that they had exhausted all treatment options.

> *. . . people, that haven't been in services so long, or haven't tried everything, approaching them, it's just very different. Because, I suppose maybe their hope is still that there is still lots of other treatments that might help them. The cons don't outweigh the positives . . .*
>
> *HCP Researcher 6*

Uncertainty about research

The profile of research was raised in public consciousness because of the COVID-19 pandemic; discourse and debate around vaccine trials in mainstream media and social settings may have contributed to patient concerns about investigational trials. Some patients were cautious of partaking in PAX-BD due to the view that research is experimental with unknown drug characteristics and potentially harmful side effects.

> *I think it was, they weren't sure if it was a new drug or if it was one that- Because we've had all the stuff with the vaccines recently and things like that, 'Is this something that we know anything about?'*
>
> *HCP Researcher 6*

> *. . . read things and watched things before about people taking research medication, that has really scared us . . .*
>
> *Participant W12 > 2*

> *I think the whole stigma of research itself . . . just because it's a research trial, they just didn't really want to come straight onto it . . . it's a clinical drug trial, people have that stigma to think, 'Oh, no. I don't want to be as part of a research guinea pig'*
>
> *HCP Researcher 11*

Patients without prior involvement or knowledge of trials expressed general apprehension, particularly around the RCT design. For these patients, learning about the placebo arm was surprising and this was a major consideration in the decision to participate, as discussed under the 'Treatment Profile' subtheme.

> *I have never done anything like this, no, so it was completely new . . .*
>
> *Participant W12 > 2*

> *I didn't realise at the beginning what it meant, the trial, because I could be on a placebo. So, when I heard that, I thought, 'Well, what's the point of doing something?'*
>
> *Participant W12 > 1*

> *. . . these are quite new ideas to some of our patients. This particular man that I was attempting to consent hadn't thought about that at all. I even put to him that there were patients with terminal cancer diagnoses that are entered into placebo-controlled trials, and he was shocked to find out that happened. It is a relatively new concept for patients.*
>
> *HCP PI 4*

Relationship with care team

A patient with a negative view of their care team declined the opportunity for participation. The prospect of closer monitoring by the research team highlighted frustrations around the lack of sufficient support from their clinical team.

> *. . . felt that she would have a lot of contact from the research team, which wasn't in itself a problem. But because she wasn't getting the contact from her care team . . . that made her really angry and resentful . . .*
>
> *HCP Researcher 4*

During the study, some patient participants reported a lack of direct involvement from their local site teams. This was particularly challenging when they felt they required one-to-one clinical support, or struggled to manage the accumulating tablets from previous dispensings due to delayed or missed collections from site. COVID-19 may have

contributed to the lack of capacity for face-to-face visits and staff availability. Overall, patient views of their local team influenced their general level of satisfaction, perception of support and ability to carry out study activities with ease.

> *. . . my care got transferred over . . . because I moved part way through the study, and I've not really known who I need to contact. I found that a bit more difficult . . .*
>
> *Participant W12 > 5*

> *Another thing was there was a lot of input from the research assistant side of things, but there was less contact from the study doctors, from my team. So I did think there may possibly have been a bit more contact on that side.*
>
> *Participant W12 > 6*

> *. . . the only person who I have got the number of is my research assistant . . . The medication people who collect it, I have got three bags of it sitting in my cupboard, and I have no idea when they are going to come and pick it up.*
>
> *Participant W12 > 7*

> *. . . they've all gone down with COVID so obviously we've had no communication apart from phone calls.*
>
> *Participant W12 > 10*

Trial material

Some participants highlighted the complexity and amount of trial material they received; the documents were described as difficult to process and retain, often requiring multiple reads and the help of another person to break it down.

> *I have to get somebody else to read it and then tell me because I do not always retain information very well.*
>
> *Participant W12 > 2*

> *. . . reading through the information sheet, it was a lot to take in . . . a case of going over it a couple of times, and now I understand it okay . . .*
>
> *Participant W12 > 6*

> *I think it could be challenging for some people . . . I don't know about easy. As long as I concentrated, it was alright . . . you do have to think about it . . .*
>
> *Participant W12 > 1*

> *I did find it a little bit difficult. There just seemed a lot at once, sometimes, at the very beginning of the trial.*
>
> *Participant W12 > 3*

Participants expressed that processing this large amount of material felt overwhelming, particularly at the beginning of the trial when the influx of information was greatest. Some admitted that rather than refer to the information sheet, they instead relied on conversations with HCPs for understanding and clarifications. This suggests added burden on staff time, as the intricacy of the trial required multiple in-depth conversations and patient visits. For instance, some patients were alarmed by references to hospitals.

> *. . . they do get given quite a lot of written information first, must admit they don't tend to read it . . .*
>
> *HCP PI 4*

> *In the patient information sheet it says about, 'You need to go into hospital for these tests', or 'You need to go into hospital for this'. It means going to a community mental health unit, it's not like going into hospital and staying in hospital. But yes, the two people I consented both asked, 'What does this mean?' . . . 'Why does it say I need to go into hospital then? What are these tests? Do I need to stay overnight?' . . . I think that's more of the term, hospital, was probably a bit misleading for them. It was more around the information and how it's put in the patient information sheet. They're very accurate, you need to go into a hospital or centre to . . . Technically it is a test . . . I think it's just that thing of just taking that time and explaining . . .*
>
> *HCP Researcher 6*

The exclusion criteria for active substance misuse, impulse control issues, mania and psychotic symptoms were additionally outlined in patient information sheets; however, patient participants expressed hesitation due to historical challenges which indicated that the document was somewhat unclear.

> *. . . in the information that is given it said not to take part if you've had addiction problems and addiction, you know, involved in sex in an inappropriate way, both of which I've had.*
>
> *Participant W12 < 1*

One participant who was retained beyond week 12 stated there were existing gaps in their knowledge of trial processes due to the density of study information.

> *It seemed like a lot of information to take in. And if I was quizzed on it, I probably will struggle to answer everything . . .*
>
> *Participant W12 > 7*

Treatment profile

This subtheme relates to preferences for the active drug, concerns about medication changes and the profile of pramipexole in the context of risk to patient well-being. The findings indicated that risk–benefit analyses for referral, participation and continuation in the trial largely centred on the barriers identified in this section.

Clinician attitudes

Clinical Studies Officers noted that sceptical clinicians viewed research as detrimental and/or disruptive to patients' mental health, thereby withholding access out of desire to protect the vulnerable patient. It appeared they were swift to cite ineligibility despite lack of familiarity with PAX-BD and without meticulous screening against the full criteria.

> *I think that there are lots of people who hold the view that it is not actually good for patients to be part of research . . . it can destabilise them . . .*
>
> *HCP PI 1*

> *. . . some clinicians are a little bit more protective over their patients than others . . . were like "This person is not suitable. This person is not suitable'. . . . just saying, 'No, no, no, no, no'. . . . kept saying, 'This person is not eligible. This person is not eligible'.*
>
> *HCP Researcher 11*

One PI expressed general anxiety about the experimental nature of pramipexole for the treatment of BD, perhaps compounded by lack of prior experience prescribing or managing patients on the drug. During the trial, these challenges arose when they were required to assess the causality, expectedness and relatedness of AEs. They stated it was difficult to act in the best interest of their patients or resolve issues quickly, requiring them to first seek guidance from external resources.

> *. . . we do get reports of certain effects which I'm not very familiar with to be honest . . . difficult to actually provide advice . . . it's a bit of an anxiety. I wouldn't discount that, as a clinician, that it is a new medication. We don't know very much about it . . . that anxiety does perhaps pick up a bit when some people report side effects and we don't know whether it's actually part of the trial medication or not.*
>
> *HCP PI 2*

Medication changes in pre randomisation

Prior to the amendment allowing use of antipsychotics in the randomisation stage, there was a reluctance to withdraw antipsychotics due to the possibility of destabilising patients and triggering relapse of manic or psychotic symptoms.

> *. . . as part of their bipolar disorder there have been distinct features of psychosis, which have been severe in the past. I've been rather reluctant to get them off psychotic medications . . .*
>
> *HCP PI 2*

> . . . clinicians themselves did say, 'Actually, it's not safe for them to go any lower on this particular dose'.
>
> *HCP Researcher 11*

> *I've tended perhaps to select people . . . where the risk, for example, of developing psychosis wasn't really a major risk, or people who aren't massively impulsive. I tended to maybe go more for those when I was thinking about participants for the trial.*
>
> *HCP PI 3*

Healthcare professionals reported many patient refusals due to the requirement to withdraw antipsychotics; thus, the fear of deterioration was shared by patients as well as their clinicians.

> *. . . reluctant to come off their anti-psychotics because they were aware of previous relapses . . . reluctance for patients that are on doses higher than the maximum doses . . .*
>
> *HCP PI 4*

> *I was concerned about reducing the aripiprazole . . .*
>
> *Participant W12 > 5*

> *[T]hey weren't happy to change medication . . . they were interested and wanted to try the study, it was just a decision they weren't happy to make . . . That was the main thing that put them off in the very early stages . . .*
>
> *HCP Researcher 9*

Patient views suggested that those who were required to make changes to existing medication were likely to express stronger concerns about placebo. This may indicate patients felt withdrawing medication to take a placebo would amount to less help, stagnate recovery at best or result in relapse at worst given their mood was already low on the existing treatment regime. Placebo-specific concerns are discussed in the next subsection.

> *. . . they've got a change in medications, and waiting between one to two [Stage 1 pre-randomisation to Stage 2 randomisation], it is quite a long time.*
>
> *HCP Researcher 11*

> *I was most worried about, which was that my condition would get worse, or not better . . .*
>
> *Participant W12 > 1*

> *'Will I be able to stay on my current medication? If I'm allocated to the placebo arm', . . . 'I'm worried that I'm not going to be taking anything, right? If I'm not allowed to take my current medication, if I have to stop that to come on the trial, I'm worried that, yes, I won't be taking anything . . . '*
>
> *HCP Researcher 7*

The obligation to commence a mood stabiliser was challenging for patients who had experienced intolerable side effects in the past and/or felt they had been ineffective. For these participants, the requirement may have felt arbitrary. Issues were observed in the pre-randomisation stage whereby adjusting to new medication was challenging for patients and failures were demoralising. Medication changes also extended the 4-week minimum spent in pre-randomisation, thereby further delaying the start of treatment and extending the overall length of the study. Patients expressed uncertainty about whether these efforts to change medication would yield treatment benefits if they were randomised to placebo or had no response to pramipexole. One participant persisted with changes for 52 weeks in pre-randomisation attempting to stabilise on medication. They were ultimately withdrawn.

> *. . . some side effects that people may not want to tolerate just don't want to go there, might have some sensitivities . . . one of our participants really, really wanted to go on to stage two, she couldn't tolerate another mood stabiliser. She kept having a skin reaction to everything.*
>
> *HCP Researcher 4*

I think people do, then, become a bit more like, 'Is it worth the effort to mess all this around, is it going to be worth it?'
HCP Researcher 7

. . . something that's come up with every person we've had through that making it very clear that you won't start the medication straightaway. Because that one, 'When will I start the medication? When will I start the medication?' Saying, 'It won't be straightaway. We need to make sure everything is okay first'. Saying, 'You will be in this period first'. You could feel that, for people, was quite difficult. Maybe borderline disappointing for them that it wasn't going to start straightaway.
HCP Researcher 6

It did make the recruitment slow because they would only count as an [occural 0:11:49] once they had reached stage two.
HCP Researcher 11

Placebo

The possibility of being randomised to placebo appeared to give many patients pause when considering participation in PAX-BD. HCPs reported that although patients expressed initial interest in the trial, they strongly reconsidered when presented with this information. In overall cost–benefit appraisals of participation, patients seemed to perceive randomisation to placebo as a risk factor. This seemed to be largely influenced by debilitating mood episodes discussed in 'Expressions of Symptomatology' which fostered a desperation for effective treatment, that is the active drug.

I felt like I really needed help there and then . . . That was very discouraging . . . I could be sitting around for months on this placebo, not getting any better, not getting any help . . . I did think about it for a while because of that . . . I had to get my head around that . . .
Participant W12 > 1

. . . people who think, 'Oh, I'm going into a study to get medication', and then you say, 'Well, actually, you might end up on placebo', and it is like, 'Oh, really? Right, okay'. They are not saying, 'No', but you can see maybe they are thinking about what that might mean for them.
HCP Researcher 3

We've had at least one person who has dropped out of stage one . . . they did change their mind because they didn't want to risk being on a placebo medication . . . another person who didn't come into the trial for that reason . . . didn't want to take that risk.
HCP Researcher 4

I think with this one, it is a big ask of people . . . the risks that they're not going to get the Pramipexole, there is definitely awareness there . . . it has put other people off. One person, we got the permission to approach, but they didn't even want a patient information sheet or anything.
HCP Researcher 6

The resistance to placebo appeared to be exacerbated by the length of the study, whereby the prospect of completing study activities over the span of 48-weeks to discover they were taking a placebo would feel as though their time and effort had been squandered.

. . . taking medication that you don't need for 12 months, and doing all those, what word am I looking for? [RA] would ring me every Friday, loads of questions and that on how I felt, so that was the only drawback. If I had been under proper med, then I would have been more hopeful that I might feel a bit better afterwards . . .
Participant W12 > 9

Pramipexole

Healthcare professionals expressed major concerns about impulsivity and mania as potential side effects of pramipexole in bipolar patients. For some clinicians, this was compounded by the view that they could not intervene per usual clinical care due to restrictions in the first 12 weeks of the study. Hence, a risk-averse approach was employed with patients perceived to be more vulnerable but not definitively ineligible.

> *. . . difficulty with the PAX study is the side effects . . . Put my depressed bipolar patient on something that might make them manic as a side effect is concerning . . .*
>
> *HCP Researcher 4*

> *. . . worry about becoming more unstable on the medicines or gambling issues . . . I've tended perhaps to select people who are more on the bipolar spectrum, where the risk, for example, of developing psychosis wasn't really a major risk, or people who aren't massively impulsive. I tended to maybe go more for those when I was thinking about participants for the trial . . . anxieties about not being able to actively treat them . . . I think for this trial you couldn't really tweak their medicines for a number of weeks . . . not being able to precisely do what you would normally do in a particular situation, given that somebody is in the trial, is a barrier both for patients and for clinicians.*
>
> *HCP PI 3*

These worries were echoed in patient interviews; they were fearful of the possibility of triggering mania and *International Classification of Diseases* (ICDs), relapse and general deterioration of their mental health. During the trial, AEs of mania and impulsivity mainly occurred in the titration phase; as a result, some patients were not able to reach the maximum dose, and doses were adjusted multiple times throughout the trial to stabilise fluctuating manic and depressive states.

> *The only ones were the impulse-control disorders, which I had had [some misuse with 0:06:08] in the past . . . can cause symptoms such as depression and psychotic symptoms. There was a slight concern in terms of that . . . I started to have issues with the impulse control side of things . . .*
>
> *Participant W12 > 6*

> *. . . there is a chance that it will make you more hypomanic or manic, and people who have got a history with gambling or being sectioned . . . That is what I really worried about . . .*
>
> *Participant W12 > 7*

> *Twice, my doctor had to reduce the amount I was taking because it seemed like it was making the swings between the hypomania and depression worse, and that it was also bringing the mania out . . .*
>
> *Participant W12 > 7*

Concerns about general side effects and anxiety around trying new medication were present, particularly if patients had negative experiences with similar AEs or psychotropic medications in the past. One patient noted that mention of heart failure in the patient information sheet was specifically alarming. Two patients were apprehensive that severe side effects may also impact on their ability to work.

> *I obviously had some concerns about potential side effects . . . adversely affect my capability to work . . . I have had a number of side effects which have been of concern . . . I'm currently titrating down to come off the medication, because they have proved too significant to overcome . . .*
>
> *Participant W12 > 4*

> *. . . really scared of side effects of things. I had read through some of the side effects, and there was a few of them which really concerned us . . . apprehensive as to how I would be affected . . . heart one was the biggest one that I was concerned about . . . I get really bad side effects from things, but that sometimes messes with my mind . . . if I was going to throw the towel in I think that might have been the point, because the tremor was quite bad . . . I do feel quite foggy quite a lot of the time . . . it has been a little bit worse since I started doing the trial.*
>
> *Participant W12 > 2*

One CSO flagged discussions with women about the effect of pramipexole on pregnancy; the requirement to take contraception for the duration of the trial was a barrier.

> *I've had a couple of young ladies who are unsure and they want to have the option . . . some queries about pramipexole on pregnancy . . .*
>
> *HCP Researcher 7*

Patient participants also stated they reconsidered continuation in the trial due to either discomfort from side effects adversely impacting their mental health, or disappointment at the lack of treatment response and subsequent belief they were taking a placebo. When participants felt the burden of trial activities were not compensated by treatment benefits, HCPs noted the difficulty of retaining them over 48 weeks.

> *I was pretty disappointed, pretty . . . I was quite sad that I had to come off the course. It was something else I'd tried and hadn't worked basically.*
>
> *Participant W12 < 1*

> *It was a bit monotonous, to be honest, because I didn't feel there were any great changes . . . I did say, when I was actually still on it and I didn't feel that I was on the proper medication. I did say, 'I want to stop it'. . . . I didn't feel I was getting anything from it.*
>
> *Participant W12 > 9*

> *. . . a lot of side effects taking IMP, and he was struggling to cope . . . symptoms became too much for him to manage for the length of the study participation, so he withdrew . . . I don't really think he realised they could be that severe for him, and he just couldn't cope with them.*
>
> *HCP Researcher 9*

> *. . . length of the trial has been something that has come up…it is a long trial and that has been an issue for people . . .*
>
> *HCP PI 4*

Deterioration in mental health led to disengagement from study activities and safety monitoring for some affected participants, of which a proportion were later withdrawn. Others re-commenced antipsychotic medication in pre-randomisation to resolve mania and ICDs, which may have perpetuated a feeling that the initial time and burden was in vain. For other patients, intolerable side effects combined with a lack of significant treatment response resulted in withdrawal from study medication.

> *He stopped responding to the RA contacts. He stopped filling out the diary on the TrueColours, and he just gradually started to withdraw his attention and participation from the study before he'd made the decision to stop.*
>
> *HCP Researcher 9*

> *I did end up going back on that at a low dose . . . I do find I have difficulties when I am not on the aripiprazole.*
>
> *Participant W12 > 5*

View of trial processes and procedures

This subtheme considers challenges arising from the trial design and study processes which may have impeded recruitment and retention for HCPs conducting the study and patients completing trial activities.

Administrative duties

During the trial, HCPs reportedly found it difficult to keep abreast of the numerous protocol changes and maintain administrative files, particularly in line with pandemic guidelines. PIs struggled to complete research tasks within study timelines, especially when accounting for their restricted availability. These challenges resulted in deviations which also required timely reporting and resolution.

> *In regards to the understanding of the study, it's quite complex as well. I don't know, you've done research a lot longer than me, so you might be like, 'I've worked on much more complex ones'. But for me, there is quite a lot to get my head round . . . .*
>
> *HCP Researcher 6*

> *lot of protocol changes . . . that was a lot to keep on top of throughout the pandemic . . .*
>
> *HCP Researcher 9*

> *. . . quite difficult to remain organised and respond in a timely fashion to the number of adverse events and protocol deviations . . .*
>
> *HCP PI 4*

Eligibility criteria

Although reflective amendments were made to the eligibility criteria, some HCPs stated this did not significantly increase recruitment. HCPs thought this was in part, because the eligibility criteria were limiting and did not accurately represent the normative bipolar patient, thereby reducing a sample size which was already small by virtue of the condition. Criteria around comorbid conditions, manic and psychotic symptoms, and treatment resistance were repeatedly flagged as stringent and restrictive, rather than practical. For example, one HCP reported that patients were excluded on the basis that they had not trialled enough ineffective treatment, but may have benefited from participation, nonetheless. As noted previously, HCPs widely highlighted that the requirement to recruit from secondary care and adjust antipsychotics and/or mood stabilisers was a significant barrier to recruitment.

> *. . . patient group that we are targeting, it is a relatively small number of people . . . only looking for patients with a diagnosis of bipolar . . . other barriers to recruitment like the fact that they have to meet eligibility criteria for treatment resistance, which has often meant that again, it might be more appropriate for them to try a different treatment first . . . now that the protocol has changed to allow a certain dosage of anti-psychotic . . . there has still been some reluctance for patients that are on doses higher than the maximum doses, yes.*
>
> *HCP PI 4*

> *. . . presenting with their bipolar in terms of their mania and perhaps psychotic episodes rather than the depression side of things . . . excluding in terms of having renal problems or cardiovascular problems . . . more newly diagnosed people, either they've not had enough time to try multiple things so therefore they're not eligible.*
>
> *HCP Researcher 7*

> *. . . finding participants who were fully eligible was just difficult . . . a lot were almost eligible but one or two things . . . not having tried quite enough medications to counter-treat resistant . . . a huge portion of people with bipolar are on antipsychotics. That was tricky.*
>
> *HCP Researcher 5*

> *If somebody had given me the PAX-BD to study, to look at before the study started and said, 'Well, how do you think you are going to recruit to this?' I would have immediately said, 'Well, you are going to be cutting out 90% of bipolar patients straightway because of the antipsychotics exclusion and things like that'.*
>
> *HCP Researcher 8*

Patients were also reportedly eager to access talking therapy; however, this was outlined as a restriction for the duration of the trial. Although there was scope to reconsider this post 12 weeks, participants recounted this as a constraint, suggesting the flexibility was not explicitly highlighted or clarified. This may have been discouraging for patients who felt they would gain significant benefit and/or for those who had spent a considerable amount of time on extensive waiting lists for psychotherapy.

> *. . . she was quite keen to start some psychotherapy . . . one of the exclusion criteria for the trial is patients wanting to have psychotherapy.*
>
> *HCP PI 4*

> *I don't think I was supposed to start any counselling or anything like that either and interventions . . .*
>
> *Participant W12 > 5*

> *. . . not going down the route of, say, psychological treatment. So if that option did become available, you wouldn't be able to do it for at least a year.*
>
> *Participant W12 > 6*

Medication processes

Healthcare professionals indicated that the independent management of study medication was a risk factor for patients in remission from substance misuse and/or impulse control issues related to bipolar or as a side effect of pramipexole. HCPs expressed concerns about the capability of patients to independently manage study medication, particularly if they were in remission from substance misuse and/or experiencing impulse control issues related to bipolar disorder or as a side effect of pramipexole. In these cases, they appeared to regard the independent management of medication as a risk factor.

> *. . . maybe comorbid drugs and alcohol, or even risk because they would be expected to manage medication on their own for quite some time . . .*
>
> *HCP PI 2*

For participants in the trial, challenges were oriented around managing the large supplies of study medication. Findings indicate this was in part, due to the dispensing of up to 2 months of medication at a time, as well as start and end dates for batches which caused confusion. It was further difficult to organise batches if medication collections were delayed; some participants were unsatisfied with the infrequency of this, which led to a substantial accumulation of tablets and bottles. These collections were also burdensome on staff resources, particularly during and in the aftermath of the COVID-19 pandemic.

> *. . . we've had to do ad-hoc medication collections at week 13, because they end up with too much medication, and it leads to confusion.*
>
> *HCP Researcher 9*

> *. . . the hardest thing sometimes has been arranging for them to come and collect medication.*
>
> *Participant W12 > 2*

> *What was annoying is that they sent you out batches of medication . . . and you have to send it all back. You know, when week X starts you have to put that batch away and start a new one. So a couple of months ago, I lost one of the bottles, which was shipped to me . . . But then I had to go through all the different batches of medications that I did have, because they said, 'Well, here is a bottle, but you have to combine it with another one from that batch'. It is just too many batches to, you know, get right sometimes. I do not understand why it has to be done in batches . . . The medication people who collect it, I have got three bags of it sitting in my cupboard, and I have no idea when they are going to come and pick it up.*
>
> *Participant W12 > 7*

Participants also indicated they did not receive tracking information for packages directly, thereby missing deliveries and contacting central RAs to arrange redelivery at a more convenient time.

> *The medications, the only thing with that was I didn't receive the tracking. So I didn't actually know when they were due to arrive. The Royal Mail tracking wasn't working so they would just turn up, and if I hadn't been in at the time, I wouldn't have known when they were due. It would have been helpful to have had the tracking information.*
>
> *Participant W12 > 6*

Challenges in the 4-week titration phase were reported by participants who found the dosing schedule complex and struggled to keep up with 0.25 mg increments every 3 days. The amount of tablets required to make corresponding doses also changed, as participants were supplied with 1 mg and 0.25 mg tablets. Some elected to use their own dosette box, but this still required participants to work out the number of tablets needed for doses in the days ahead. This was particularly burdensome if doses deviated from the paper schedule due to changes advised by study PIs.

> *I found it really confusing, the medication, at first, if I am being honest. I found when it was increasing, on a weekly basis, I found it quite complicated . . . I had to get my daughter to put them in my box, because I was struggling because they were changing every three days. I used a Dosette box, so it was confusing us a little bit as to how many tablets I was having to put in each week.*
>
> *Participant W12 > 2*

> *. . . it's just the changes. It's just the changes. So, for example, you go- in the beginning, you take 1.25 tablets, and then you do that for a number of days, and then you build it up to two, and all that sort of thing. As long as you keep on the ball and follow the instructions, you're alright. But you do have to think about it. It's not like, oh, you just take one, and you know, one a day. So, you know, you do have to think about it.*
>
> *Participant W12 > 1*

Some participants' medication was managed by family members or supported-living staff. One patient reported receiving a dose three times higher for the first 5 days of titration, causing severe side effects such as nausea. They felt this confusion was due to the complexity of the trial and more support should have been provided to their partner.

> *My partner does my tablets. She got them mixed up. She was giving me three times as much as what I should have been having for the first five days . . . I just get the tablets. I don't check it. I just take them . . . Maybe a little bit more information for the first week. Because it's a trial and everything else, it had got my partner confused.*
>
> *Participant W12 > 10*

One patient participant described receiving contradicting information about medication from their clinician, compared to study resources and central RAs. These miscommunications added confusion on top of the existing complexity of titration.

> *. . . couple of things in terms of making changes to dosage where I got differing information from the documentation and yes, and from the researchers . . . perhaps the study was more focused on medication than individuals . . .*
>
> *Participant W12 > 4*

Safety monitoring

Remote trial monitoring in PAX-BD was a barrier for patients who were reportedly lacking computer literacy or access, fearful of technology and/or had anxieties around answering the telephone. HCPs stated this excluded some of their older patients who had not adopted the use of computer technology and would therefore struggle to navigate unfamiliar digital platforms. Although the central team provided workarounds for digital monitoring, many sites did not have the resources or capacity to accommodate them.

> *. . . participants who are either uncomfortable using the internet or don't have internet access at all . . . anxiety around answering the phone or using the phone.*
>
> *HCP Researcher 2*

> *I am one of those rare people who can't use a laptop really.*
>
> *Participant W12 < 1*

> *. . . a lot of the people within the community health team may be not as tech [sic] aware and socially media aware as maybe some younger people, people in the wider community . . . haven't adopted the use of things like smartphones, use of apps, the computer side of things . . . A lot of our people struggle with using things like Amazon, for example, ordering things off the internet, they find that is a challenge or paying bills is a challenge. We are asking people to use the TrueColours as an outcome measure, one of the outcome measures, and I think that may prove challenging for some of our customer base.*
>
> *HCP Researcher 3*

Central RAs observed that if participants experienced issues with the digital platform on first use, frustration developed at an early stage which meant they were likely to be less tolerant of continuing faults. RAs believed this negatively impacted the credibility of study processes and led to early disengagement with questionnaires. Technical issues later in the trial produced similar responses, but they were comparatively better received and less likely to cause disengagement.

> *I think the online system has had quite a lot of glitches. I think an online platform that asks people to fill it in, it's got to work, and it's got to work the first time. If it doesn't work the first time, then it causes issues, it causes frustration . . . People don't want to engage.*
>
> *HCP Researcher 1*

The user experience was impacted by issues logging in and responses failing to save after participants had spent up to an hour conscientiously filling in questionnaires. On other occasions, questionnaires would cease to work towards the end of completion and no prior progress was saved. One patient participant highlighted that although the platform was accessible on mobile, this was not optimised and often crashed. They relied on computer access which was inconvenient when they were frequently away from home. These issues shifted the burden to HCPs to provide digital assistance or complete questionnaires over the phone.

> *There was the odd time when there were issues with the system, so a couple of times I had spent quite a long time filling it in. Then I had lost everything because when I went back into the page, it wiped all the questionnaires . . . few little niggles with the system itself, so the TrueColours. So certain questionnaires, some of the questions, it wouldn't allow you to actually answer it. It was on one of the long ones, the work-related one. I can't remember the name of it, but there was [a certain 0:17:00] list of questions. One of the options, it just didn't let you select it, and it held you up then, trying to complete the questionnaire, so it just delayed matters. Then there were other just minor niggles with the questionnaires. Yes, I think that was the main issue, really.*
>
> *Participant W12 > 6*

> *It is easy to access and do it on your phone, but only if it has got three questionnaires. If it is four or sometimes seven, when they ask you to do how happy you are with the medication etc., that crashes and you cannot do it on your phone, you have to have access to a PC or laptop, which is annoying if you are away.*
>
> *Participant W12 > 7*

> *I have to, or have had to call them almost weekly . . .*
>
> *HCP Researcher 4*

Patient participants reported that the frequency and volume of questionnaires were time consuming, particularly during periods of poor mental health or stressful life events.

> *. . . sometimes, if you've had a very busy week, it's, 'Oh, no, not another one'. And then you find it's past Sunday, and you've missed the deadline . . . Sometimes there's extra ones, which take a bit longer.*
>
> *Participant W12 > 1*

> *At the start, I was quite well motivated, and then a couple of months in or so, as my motivation dipped- when my mood went low, I did struggle a bit with the motivation. Occasionally, you would forget that it was due- [at first 0:11:04], I would remember it was due on the Friday, and then it would come through by email, and then you would be, 'Oh, I have got to fill that in'.*
>
> *Participant W12 > 6*

> *. . . on a couple of occasions there were, I don't know, 7 or 8 questionnaires to fill in all at the same time, which was perhaps a bit much.*
>
> *Participant W12 > 4*

> *. . . once a month you have to fill out more questionnaires than the usual questionnaires, and you are like, 'Is this ever going to end?'*
>
> *Participant W12 > 3*

A few patient participants described challenges interpreting questions and corresponding responses, for instance, distinguishing items in the QUIP-RS due to the similarity and repetitiveness of the content. Some were also unsure about rating the severity of symptoms which they felt were caused by physical ailments rather than depression. Others

indicated that the questions did not feel representative of their experiences, stating their symptoms were somewhere in-between or not applicable on any given range of severity. These challenges caused concerns that their scores were inaccurate, representing their state as either too severe or in remission when they were struggling considerably. Uncertainties led patients to spend more time pondering responses, worrying about score interpretations by HCPs and under-utilising resources such as mood trajectory graphs.

> *There's one of them that I find difficult to do, because it's quite- it's not very clear what they're asking for, and I'm never quite sure about it . . . What happens is they ask you five questions, which are very similar . . . It's the impulsive-compulsive . . . I find that a really difficult one to do . . . to differentiate between them . . . the depressive one . . . in relation to the sleeping patterns, one of the questions asks if you get up during the night, and/or about your sleeping patterns. And both of them, I have, sort of, a negative response to. But it's because of my diabetes. Rather than anything to do with depression. But of course, it comes out as a depressive score. So, how you'll get round that, I don't know, but I know that is an anomaly.*
>
> *Participant W12 > 1*

> *I sometimes find the questions, sometimes I am a little bit in between. So I struggle sometimes to answer the questions as accurately as what you are probably looking for, because sometimes there is no in between in there . . . struggle because it is not one or the other . . . I do not want to look because I think maybe I am going to look worse than what they are . . .*
>
> *Participant W12 > 2*

> *. . . sometimes I really think that TrueColours is either not asking the right questions or asking some wrong questions. It would have also, kind of, been nice to have the vaguest idea of how it figures things out, because there were questions about insomnia . . . I think they basically make it sound like I am doing really well, which is not the case . . . insomnia for example. One of the questions is, when did you wake up? It says, 'I do not normally work off more than half an hour. I do not wake up more than . . .'' and then two hours. You see, I am so sleep deprived, and I sleep, maybe, every second day, at the moment, with [___ 0:11:52] medication, before it was every third day. So when I do manage to fall asleep there is no chance I am going to wake up, you know, a minute early than my alarm goes off. But I still have to say, 'Yes, no more than half an hour'. . . . Other question is, 'Do you wake up during the night?' 'No, in the three hours of sleep that I get I do not wake up in the middle of the night'. . . . it is not personalised to your experience. It is very standard, kind of, questions, isn't it, which can be difficult to answer . . . when it talks about depression, about feelings, there is one question, 'Do you feel sad?' I do not feel sad, I feel sad and lonely half the time. Well, sadness is not the only way for depression to manifest itself . . . expects you to feel something.*
>
> *Participant W12 > 7*

For one participant who had experienced a significant treatment response, the questionnaires seemed to feel monotonous and futile given how disparate the symptoms were to their mental state.

> *I get fed up of the same questions . . . How's your mood? Have you been manic? Are you feeling suicidal? I know you've got to turn around and be honest about these things, but at the moment things are alright.*
>
> *Participant W12 > 10*

Likewise, for some participants who experienced either a treatment response or no change, it seemed trial activities centred on low mood and mania also felt repetitive and uninteresting. Weekly calls were unappealing to some patients due to the frequency and intensity of this monitoring, particularly in concurrence with life factors such as work or moving home. Transcripts indicated that for some patient participants, the burden of the trial in terms of completing questionnaires and engaging will calls over a 48-week period were not equalised with the treatment benefits, or lack thereof.

> *I have struggled a little bit with some of the recording and things, and some of the monitoring. I was concerned about having to speak with someone every week for the last 12 weeks . . . I have had a bit of a blip in the middle . . . loads of events that happened in a short time . . . hard to make time to do the things for the trial.*
>
> *Participant W12 > 2*

> *. . . participants don't engage well with the RAs or myself, and that is just a part of their presentation, low mood, potentially quite a chaotic lifestyle . . . One I'm thinking of, she does engage enough that we feel that it is safe, but we have had to write to her before, and remind her, her responsibilities on the trial . . . actually, he was really resistant to phone calls initially. He wouldn't take the phone calls from the RAs . . .*
>
> *HCP Researcher 4*

> *Sometimes you get people who don't want to engage. They're just, 'No, I don't really want to engage. I want to be part of the study, but I don't want to engage'. That engagement is so important. If you're giving a medication like Pramipexole, it's important we keep an eye on them on a weekly basis. If they're not going to do that, that's something we've got to look at. It's part of the protocol, they must engage. They must engage with the RA's and must engage with TrueColours, the online platform.*
>
> *HCP Researcher 1*

Central RAs felt some sites could have been more proactive in emphasising the requirement to comply with monitoring activities during trial promotion, and reminding participants of their responsibilities throughout the trial.

> *Considering PAX-BD is a remote trial, both non-engagement and lack of internet access can make participant monitoring really difficult . . . sites could do a little bit more to emphasise the importance of engaging with those phone calls. So maybe from the participants point of view, they think it isn't really necessary, and so they don't respond . . . reiterating from the beginning to participants that one of the compulsory aspects of taking part in the study is engagement with the phone calls.*
>
> *HCP Researcher 2*

Healthcare professionals noted difficulties engaging participants, and the reliance on a remote design led to gaps in crucial safety monitoring which resulted in recommendations to withdraw participants if they did not re-engage. Overall, reasons for disengagement included low mood and lack of treatment response discussed in the context of other subthemes, as well as frustrations with the digital platforms and/or desire to access treatment without frequent follow-up.

Facilitators

Marketing

This subtheme recounts trial promotion strategies with consideration of underlying factors which facilitated successful marketing and subsequent participant recruitment.

Promoting to clinicians

The central research team regularly contacted sites about PAX-BD, which served as ongoing reminders and helped HCPs maintain recruitment goals at the forefront of their duties.

> *. . . you and your colleagues will get in touch with us to just jog our memories sometimes and say, 'Will you have a think and see if you've got anybody who's suitable? . . . So, there's a lot of contact . . . I find research teams incredibly helpful with information, with updates, with communication . . . the liaison part of it is extremely easy.*
>
> *HCP PI 3*

Chief Investigator involvement in promoting the trial was highlighted by HCPs who expressed the effectiveness of a credible expert outlining limitations in the treatment of BD and emphasising the subsequent salience of trial objectives. HCPs believed that this peer-to-peer promotion was critical in obtaining support from clinicians. The study CI was praised for suggesting useful recruitment strategies to sites, as well as providing 1 : 1 consultation on eligibility queries.

> *[CI] and the team, everywhere, where there is an audience, they've been to it and promoted the study and that. I think they have gone the extra mile . . . met with [CI] and the research team regularly, really since the point of recruitment and we've discussed several strategies.*
>
> *HCP Researcher 3*

. . . really, really helped that [CI] came to speak to the medics, rather than it is just me going around MDTs with a little flyer and people going, 'Oh, that nurse doesn't know anything about my medication'. They would be right, I don't . . . It just gives it more weight if it is a medic who is really pushing it and promoting it . . . It really needs to be medic led because it is the medics, it is the doctors that will say, 'Yes, I want to refer my patient', or, 'Yes, I will give them this information'. . . . presented by someone who knows what they are talking about . . .

HCP Researcher 4

That was brilliant. They are both brilliant speakers. You can watch them, can't you, and you stay engaged with them. To be fair, [CI delegate] would offer at one point, he said, 'If you want me to come to meetings and meet with clinicians and talk with them'. They've got a very good way of, almost, simplifying the study and talking about it in a way that interests people but doesn't overwhelm them.

HCP Researcher 6

I send a lot of eligibility queries to [CI] and he does come back within minutes. He's really on it . . . That is so helpful . . . We're not waiting days for a response as well.

HCP Researcher 7

Locally, PI networks seemed to be especially important in raising the profile of the trial. Their established integrity and existing relationships appeared to elicit more clinician engagement, particularly compared to non-medical staff. HCPs expressed the importance of having research-active clinicians embedded in treatment teams to broaden existing networks, obtain peer interest and access clinical meetings. These HCPs had the capacity to be proactive in utilising multidisciplinary meetings as opportunity to raise the profile of PAX-BD in a clinical context. This strategy was successful in engaging clinicians who referred their patients to the trial. PIs were additionally able to draw on their clinical experience to identify underutilised clinics and focus recruitment efforts there.

. . . our strategy in general has been very connections based. [PI delegate] has obviously been here for a long time, he knows pretty much everybody. If there's someone within the faculty that might be seeing relevant people for the study, then he probably knows them, or at least the team they work in . . . It has very much benefited from having both [PI 1] and [PI delegate] speaking to teams they know, and us reaching out to them, and doing mini presentations with them in MDTs, and before research meetings that they already have . . .

HCP Researcher 5

I have a lot of links with clinicians within this area, so as, I suppose, an ambassador to promote the study as well within the community mental health teams, where we always thought there might be some problems with recruitment . . . I've got a lot of connections, especially with community services in here, but also I've worked in the south of the trust as well, so I'm a friendly face to open a few doors really.

HCP Researcher 3

. . . our PI used to be in our trust for, I think, 20 odd years. So, that helped quite a lot that he knew and had relationships with a few of the clinicians around the trust who I did contact. So, if they didn't reply to me, I would just ask them, 'Can you get in contact with them and ask them if they can?' And so, that made it a bit easier.

HCP Researcher 11

. . . patients that we've identified have come through colleagues who have identified patients on their caseload, I think. The important thing there has been that clinical colleagues have engaged and thought about the study. I think that anything that helps that, helps recruitment . . . it is all about making links with people, who the research team don't have access to patients, there are other people who do. They need to be in the teams somehow . . . clinical research network delivery team more engaged with clinical teams, so being half time clinical, half time research . . . we've had 2 or 3 people who presented the research at postgraduate meetings and such like . . . it is an important thing to do both for the person who is doing the presenting because it makes them stop and think about the study a little bit more, and for the audience because it just raises the profile for them a little bit, and that is something that we will look to continue.

HCP PI 1

Research-active trusts had dedicated teams, and HCPs at such sites seemed better able to promote the trial due to established networks and sufficient resources. HCPs at less established research sites mitigated lack of prioritisation by proactively using special interest time for the trial. They also described adopting an assertive approach when clinician referrals were lacking; contacting patients directly expedited the rate of recruitment as it shifted the burden from busy care teams.

> *. . . being quite proactive has been helpful . . . if we come across somebody who appears to be eligible in the notes, we actually make first contact without speaking to their usual team. We send them a letter with an appointment for a telephone conversation, and then either myself or the other doctor working on PAX-BD then gives them a ring . . . once we've had that telephone call with them, we will tell them a little bit about the trial and express enthusiasm about it . . . then go to their team and ask if there are any concerns about the trial and that particular patient . . . I think that being quite proactive and making that first next step has been a really good thing, that has really improved recruitment for us . . . I use specialist interest time to run the study, and the other SpR that I work with uses specialist interest time as well.*
>
> *HCP PI 4*

> *We also, with permission, I've done several letters now to service users who aren't on my caseload, but I've had permission from clinicians to write to them to say, 'We are running this study. Would you be interested in taking part in the study?' But the letter appears to come from either the CPN or the doctor involved, but it is me that is writing it really . . .*
>
> *HCP Researcher 3*

An additional appeal of PAX-BD was the opportunity for professional development from upskilling research and clinical competencies. This was gained through GCP training, use of the MINI as an assessment tool and experience in the management of complex bipolar depressed patients on pramipexole.

> *. . . to be part of such a big study is very satisfying and it's actually given me an appreciation of what actually goes into the ins and outs of the design and the journey that participants actually take from being identified to successfully completing the trial.*
>
> *HCP PI 2*

> *. . . learn a little bit about how clinical research is carried out, how patients are screened and recruited, and using qualitative, not qualitative, objective interviews to assess eligibility is a new kind of experience for me . . . using those interviews helped me in my development as a clinician outside of the trial . . . more people being involved in research and having their GCP would be helpful to increase the pool of doctors who are qualified to get involved in research . . . I was motivated to get involved with it because at present, we don't have anybody working in general adult psychiatry in Sheffield who do psychopharmacological clinical research. I'm hoping to be involved in more research like this in the future, and bring that kind of research to Sheffield, because there is a bit of a gap there.*
>
> *HCP PI 4*

Promoting to patients

Healthcare professionals found the ability to promote the study in clinical appointments efficient and effective, particularly when the opportunity to partake was juxtaposed with medication reviews of unsuccessful treatment, or proposed as adjunctive to patients' existing treatment. Re-promoting the study to patients who had previously declined helped some clinicians eventually recruit those participants. This demonstrated the scope for reconsenting or revisiting the trial as an option, notably in the context of fluctuating mood states characteristic of BD and amendments to the trial eligibility criteria.

> *I think probably talking to service users and actually telling them about the study, and raising it in clinical reviews, that is probably the most useful, the actual face-to-face dialogue or telephone dialogue with people.*
>
> *HCP Researcher 3*

> *I mean, when I first heard about it . . . he'd mentioned it once or twice earlier on, and I hadn't really been interested. And then later on . . . I thought, 'Well, we might as well give it a go, and take it from there'.*
>
> *Participant W12 > 1*

> *In a few months they might be different, so we try to rescreen and go back and make notes and put times to then go back and review that person to see whether they've come out of that episode and maybe they're in a depressive episode . . .*
>
> *HCP Researcher 7*

Some PIs adopted the strategy of framing PAX-BD as a 12-week trial and found this approach was more palatable to patients compared to the somewhat daunting prospect of 48-week participation. This was achieved by underscoring the significance of the first 12 weeks in assessing treatment response and emphasising the opportunity to review progress thereafter, as well as their right to withdraw at any time.

> *I think that is achievable, the 12-week one, but to try and keep people in for up to 48 weeks, I would imagine that is quite a challenge. 12 weeks I think is reasonable and doable.*
>
> *HCP Researcher 3*

> *. . . went into the trial and stuck at it for the initial 12 weeks, we could review her progress . . . primary outcome point at 12 weeks so I figured that it was helpful for the researchers to have somebody in there for 12 weeks, even if they don't make it to the 52-week outcome.*
>
> *HCP PI 4*

Patients generally reported positive impressions of the trial design. Comprehensive trial resources and organised processes transmitted a sense of legitimacy and credibility, which facilitated consideration of participation and self-monitoring during the study.

> *It all seemed well organised and well laid out . . . then there was all the documentation that came with it, that suggested that it was running or had been running for some time . . . I didn't find it difficult to follow at all. I found it quite straightforward.*
>
> *Participant W12 > 4*

> *Well, this study is legit . . . I went through everything that you had to know, you know, terms and conditions if you would, I went through that on my own and went through that with my doctor. It seemed fine and it seemed pretty clear.*
>
> *Participant W12 > 7*

Patient participants stated that although the study processes were vast and complex, the language in the documents was clear. Some also acknowledged that the volume of information was vast but necessary for making informed choices about participation, thereby potentially reducing the risk of disengagement from the trial.

> *It was right, it was about right, I think. It was good to have lots of information about the trial and . . . It wasn't too much information, it was good.*
>
> *Participant W12 > 5*

> *. . . there was plenty of information within the information sheets to be able to make informed choices as to whether to take part . . . just reading through the information sheet, it was a lot to take in, but once I had read through a couple of times, I was able to understand it. It covered everything which was needed.*
>
> *Participant W12 > 6*

Trust

This subtheme highlights the significance of perceived credibility, safety and agency, as well as the impact of endorsement by valued individuals on recruitment and retention of trial participants.

Trial design

One patient response indicated that the research focus on treatment for BD validated their experiences of chronicity and debilitation; HCPs also recognised the salience of this in a professional capacity. This symbiotic interest may have contributed to a positive view of the study objectives.

I was trying to see if there were any answers, really, to see whether there was anything that could be done for my [___ 0:01:47] treatment. So it came at a good time, really. It gave me, reading through, some hope that something was being done to actually look into that.

Participant W12 > 6

I'm very aware of the need for new medication strategies for people with bipolar depression. I think that this research is potentially important for that.

HCP PI 1

We often find that we don't have a huge number of options available to us in terms of treatment . . .

HCP PI 4

Interview participants widely described the trial design as robust and organised, stating that the thorough schedule of day-to-day study activities demonstrated an understanding of the topic and careful consideration of patient safety. Overall, the quality of trial material and discussions with knowledgeable HCPs conveyed an essence of integrity and legitimacy.

. . . a lot of positives. It was very well structured and had been set up very well. Each day had just been carefully thought out and a lot of safety measures put in place . . .

Participant W12 > 6

. . . it did seem really, really well organised and thought out . . .

Participant W12 > 9

PAX-BD was a CTIMP of pramipexole with an existing profile of product characteristics, side effects and previous research. In psychiatric practice, pramipexole is also prescribed off-licence for mood disorders.[27] This evidence base was accessible to HCPs and patients; combined with study information and discussions with HCPs, this may have perpetuated a perception of pramipexole as relatively low risk, as there seemed to be less association with the negative connotations of an 'experimental' drug. Some PIs also stated that known side effects of pramipexole were not highly concerning for the cohort of patients eligible for PAX-BD. For instance, many comorbid conditions and patients with impulse control, manic or psychotic symptoms were excluded from the study. HCPs were also provided study resources and access to specialists for advice on prescribing pramipexole and the management of impulsivity, mania and psychosis as side effects, discussed in more detail later.

I did a bit of reading up on what the side effects could possibly be.

Participant W12 > 4

. . . they weren't sure if it was a new drug or if it was one that . . . 'Is this something that we know anything about?' And explain, 'It is something that we know about. We do use it for treatments, but just not for this group of people yet'. . . . reassured when we said, 'Look, it's got a profile. We're able to tell you about how it interacts, potentially with quite a vulnerable population of people. People with Parkinson's use it currently'. So that was helpful in relieving those worries.

HCP Researcher 6

. . . side effects of pramipexole, I don't think that's actually been a major factor in the clients we'd actually felt it would be useful for, for a study . . . reported side effects, those were of brief duration and didn't require any adjustments to their medication . . .

HCP PI 2

Medication collection procedures provided the opportunity for site staff to collect empty bottles and unused medication. This potentially had the inadvertent benefit of informal adherence checks to mitigate HCPs' safety concerns around independent management of trial medication.

I've had to go and collect some old medications, and everything. And just seeing what medications are currently there.

HCP Researcher 11

Central research team

As discussed, the CI was notably active in promoting PAX-BD and providing guidance to HCPs beyond their obligatory duties. This endorsement illustrated integrity and garnered credibility from colleagues, as well as reinforcement that access to clinical advice would be available throughout the trial.

During the trial, the central team organised regular teleconferences attended by multiple sites to discuss progress and provide updates. The team were described as supportive, competent and attentive. They were understanding of recruitment challenges and collaborated with sites to implement alternative strategies, rather than applying idealistic pressure. This approach was particularly beneficial to less-experienced sites, who additionally appreciated the assistance with procedural, administrative and medical queries. Reflective amendments to study processes and the eligibility criteria in response to challenges at site demonstrated that HCP feedback was valued and tangibly implemented. Active methods of communication thereby established positive and effective working practices, facilitating engagement and transparency for HCPs.

I've been very well supported by the research team because it's all been very new to me. It's always been useful to have somebody to speak to with regards to making sure we're doing the right things, for instance filling out the right forms or even doing the screening for eligibility to enter the study. I think it's all been very good overall . . . very complimentary of the fact that the support from the research team is excellent. If in doubt, I know who to turn to, to make sure I'm doing the right thing.

HCP PI 2

. . . you get that extra pair of eyes on a patient from the research team, who are thinking about that person as well as you, which can be helpful to get that extra perspective . . . able to find a way around it and actually access a suitable treatment for that patient which was absolutely fine and didn't mean that patient had to come out of that trial . . . You might think there's a barrier or a problem but actually if you go and have a chat, there isn't one . . . You do communicate regularly. You do get in touch regularly. You respond very quickly to communications. You provide easy to read information. If there are questions, they're quickly answered . . . the research team is always there on hand. I feel like I know quite a lot of the research team personally.

HCP PI 3

. . . the study team were really good in terms of they were listening to what our barriers were And then they did make amendments according to that, to make it easier. So I think that did help. And they were very attentive towards that, because not all study teams are . . . you guys are under the same pressure as well to recruit to make sure that your study stays open . . . the way that you guys had done it, it was nice to know that you were there to listen but also offer advice and say, 'Maybe try this or try that'. . . . you guys understand that there's only so much that you can do. But, yes, I think the way it was handled was quite nice

HCP Researcher 10

. . . help that's been provided has been brilliant especially with having to withdraw one of our patients, well our only patient, because she [turned 00:20:13] manic unfortunately so . . . Yes, there was a lot of good support around that. Yes, I don't think we can ask for anything more from the team. The teleconferences are great, they're great to keep us updated . . . It's such a good way to communicate and have open dialogue, I wish more studies would do that.

HCP Researcher 6

Relationship with care team

Positive and trusting patient relationships with secondary care teams was a key facilitator of recruitment and engagement throughout the trial. Some participants stated they would not have considered participation if the trial was not advocated by a familiar clinician. Moreover, where the secondary care clinician was also a study PI, the continuity in provision of care, clinical responsibility and knowledge of individuals' symptomatic framework were appealing. Some HCPs involved in the study made pointed efforts to travel to patients' homes or join their clinical sessions for preliminary face-to-face discussions, which patients indicated helped them feel valued, minimised burden and put

them at ease. Joint discussions with research staff therefore demonstrated collaboration and may have facilitated a transference of trust to the research team.

> *I have been under the care of the mental health team for quite some time now, I think it is building up a trust . . . [Interviewer: . . . suggested . . . by an external body and had not come from your own team, do you think you would have been willing to participate?] I would not have done it. I just would not have done it at all.*
>
> *Participant W12 > 2*

> *. . . my psychiatrist advocated it . . . some of the people on the study came up especially to see, or at least to join in with my sessions . . .*
>
> *Participant W12 > 4*

> *There's a sense of that additional expertise being brought to bear on their case.*
>
> *HCP PI 3*

> *. . . it was made pretty clear that it was run in tandem with collaborating with your psychiatrist or mental health team . . .*
>
> *Participant W12 < 1*

> *. . . knowing that they're still going to be cared for by their actual local clinician . . . the clinician's responsibility was still there, made quite a positive- gave a positive experience to people . . .*
>
> *HCP Researcher 11*

Informed consent

A strong sense of autonomy was emphasised by patient participants, achieved by extended discussions with an emphasis on their right to exercise agency and withdraw consent at any time. Overall, patients described feeling well supported to make informed choices.

> *. . . little bit of a no brainer . . . something I was doing that I really did not want to do then I could stop at any time. If I had any concern about my health I could stop at any time. So that was really reinforced all the way through it as well, which is quite important to me, because I did not want to start taking something and start feeling part of something that was going to be an issue to stop, should I want to . . . I feel in control, and that I do not have to do it should it come to a point where I did not want to.*
>
> *Participant W12 > 2*

> *. . . if need be, you have every right to withdraw. So I think you can always answer those questions if people do have reservations because of it.*
>
> *HCP Researcher 10*

Patient participants highlighted the lack of pressure to consent as a facilitator of trust; multiple opportunities for discussions provided scope to understand the trial design, potential side effects and clarify misunderstandings. Emphasis on 'time-to-consider' participation indicated that demonstrations of patient-centred care are significant in building and maintaining trust, which in turn facilitates willingness to participate.

> *. . . the approach is always quite gentle. I would ring and I'm always checking if they want more time or if they want me to go over and speak to them and explain it. And things like that. Just trying to make it very clear that there's no pressure. If you decide to meet up with me and I talk to you more, it doesn't mean you have to engage or anything. They have said that, 'This is really good'.*
>
> *HCP Researcher 6*

> *I have never been pressurised, and having the control of knowing that if I did not want to take it I would not have to take it. So I feel like I have been really well informed and it is trusting . . . I feel like I did have a really good think before I did start taking part.*
>
> *Participant W12 > 2*

> *. . . a fortnight, I would say, maybe. At least a fortnight . . . Probably the whole process of deciding to actually go on the trial was about a month.*
>
> *Participant W12 > 1*

In one interview, a patient reported they were informed of upcoming amendments to the eligibility criteria and advised to provide consent after approval, minimising burden by preventing disruption to their treatment regime and reinforcing values of protecting patient interest.

> *I waited until the amendment to the trial was put through so that I could carry on . . .*
>
> *Participant W12 > 3*

Interview accounts emphasised that the consent procedure was more manageable for patients when CSOs invested time to break down study information and explain processes. This helped patients understand and accept double-blind RCT processes. These discussions potentially also facilitated retention, as randomisation to the active drug or placebo was expected pathways.

> *I think it's just that thing of just taking that time and explaining with them, saying, 'This is what will happen'. Putting it in those layman terms and things like that.*
>
> *HCP Researcher 6*

> *I mean, we talked through everything, really, anything, any worries that I had, we talked through a few. And also, how the whole scheme would work . . .*
>
> *Participant W12 > 1*

> *I went through everything that you had to know, you know, terms and conditions if you would, I went through that on my own and went through that with my doctor . . .*
>
> *Participant W12 > 7*

> *I was fully informed along the way, and there was plenty of information within the information sheets to be able to make informed choices as to whether to take part. Then the research assistants I was working with, they explained everything very clearly as we went along.*
>
> *Participant W12 > 6*

Access to support systems outside the study enabled some trial participants to join the trial and engage with study activities. Patient participants described family members employed in health care encouraging participation and drawing their own conclusions, resulting in greater autonomy in decision-making independent of study personnel.

> *So I had talked to my family quite a lot, before I did it, to get their opinions and see what they thought . . . I have got a daughter who is a specialist nurse, and she thought that it was a fantastic idea. She was telling us about how if nobody does trials then nobody ever knows whether anything works . . . how everything, all treatments that we get, have been trialled. We talked quite a lot about that . . . we researched it quite a lot . . . they read everything to us and reassured us, so I felt really informed.*
>
> *Participant W12 > 2*

> *I was lucky enough in that I had my mum to break it down with me and go through it . . .*
>
> *Participant W12 > 3*

Attitude to risks

Some participants de-emphasised potential risks of the trial, adopting the stance that consequences of participation would be either neutral or beneficial whereby symptoms would improve at best or remain stagnated at worst. This

illustrates the role of treatment resistance in yielding openness towards trials; they did not fear further deterioration in mental health, and therefore there was nothing to lose but potentially plenty to gain by participating.

> *If I was on the placebo, I felt well, I'm no worse off than what I was when I started the trial.*
>
> *Participant W12 > 5*

> *I wasn't concerned that it would worsen my mood, no. I think that my mood was as it and yes, there were only positive things that could happen because of the new medication.*
>
> *Participant W12 > 4*

> *I was interested. I asked him a lot about it and, to be honest, the reason I tried it was I have tried things and it was not like I was going to lose by trying this . . .*
>
> *Participant W12 > 7*

Prior experience with medications contributed to this attitude. Patient participants felt they had fostered acute awareness of their response to drugs and felt confident in their ability to quickly identify side effects to prevent escalation.

> *. . . it can cause symptoms such as depression and psychotic symptoms. There was a slight concern in terms of that, but I am usually able to identify quickly side effects because I do tend to analyse things quite a lot. So I was quite confident I would be able to pick up on things quite quickly . . .*
>
> *Participant W12 > 6*

> *I'm pretty good these days knowing when I'm going a bit high. I've not had a manic episode for six years. I know when I'm not feeling well . . .*
>
> *Participant W12 > 10*

Some patient participants noted that the side-effect profile of pramipexole was not dissimilar to their existing psychotropic medication; hence, this was not cause for undue concern.

> *I had a very in-depth chat with my consultant about potential side effects, and things, and there were not any that really concerned me any more than the medication I was already taking.*
>
> *Participant W12 > 3*

> *[Interviewer: . . . were you concerned about side effects of medications or anything like that?] Not really because, that can happen with any medication so . . . I wasn't any more worried about it than I had been previously with other medications . . .*
>
> *Participant W12 > 5*

In terms of antipsychotic and mood stabiliser adjustments, some indicated that they were more receptive to changes as the current medication was ineffective.

> *. . . we had a change to medication shortly before the trial started, but that wasn't a particular concern to me because my medication at the time wasn't working as well as I was expecting anyway . . . the fact that we changed something before the trial didn't give me cause for concern . . . we didn't take me off any medication. It was just an additional medication that we added and it was something I think I'd had before and tolerated fairly well before. Yes, so it wasn't something that concerned me unduly.*
>
> *Participant W12 > 4*

Many patients also appeared to have an implicit belief in HCPs' duty of care, diminishing excessive concerns about trialling an experimental drug or the severity of side effects.

I just thought, 'I am pretty confident nobody is going to make us take anything that is going to be really, really dangerous'. So it became a little bit of a no brainer.

Participant W12 > 2

. . . the doctor is not going to give you dangerous medication . . .

Participant W12 > 7

Central research assistants

During the study, participants had regular scheduled contact from central RAs, as well as capacity for additional contact if the need arose. Constructive relationships and rapport were established with weekly calls during pre-randomisation and the first 12 weeks of randomisation. RA monitoring provided a continuation of support they received prior to starting the trial, and patient participants stated their queries and concerns were addressed attentively. For instance, support with AEs was swift, practical and reassuring with flexible dose adjustments based on symptoms, rather than pressure to reach or maintain the maximum dose. Demonstrations of reliable assistance and patient-centred care fostered participant trust, which may have encouraged fruitful engagement with a higher completion rate of monitoring activities and candid discussions with RAs.

. . . just being able to talk about that, and realise that no, I wasn't going to be just left a year . . .

Participant W12 > 1

. . . always somebody, as I say, that I could talk to with any concerns . . . when I had issues because of potential side effects then I was contacted very quickly by someone in the study team . . . I was happy that I had my weekly check in, that was good . . .

Participant W12 > 4

. . . there's [RA] . . . I would have a contact point if there was something I wasn't sure about . . . if I had a question, I would have contacted [RA] . . . I felt like I had the support I needed to do it, so, I was quite happy . . . whenever she phones, I answer whatever questions she has for me, and then I always feel like I can ask any questions that have, and I do . . . I would just say that the person, you know, the human side of the trial is actually good. You know, when you phone up to cancel your broadband you usually deal with someone who is not very pleasant, and she is pleasant, easy going, and she does the job well, basically.

Participant W12 > 7

If I had any questions, yes, they answered it very quickly and they were very supportive . . . I think it was actually a really well put together trial. It is the first one I have participated in, but I have actually felt really supported. The research assistant, who I speak to on a regular basis, always remember things that I have told him. He is positive, he is supportive, and just lovely.

Participant W12 > 3

. . . the chats with the [RA] every week . . . he always rang when he said he was going to. He was very sensitive with his questions, and I was very honest with him. I really felt comfortable and could have told him anything . . .

Participant W12 > 9

Perceived benefits

This subtheme explores the factors influencing cost–benefit analyses of trial involvement in favour of participation.

Access to treatment

PAX-BD provided clinicians the opportunity to access a new medication option and corresponding medical expertise in an otherwise limited treatment framework.[3] This particularly resonated with clinicians who felt they had an additional treatment option beyond the guidelines.

We often find that we don't have a huge number of options available to us in terms of treatment, because by the time patients who are suffering with depression reach secondary care they've often had first-line, second-line, even third-line

> *treatments with their GP. We do often find ourselves knowingly using treatments that don't have particularly increased efficacy over and above what they've already had . . . I'm quite comfortable with the ethics of providing a placebo to patients in the context of research. But I guess that I've had a lot of time thinking about medicine and thinking about how we generate evidence to address those sorts of things.*
>
> *HCP PI 4*

> *The importance of not just cycling through the same old treatments . . . just that sense that the patient is having absolutely every opportunity they could possibly have to get better is really important and gives you a sense of hope, perhaps. You're not leaving any stones unturned for the patient . . . the thing that swayed me is I want my patients to get better. So, that's it. If there's anything out there that might help them to get better, I'll go for it.*
>
> *HCP PI 3*

> *. . . clinicians who are pro research, and were more than happy to find the time, because a lot of clinicians were happy to have extra input. Someone treatment resistant that they've been trying to care for, for ages, who's still in a mood episode. It's [___ 00:08:33] more than happy for the input on.*
>
> *HCP Researcher 5*

Healthcare professionals anticipated that demonstrating treatment efficacy would strengthen the evidence base for pro-dopaminergic strategies, thereby increasing the possibility of gaining local prescribing approvals for long-term benefit to patients within their trust. The trial also allowed them to gain clinical experience of the prescribing and management of bipolar patients on pramipexole, with wider specialist guidance from the CI and PIs.

> *I think that pro-dopaminergic strategies are potentially really quite exciting, and so if this drug works that will be a big step forward. The whole sort of reward story I think is really important.*
>
> *HCP PI 1*

> *We have been given the permission within our trust, if we find that pramipexole is effective, to continue prescribing it. That's quite good. We'd like to make that framework that supports . . .*
>
> *HCP Researcher 7*

For treatment-resistant participants, a strong component of hope was present. They described feeling they had exhausted all psychiatric options and were desperate to find medication which would improve their mood and overall quality of life. Complex mental health needs, treatment failures and lack of subsequent options thus contributed to rejuvenated autonomy, enthusiasm and willingness to partake in PAX-BD; participation seemed to be a natural next step.

> *. . . people with bipolar who suffer from depression, can be all it is is, it is really debilitating. People's experiences can be quite severe, their depression . . . I do think that is something that the people who were recruiting on, who were eligible, it was a real positive for them to think, 'I've tried everything. Mood stabilisers don't work or they've got side effects. I'd love to have the opportunity to try this' . . . certainly the fact that there were so many people who were really debilitated by that depressive phase or depression within bipolar.*
>
> *HCP Researcher 4*

> *I was in a period of bipolar depression that had lasted several years and was treatment resistant. So we discussed the trial, and I was obviously keen to try . . . I was just willing to try anything by that point . . . I had got to the point where I had tried everything, or it felt like I had tried everything. I had gone through therapy. I had had ECT and all the other treatments. So I was willing to just focus on this one thing.*
>
> *Participant W12 > 3*

> *I was interested because I had been ill for so long, and I wanted to give anything a try . . . I was open to try anything out, I was ill for so long . . . There is just not enough help out there or not enough treatments out there.*
>
> *Participant W12 > 9*

This was a significant factor in recruitment, as interviewees stated they would have been resistant to experimental trials when they were first diagnosed due to the range of untried options at the time.

> *. . . it's a pool of people that really have tried everything . . . they just so desperately want something to help because nothing has helped so far. But these are people that have been in the system for a long time. Everything has been tried. I suppose, for those people, the benefit of being in a study where they potentially won't get the medication, it's a new medication, all the pros and cons, it outweighs them. Whilst other people, that haven't been in services so long, or haven't tried everything, approaching them, it's just very different. Because, I suppose maybe their hope is still that there is still lots of other treatments that might help them. The cons don't outweigh the positives.*
>
> *HCP Researcher 6*

> *I was really willing to try something, because I was feeling really unwell, so I was really willing to try something . . . it was just an option . . . other medications were not suitable, there was not anything that I want was prepared to try because of some of the side effects . . . I was starting to feel a little bit desperate because nothing was working . . . I was taking quite a lot of medication to start with, but felt a little bit like I was taking it but it was not really making any difference . . . it felt a little bit pointless that I was taking all of the medication at that point . . . When I first was diagnosed I would never have taken anything that was a research drug.*
>
> *Participant W12 > 2*

For some patients, the chance of long-awaited improvement also outweighed the possibility of receiving the placebo and facilitated openness to adjusting concomitant medication for the trial.

> *I knew I [had longer- I had- persistent symptoms had been clear] even between bipolar episodes. I was feeling quite hopeless about that and experienced long-term lack of motivation, tiredness, things like that . . . I have tried a lot of medications which haven't worked . . . It was just a case of analysing the risk versus the benefits . . .*
>
> *Participant W12 > 6*

> *I was going on the course because, yes, I had hopes that it would really help me . . . I've been consistently resistant really to medication to help lift my mood. My mood does sort of lift, you know, at different times. It has never seemed to be for a particular reason, it just sort of lifts. I was hoping, yes, that this would work better or alongside the other medication that I take . . . hoping that I would be on the actual drug and not on the placebo. But I did accept that is the only way trials can be done.*
>
> *Participant W12 < 1*

One patient described harrowing experiences of inpatient admission and diminished quality of life; relapse prevention and desire to engage with family members appeared to serve as a motivator for participation.

> *Anything that I think might help me, I'll take part in . . . for the last five, nearly six years I've been on quetiapine and I've not been [getting up while dinner time 0:00:57] and my lifestyle has been rubbish. I've got grandchildren; five, six years old and I want to spend a bit of time with them. I don't want to be in my bed all day . . . I'm all for it because I've been struggling for 30 years. It's not something new. It's not nice. I've met many people who've struggled. Manic depression is terrible. You can't control it. You can't control what you're actually doing . . . I've had, I think, 14 sections now in all different parts of the country. The last time I was in Sheffield it was awful, the experience . . . I'd been in so many times before . . . So I've turned around and said, 'I don't want to repeat that'. Do you know what I mean? 14 times being locked up for a month, it's no fun . . . I don't wish to return to hospital again. The last time it was horrific . . . I spent most of the time in my bedroom. I didn't like it one little bit . . . absolutely fed up of being in my bedroom watching TV in my bedroom. Turning the television on and off, on and off because I can't concentrate on the telly. That's why I've asked to go on this study and see if there are any benefits.*
>
> *Participant W12 > 10*

Altruism

Many participants expressed altruistic motives for participation facilitated by experiential awareness of limited treatment options and an understanding of the implications of research on clinical practice. This aided in recruitment

due to the reconciliation of personal preferences for the active drug, as receiving placebo was nonetheless meaningful for utilitarian purposes. During the trial, some participants did not observe a treatment benefit but were retained as they elected to continue for the broader scientific cause.

> *Generally speaking, patients are very interested in taking part in research trials and benefit a lot from being involved in trials. They can get a lot out of it psychologically. A lot of them feel like they're a burden on others whereas, if they're involved in the research trial, they can get that psychological boost and feel that they're making a contribution . . . I think it's extremely beneficial for patients.*
>
> *HCP PI 3*

> *I'm very positive about research and the fact that, yes, in this case it may have helped me or may not, but it was worth taking the study to find that out . . . it may help other people in the future . . . I wasn't worried about the randomisation part of the study as such . . . I thought that was a fairly standard way of running the study . . . I'm glad that I did it, that I've done it and participated in the study because yes, it may help other people in the future . . .*
>
> *Participant W12 > 4*

> *. . . a good thing for people to do . . . I have got an engineering degree so I, kind of, understand the importance . . . To be honest, I do not think it has done anything. I do not [think if they asked me 0:15:56], 'It is not doing anything, do you want to stay in this study?' I am, kind of, staying in this study for the sake of the research.*
>
> *Participant W12 > 7*

> *. . . it would be helpful, it's always helpful, a study, even if it doesn't work out for you . . . I'm glad I've tried it. At least I had a go and hopefully it will be something that will, you know, help in some way. I mean any experience in a trial presumably is some help.*
>
> *Participant W12 < 1*

Safety monitoring and support

In the PAX-BD trial, participants received weekly and 4-weekly safety calls alongside questionnaire score monitoring from the RAs, as well as clinical reviews of AEs and medication dose. Compared to routine clinical practice, this approach was more robust, frequent and personalised, providing quick intervention in matters of patient safety. This may have helped prospective participants mitigate concerns about partaking in an experimental trial. For HCPs at sites, this alleviated some burden while allowing them to maintain oversight and clinical responsibility for their patients, resolving major concerns about side effects or relapse.

> *. . . one of the things that we always say is, 'You're under a PI here who will check your scores'. You'll get a research assistant from the study and every week they check in, or two weekly . . . it's been really great how the PAX-BD team have taken a lot on themselves . . . weekly check-ins, doing all the [quids 0:16:08] and stuff like that . . . we knew that we would have to do a prescription at every visit and it wasn't a lot of work for us. Whereas I think if we were having to do that for, say if we had 10 patients, it would have been quite a lot . . . nice that the PAX team were doing that and just checking in with us. And then we could see how the patient was actually doing. It was one less thing for us to do. So I think that was really helpful.*
>
> *HCP Researcher 10*

> *They are being monitored by research assistants, and getting those weekly phone calls. If there's anything, that I'll let them know as well. So, letting them know that they're not actually doing any more work, I think, helped quite a lot.*
>
> *HCP Researcher 11*

During the trial, HCPs and patient participants indicated that the safety checks were indeed comprehensive and reassuring. For instance, when hypomanic symptoms occurred, central RAs utilised multiple sources of monitoring to identify this at milder stages. Risk of relapse was minimised with early intervention and encouraged participants to continue engagement with monitoring activities, thus progressing through the trial.

I was happy with the way that things were being dealt with. Yes, when I had issues because of potential side effects then I was contacted very quickly by someone in the study team. Yes, that was good in that respect.

Participant W12 > 4

. . . one of my participants scored quite highly on the ASRM, the questionnaire for mania. Only by a couple of points, but it was enough to send me down a different pathway . . . What I did was, I did what was usual, I contacted the site. I said, 'This patient has described X, Y and Z. Could you please talk to her clinician?' I advised the individual, 'Maybe this is something you ought to bring up with your GP and your clinical team'. It was last thing on a Friday. As it was, she did contact her clinical team, she did contact the study person after she got off the phone with me. That got dealt with . . . That came off me just looking at her TrueColours and thinking, 'There's something going on here. That was quite a high move between one week and the next week'.

HCP Researcher 1

. . . if there is something where you're showing that you've got side effects of something, then our consultant will always check in and make sure that you're okay.

HCP Researcher 10

Central RAs flagged any cause for concern to PIs indiscriminately, which inadvertently facilitated regular holistic clinical input for AEs independent of the trial medication. Patient participants highlighted this, indicating a mediatory benefit of central RAs. Some reported an increase in clinician involvement and associated satisfaction; others described RA monitoring as bridging a gap in the scarcity of appointments in routine clinical care. Equally, some patients noted that reflective conversations with RAs and general support enabled them to extend the time between clinic appointments and seek less psychiatric input, indicating potential health economic benefits.

. . . go off and find out the information, she would get the Dr to give us a ring, and she would discuss the side effects. So she was really good because she signposted us to where I would get the advice from . . . probably the support, because you do not see your psychiatrist all the time. So I think being able to speak to someone on a weekly basis, and it has now gone to a monthly basis, but I think you are speaking to someone and you are discussing how you feel on a weekly basis. So I think that has actually has really helped. I think, at the beginning, had I thought of it that way, you know, that is a really positive part of it because you are able to verbalise how you are feeling. So I have found that really helpful and I do think my mood has improved, and I do not know whether it is because I am talking about it a lot more than what I normally would be, because I can go three to six months without seeing a psychiatrist.

Participant W12 > 2

She is really helpful. Because of [RA] I have been able to actually have a bit more help from my psychiatrist.

Participant W12 > 7

We stay in good contact with the RAs. We've got a good relationship with [RAs], because they, obviously, speak to them a lot more frequently than we do, so they're able to point out- It was flagged to us, with the one that withdrew, by [RA], saying, 'The attention is being withdrawn and he's not engaging as much'. So we were able to notice it.

HCP Researcher 9

Patient participant accounts illustrate benefits of close monitoring independent of trial medication. Some patients also surmised that the study activities aided self-reflection on facets of well-being and their mood trajectory, additionally emphasising the positive rapport built with central RAs which may have sustained participation.

I also think the documentation every week you know? The saying how you are and being able to see where you are in terms of your mood electronically was really good. I think that's been helpful to me.

Participant W12 > 5

. . . normally they have been every Friday and they have been fine, and they have never taken that long . . . phone call is an opportunity to ask questions, so it is helpful . . . I really initially thought that I would feel really stupid if I got to the end and I thought I had side effects and it was not because it was placebo. That crossed my mind a little bit. But then again, I spoke

to my daughter and she was like, 'You know, having the support for that year might be the thing that is making you feel better', because I do feel like my mood has improved . . .

Participant W12 > 2

Treatment response

A large component of participant retention and motivation for continuation in the trial centred on treatment response. Some patient participants noted improvement and/or emerging or worsening side effects in the titration phase; both appeared to be attributed to a belief they were randomised to the active treatment arm. Improvement in mood during the trial provided clear reason to continue participation, and tolerable side effects appeared to have a similar impact, potentially due to hope that a treatment response would eventually transpire. HCP participants similarly indicated that observing a decline in symptoms reinforced the possible benefits of the trial, potentially encouraging them to continue recruitment.

It has been lifechanging . . . There has been an immense change in my mood, for the better. My motivation is better, and my concentration is better. My confidence is improving. I no longer have suicidal thoughts. I do not think about death every day. It is genuinely night and day from before being on the trial drug to what it is like now . . . I am really positive about it. Everybody, like my mum, is positive about it.

Participant W12 > 3

When I first started, it did feel like [I could possibly be on the study medication 0:13:39] based on the side effects, and I did start to notice some initial benefits. Starting to be able to get things achieved and less suicidal thoughts, less physical symptoms . . . some initial improvement . . . The usual episodes, they did come in still. So possibly they weren't as severe as previously. So it may have still been having some benefit, but it didn't reduce them completely. So some benefit but not an overall great benefit, I suppose.

Participant W12 > 6

When I first met him his mood was very low. He was really struggling. Now he has started on to stage two, so we don't know obviously, we are blind, whether he is on the IMP or not. But he did improve and has remained improved over the last year. We don't know of the reason for that. It could be that he is on the IMP and it is helping. But we wondered whether part of it might be the fact that he gets quite regular contact from the RAs . . . I think he gets on with the RAs now he has found that support. He has found contact with myself supportive, and some of the home visits that I make as well. Again, that is a secondary effect of being on the study . . . a facilitator to his engagement and mood as well.

HCP Researcher 4

For some participants in the trial, the improvements they felt were often supported by changes in their depression scores. Their positive experiences were thereby substantiated with concrete numeric evidence in the form of data visualisation graphs accessible via TrueColours, thus reinforcing the benefits of continued participation in PAX-BD.

I think the fact that you use TrueColours, so you can see graphs . . . So I can actually see my depression score dropping as I have continued the trial is actually really positive, because it is, kind of, this physical evidence to yourself that it is working.

Participant W12 > 3

Randomisation belief, or at the very least lack of certainty about the treatment arm, also incentivised unblinding which was a possibility only upon trial completion at week 48. For instance, participants who were uncertain about a response continued in the trial due to progress observed by friends and family. One interviewee stated they believed they were in the control arm, but their parents thought differently; this provided motivation to continue with the trial to sustain improvements and access unblinding.

I do not know. I just think it is, again, maybe just part of, maybe, the side effects or part of taking that type of medication. But it is then outweighed by the fact that everyone thinks my mood is really good at the minute . . . I think it is really interesting, and I am really looking forward to, 12 months, finding out whether it has been their trial medication or not . . . I find it really interesting because if it is not the trial medication then all of the other components of it have really helped. So it will be interesting to find, at the end, as to whether I was taking it or not.

Participant W12 > 2

> *I personally think I'm on the placebo, but my parents have both said, independently that they feel that I'm not and that I'm actually taking the [pramipexole 0:06:12], so the medication, because they've seen a difference in me . . . maybe it will take me a bit longer to realise there is a difference.*
>
> *Participant W12 > 5*

> *. . . the idea of even if you didn't receive the medication in question, the placebo effect, the power of that. So I found that quite interesting. If it turned out that I was having symptoms but then eventually found out that I wasn't on the medication, I would be curious about that side of things.*
>
> *Participant W12 > 6*

Some participants ascribed improvements in facets of quality of life to trial participation, for instance asserting this had mitigated long-standing side effects of concomitant psychotropic medication such as issues with sleep and tremors. One participant indicated that they experienced a significant improvement in quality of life associated with trial medication, but study monitoring activities were not inherently helpful or appealing. They sustained engagement with questionnaires and telephone calls nonetheless, implying the benefit of treatment response made them more amenable to cooperation with trial requirements.

> *Honestly, I was hopeful that because it was a Parkinson's drug it might stop the tremor that I had, because of taking the lithium.*
>
> *Participant W12 > 3*

> *I get fed up of the same questions, but I understand that . . . I understand they've got to go through the same procedure week in and week out. I understand that . . . if it will help me have a better life then I'm all for it . . . All I know is that since I started this trial from day one, we've altered the regime at home and I've been able to get my sleep, been able to get my tablets earlier. Things have been a lot better . . . Now, with doing this study, she's actually doing the tablets earlier. With the tablets being ready I can turn around and I can take them earlier. It's such a big thing, the sleep pattern you've got. If I can go to sleep for 10:30, I get up in the morning and I feel great . . . Because of the study, she's actually taken notice and said, 'Look, I'll sleep in the other room'. It's benefitting me. At the moment, it's benefitting me.*
>
> *Participant W12 > 10*

Ability to conduct study

This subtheme describes facilitators implicated in the ability to conduct and partake in the study, highlighting processes which minimised HCP and patient burden and yielded completion of trial activities. These factors underscore the capability to recruit participants and retain engagement throughout the trial.

Trial information

Many HCP participants cited the study protocol and Clinician Manual as comprehensive base reference resources which covered a breadth of clinical nuance. They appreciated the accessibility of this material and support provided for assessing eligibility, the management of AEs and general study processes.

> *I think it's very comprehensive . . . I'm keeping a copy somewhere in case I need to make a reference to it when needed . . . I think the current training that I've been given is surely adequate . . . anxiety does perhaps pick up a bit when some people report side effects and we don't know whether it's actually part of the trial medication or not. I think the next stage is, what do we do about it? It's often useful in that case for me to refer to the clinicians' manual and to seek out further advice from the research team.*
>
> *HCP PI 2*

> *The protocol is very, very detailed. The clinician manual, which is a living document . . . It's clear, it's concise and it does give very detailed information . . . Look in the clinical manual. Look at Section 7. whatever and you'll find some answers there . . .*
>
> *HCP Researcher 1*

Other study resources such as training videos, newsletters, information sheets, participant diaries and the study website were similarly highlighted as useful source material. HCPs appreciated the ability to utilise various methods of communication to send promotional material and trial information, particularly during the COVID-19 pandemic. Although the consent appointment required face-to-face contact, they stated this was achievable in one session due to posted information sheets, prior discussions via telephone and signposting to the study website.

> *I don't think it is beyond the realms of a single-session consent discussion. Patients, they do get given quite a lot of written information first . . . There are opportunities for them to get their head around it, yes.*
>
> *HCP PI 4*

> *I think the videos were all on the website which helped. I think the teleconferences helped a lot, as well, because it kept you engaged within the team, and especially, with the study managers . . .*
>
> *HCP Researcher 11*

> *I think they are fairly concise and succinct, and they tell people what- they basically give the information about the study. The information leaflet is very useful . . . We got the PAX-BD website, you can look at that. Yes, we'll always mention the website. But I imagine the website is quite a useful source of information for people as well.*
>
> *HCP Researcher 3*

As previously discussed, interviewees were described trial processes as well considered in terms of patient safety, which additionally minimised burden. For instance, patient participants felt dose schedules with day-by-day breakdowns provided sufficient information to confidently manage their medication particularly in the titration phase, and diaries were helpful in self-monitoring of AEs.

> *. . . what I've had has been very clear. You get given instructions, you get the diary . . . the pharmacist does also send a sheet, which tells you exactly what to do. So, I have managed with it . . . As long as you keep on the ball and follow the instructions, you're alright . . . I had sufficient information . . . do the diary, just to keep- on a basic level, just to keep myself, you know, so I know where I am in terms of [___ 0:14:14] study.*
>
> *Participant W12 > 1*

> *I wrote down things quite carefully, any side effects or headaches or anything like that. I think I didn't have any problems monitoring things . . . I think it was run very well and very well thought out.*
>
> *Participant W12 < 1*

Reflective protocol amendments

The PAX-BD protocol was reflectively amended in response to feedback from sites; this resolved some eligibility constraints and expanded the pool of prospective participants, as well as mitigating clinician and patient concerns around medication changes.

> *Following the revision of the protocol, this has become less of a factor. For instance, I've got somebody well established on antipsychotic medication. Then as part of their bipolar disorder there have been distinct features of psychosis, which have been severe in the past. I've been rather reluctant to get them off psychotic medications, but I think, again, that currently doesn't seem to be a major problem with regards the new revised protocol.*
>
> *HCP PI 2*

> *. . . the change in the protocol to include people who are on antipsychotic medication. I think that has made a difference . . . certainly, it has opened up the number of participants who maybe could be recruited, that has been a godsend, that one.*
>
> *HCP Researcher 3*

Healthcare professionals and patients indicated that lack of medication adjustments in pre-randomisation reduced burden and prevented participants being stagnated for extended periods.

> *. . . inclusion/exclusion criteria has changed for PAX over the last couple of years . . . one of our participants really, really wanted to go on to stage two, she couldn't tolerate another mood stabiliser. She kept having a skin reaction to everything. I think there has since been an amendment that would mean that she could possibly be reconsented.*
>
> *HCP Researcher 4*

> *. . . the medications I was on were alright with the trial, yes. [Interviewer: . . . if it had involved having to stop a medication that you were on, or change a medication that you were on, do you think that would have influenced how you felt about the trial, or taking part?] I think I would have been much more hesitant if that had been the case, yes . . . It's a bit like the devil you know, isn't it?*
>
> *Participant W12 > 1*

> *I was good to go. The antipsychotic was only a low dose, and I was already on a mood stabiliser.*
>
> *Participant W12 > 6*

Additionally, face-to-face site visits for blood pressure and heart monitoring were removed and instead checked by central RAs, alleviating some burden on HCPs. Overall, reflective amendments increased the feasibility of recruitment and follow-up of participants throughout the trial.

> *. . . amendments came through with the study that made that a little bit more possible and feasible. Well, they removed the CSO contact with the blood pressure and heart monitoring, and replace them with the phone RA calls.*
>
> *HCP Researcher 4*

Remote design

Prior to the COVID-19 pandemic, the PAX-BD study utilised remote means of data collection and monitoring. Despite a mandatory pause in recruitment, many face-to-face processes in the trial were easily adapted to pandemic guidelines due to the existing remote infrastructure.

> *I think the team have made PAX-BD, probably, the most hands off study. Certainly the most hands off study I've ever worked on. Okay. This should have been the most perfect one for the pandemic . . . It's very, very hands off. It's a perfect set up for coming out of pandemic.*
>
> *HCP Researcher 1*

Remote monitoring additionally increased the feasibility of the study; RAs assumed the responsibility from HCPs at sites and a wider locality of patients were able to access the trial. Central team interviews expressed that technology simplified mood monitoring through data visualisation techniques which provided an overview of patient trajectory, and changes indicating cause for concern were thus easily identifiable.

> *You see the graphs of their mood over the past 6 months. They actually show it there on the screen. It's really easy to look at . . . It gives me a very, very quick overview of how they are. I can look at TrueColours and I can see what's going on with them and I have a bit more of a picture of how they are. When I do phone them and I go through my pre-randomisation monitoring or my safety and tolerability monitoring, depending on which stage they are, I've got a good picture. I can go through the questions, I'm going to ask these every week. I can go through the questions, and I can flesh out their numbers.*
>
> *HCP Researcher 1*

Participants described the ease of online self-reported data compared to clinic visits, due to the wait between appointments and travel arrangements required. Participants with computer proficiency described the TrueColours platform as user-friendly and utilised the questionnaire score graphs for self-reflection. The online system was generally convenient to access with a digital device of the participants' choosing, and reminders for questionnaire completion aided compliance with study activities. Some interviewees added that the number of weekly questionnaires were not particularly burdensome or time consuming, in part due to the ability to complete them remotely in their own time.

> *. . . no problems using the technology to monitor their symptoms. I think they've been keeping up with their telephone appointments as required. There haven't been any issues with regards their ability to cooperate in the study at all.*
>
> *HCP PI 2*

> *It does not take very long. It is fine. It only takes about 10 minutes . . . It does not really take that long to do anything . . . there has not been anything that has been time consuming, or has been inconvenient at all.*
>
> *Participant W12 > 2*

> *One thing that is good is that you get notifications for TrueColours, not just once on Thursday, when you are supposed to do it, that is the day when my study week starts, but also on Friday . . . You get reminders several times.*
>
> *Participant W12 > 7*

Medication processes

Healthcare professionals indicated that regular updates from central RAs provided comprehensive oversight of study participants, thus prescribing processes felt well informed. The use of the central CNTW pharmacy was noted to expand feasibility for sites, as this streamlined study set-up and dispensing processes. Participants additionally highlighted the convenience of receiving trial medication directly to their homes, rather than travelling to collect them. The option for CSOs to collect unused medication and empty bottles provided an additional adherence check and assurance that participants were managing medication safely.

> *I think that was quite good. Because the medications can be sent straight to the people's homes . . . I've had to go and collect some old medications, and everything. And just seeing what medications are currently there . . . Clinicians like to be updated. So, for example, if their medication changes, someone has gone up a dose or down a dose, if there's any reports that they need to know of, or just changes in the actual study, for example, the early closure, I think they appreciate you giving them an update.*
>
> *HCP Researcher 11*

In the event of prescribing delays or lost medication, participants noted that the supply of tablets in prior dispensings were often sufficient to cover this, and central RAs were able to corroborate with the relevant departments to resolve issues without disruption to treatment. Medication administration and dose instructions were described as easy to follow, and any issues, queries or clarifications were supported by accessible trial RAs.

> *I felt that the backup for the medication was sufficient, that there was always somebody I could talk to if there was a problem . . . Also, I ended up moving house as a result of not going abroad, so those sorts of logistical things were potential problems. But yes, on the whole we managed to resolve those so they didn't turn out to be problems in the end.*
>
> *Participant W12 > 4*

> *. . . a couple of months ago, I lost one of the bottles, which was shipped to me very quickly, and I had it within a couple of days, which is very good.*
>
> *Participant W12 > 7*

Some participants were unable to manage any medication independently; support was provided by entrusted family members to navigate the titration phase, dose adjustments and management of dispensings with specific batch start and end dates.

Flexibility in trial processes

The role of flexibility was identified as a pragmatic facilitator; for instance, the ability to make dose adjustments and lenient guidelines for concomitant medication and psychotherapy post week 12 made the trial more acceptable to patients and HCPs.

> *One young man particularly got a lot of benefit out of the night time sedative effects of his clozapine. But now that the protocol has changed to allow a certain dosage of anti-psychotic that has got better . . . She has also had to go back onto her antipsychotic. There was a bit of flexibility there.*
>
> *HCP PI 4*

> *I don't think I was supposed to start any counselling or anything like that either and interventions, but as it got towards the end of the study, I got told I was allowed to start that.*
>
> *Participant W12 > 5*

Although monitoring was largely conducted remotely, the central team developed a workaround plan for HCP supported paper and electronic questionnaire completion. This made the study more accessible to prospective participants without digital access, computer literacy and/or those requiring additional support.

> *He doesn't have a phone, doesn't use the internet, and we've had to come up a workaround plan to help him get that, for the questionnaires that he needs to complete . . .*
>
> *HCP PI 4*

During the study, patient participants highlighted that monitoring calls were flexibly conducted according to their availability. This increased participant satisfaction and the rate of engagement with trial activities.

> *. . . we have always managed to get it done . . . weeks where we have had to reschedule . . . never been an issue rescheduling things . . . never been anything where I would say, like, I have really struggled to manage to do the trial because there was no flexibility, because everything has always been fine . . .*
>
> *Participant W12 > 2*

Dose adjustments were similarly made with a patient-centred approach. Weighing side effects and response facilitated acceptability and tolerability of the study drug for long-term use. Some participants additionally found it helpful to time administration according to their lifestyle, for instance sleep cycle preferences.

> *There was one lady who has had to change some of her medication. She has had to take benzodiazepine, or [diazepam 0:13:11] I think it was actually, on a PRN basis, but that is okay . . . She has also had to go back onto her antipsychotic. There was a bit of flexibility there. To be honest, we also have the flexibility of changing the dates of the study medication as well, if people really need to, so the ability to reduce the dose of it if people are suffering with side effects or becoming unwell with manic relapse, and that is quite helpful.*
>
> *HCP PI 4*

> *I am just on 1.5. That was reduced about two, or maybe one and a half months ago. It seems like things have got a bit more stable. So, you know, hopefully, we have actually got to the dose where it is working . . . I am pleased that you do not have to take the medication several times a day, that it is just once.*
>
> *Participant W12 > 7*

> *I was struggling . . . he told us to stop on the lower dose for a while, until I felt like it had stabilised a bit . . . I was quite happy when he said not to increase the medication, because, I must admit, at that point, if I was going to throw the towel in I think that might have been the point . . .*
>
> *Participant W12 > 2*

Healthcare professional attributes and attitudes

Clinical experience with bipolar depressed patients and successful recruitment in previous studies appeared to expedite knowledge of effective strategies to identify, engage and recruit participants. HCPs with prior experience of research were also better able to grasp nuanced study requirements to avoid deviations and manage administrative tasks effectively. Staff at research-active sites reported utilising established research networks as previously discussed, as well as the use of multiple databases to expand patient-screening strategies.

> *I've been a nurse, qualified nurse now since 1985, so I've worked in quite a wide range of inpatient and community services . . . we deal predominantly with conditions such as bipolar disorder, as well as the range of depressive disorders, probably from the moderate to the severe range . . . I've been active in recruiting to different studies, probably over the last 10 years since I became a nurse consultant. But I've also been a principal investigator on 2 studies . . . We have some*

meetings with the CRIS people . . . That has been particularly useful to think about who might be suitable for the study and identify study participants . . .

HCP Researcher 3

. . . Northumberland, Tyne NHS Trust but I know that they are running clinics, aren't they, that is across primary care and secondary care for the purposes of patients for research? I think that is a really good idea and is something I'd like to pursue further.

HCP PI 4

I help support the research carried out within the Tees, Esk & Wear locality, but often within The Research Network. We have relationships with other localities within the same research network and the studies that we all deliver . . . I think it's gone well. For TEWV, I think, we're on line with the recruitment figures that we outlined really, which I think were quite realistic.

HCP Researcher 6

Caseload support was critical for PIs with limited availability and/or research experience. HCPs widely reported the value of CSOs assisting screening, emphasising successful recruitment would not be otherwise possible. HCPs noted that having multiple clinicians on the delegation log additionally aided effective time management, distribution of clinical duties, adherence to timelines and sufficient participant oversight.

I think I've been very well supported by the research team and very often would highlight certain clients on my caseload who might be potential candidates for the PAX-BD study. It's always been helpful to have that rather than me having to go through all my caseload to identify potential participants . . . saying, 'Yes, we've identified two/three people on your caseload who would be potential candidates for the PAX-BD study. Can you have a discussion with them?'

HCP PI 2

A very helpful research development unit is essential. I think the research nurses that we've got attached to our PAX-BD team, they are responsible for the recruitment. I must plug them as well. But if it was left to myself and the other doctor involved in the trial, we would never have managed to do the pre-screening and the eligibility check, no . . . and having 2 of us. It is myself and a lady called [PI delegate] who is another one of the SpRs. Yes, that has been helpful.

HCP PI 4

I was also doing some screening. I'm allowed to have access . . . I could pull off a report of people who had the relevant diagnosis, and work through and see people who may or may not be eligible. Then I made a list of those people which I would then show to the PI . . . for me to pull that information off in the first place I think was quite helpful . . . The PI and the other medic, [PI delegate], would go away and re-screen my pe-screen . . . It was very much a team effort . . .

HCP Researcher 4

Working values of collaboration, proactivity and dedication to patients emerged as facilitators of participant engagement. This was evident in the management and retention of participants who required support with monitoring; where some HCPs excluded such patients from the trial, others had the resource and capacity to conduct regular home visits and telephone calls to aid questionnaire completion. Participants who received this support described visits as enjoyable, and felt face-to-face contact added depth to monitoring with improved rapport and visual cues of well-being.

One I'm thinking of, she does engage enough that we feel that it is safe, but we have had to write to her before, and remind her, her responsibilities on the trial . . . one of our participants who is due to finish soon . . . I have to, or have had to call them almost weekly because we've had it agreed that he doesn't do technology. He doesn't use the internet. But we didn't want to exclude him from participation on that basis. We had it agreed that he gave me consent to set up a TrueColours, which is the online symptom reporting website, on his behalf. Then I call him and we go through it over the phone every week and do the measures. Then, when we do the long ones which are every few weeks, I go and do a home visit . . . Normally people wouldn't get weekly contact from the CSOs, but his case is special in that we wanted to facilitate

and allow him to be on the study . . . Actually, he was really resistant to phone calls initially. He wouldn't take the phone calls from the RAs, so I had to really prompt him to do that . . .

HCP Researcher 4

Qualitative study topic guides for interviews

Topic guide for principal investigators at participating sites

- What is your current role in relation to the service?
    - Prompt: prior experience with service users with depression.
- What is your current role in relation to the study?
    - Prompt: prior experience with recruitment into a research trial.
- What has been your experience of recruiting participants to the trial?
    - How well has it gone?
    - Are some people more likely to be interested? Why is this?
- Have there been any specific barriers to recruitment – anything that people mention that puts them off?
    - Prompts: health (current symptoms, fear of symptom exacerbation, side effects of pramipexole or mood stabiliser, concern over withdrawal of antipsychotic drug, concern over length of time before improvement in depression with slow titration, lack of choice over use of other treatments especially if getting worse or not improving, self-stigma, vulnerability).
    - Prompts: attitudes to research (randomisation, negative views about one of the treatment options, randomisation to placebo, being experimented on, lack of choice, data security, medical model of management alone).
    - Prompts: engaging the patient (perceived stigma, challenges of communicating the trial, burden).
    - Prompts: complexity of the study, study processes.
- Have there been any specific facilitators to recruitment – anything that people mention that encourages them to take part in the study?
    - Prompts: health (current symptoms).
    - Prompts: attitudes to research (opportunity to access new services or treatment approaches [withdrawal from antipsychotics, introduction of mood stabiliser, new drug, monitoring using digital methods (TrueColours), treatment and monitoring by specialists in bipolar disorder or BD, altruism, risk taking, hope].
    - Prompts: engaging the patient (active promotion and marketing, trust, clarity of trial process).
    - Prompts: support provided by the research team, local PI/clinician guide.
- Are there any additional training or resources needed to support recruitment?
- Are there any other strategies that could support the recruitment of participants into the study?
- If there are positives in taking part, what swayed them personally to take part or not take part? What might have made a difference to this decision?
    - Prompts: gaining research experience, being able to report this in appraisal, to support Clinical Excellence Awards.
    - Prompt: Gaining clinical experience using pramipexole, managing bipolar disorder.
    - Prompts: financial income to Trust for taking part.

Topic Guide for participants who either (1) withdrew/were withdrawn during the pre-randomisation stage, or who were not randomised or (2) were randomised but stopped taking trial medication prior to week 12

- How did you hear about the research study?
    - Who first mentioned the research study to you?
- What was your initial reaction to the invitation to participate?
    - How did you feel about taking part?
- What factors impacted on your decision to not take part in the study?
    - Why did you decide not to join the research study?
    - Prompts: health (expression of depression symptoms, fear of symptom exacerbation/risk of trial to mental health, concern over side effects of pramipexole or mood stabiliser drugs, concern over withdrawal of antipsychotic drug, concern over length of time before improvement in depression with slow titration, lack of choice over use of other treatments especially if getting worse or not improving, vulnerability).
    - Prompts: attitudes to research (randomisation, negative views about one of the treatment options, randomisation to placebo, being experimented on, lack of choice, data security, medical model of management alone).
    - Prompts: engaging the patient (perceived stigma, challenges of understanding the trial, burden).
    - Prompts: practical issues (travel to the treatment centre, required time off work or from other commitments, availability of carers).
- Were there any positives to taking part in the study for you?
- Was there anything that could have persuaded you to take part in the study?
    - Prompts: health (current symptoms).
    - Prompts: attitudes to research (opportunity to access new services or treatment approaches [withdrawal from antipsychotics, introduction of mood stabiliser, new drug, monitoring using digital methods (TrueColours), treatment and monitoring by specialists in bipolar disorder or BD, altruism, risk taking, hope) Prompts: engaging the patient (active promotion and marketing, trust, clarity of trial process].
    - If there are positives in taking part, what swayed them not to take part? What might have made a difference to this decision?

Topic guide for randomised participants who reached week 12

- How did you hear about the research study?
    - Who first mentioned the research study to you?
- What was your initial reaction to the invitation to participate?
    - How did you feel about taking part?
- What factors impacted on your decision to take part in the study?
    - Why did you decide to join the research study?
    - Was there anything in particular that persuaded you to join the study?
    - Prompts: health (current symptoms).
    - Prompts: attitudes to research (opportunity to access new services or treatment approaches [withdrawal from antipsychotics, introduction of mood stabiliser, new drug, monitoring using digital methods (TrueColours), treatment and monitoring by specialists in bipolar disorder or BD, altruism, risk taking, hope) Prompts: engaging the patient (active promotion and marketing, trust, clarity of trial process].

- Were there also concerns that you had about taking part?
    - Were there any factors that put you off?
    - Prompts: health (expression of depression symptoms, fear of symptom exacerbation/risk of trial to mental health, concern over side effects of mood stabiliser or pramipexole, concern over withdrawal of antipsychotic drug, concern over length of time before improvement in depression with slow titration, lack of choice over use of other treatments especially if getting worse or not improving, vulnerability).
    - Prompts: attitudes to research (randomisation, randomisation to placebo, negative views about one of the treatment options, being experimented on, lack of choice, data security, medical model of management alone).
    - Prompts: engaging the patient (perceived stigma, challenges of understanding the trial, burden).
    - Prompts: practical issues (travel to the treatment centre, required time off work or from other commitments, availability of carers).
    - Did you complete the full cycle of treatment? Where did you get with the trial or have you got so far? Any incidents or concerns so far?

- Having received treatment through the study, can you tell me about your views on the treatment you received?
- Are there any benefits that you have experienced?
- Have there been any disadvantages/anything you disliked about the treatment?
- How acceptable did you find the treatment?

A priori framework for analysis of barriers and facilitators to recruitment and retention to PAX-BD trial

(From Hughes-Morley *et al.*[83]).

Consider analysis across six time periods: before recruitment, withdrawal of antipsychotics/introduction of mood stabiliser, randomisation, titration of experimental drugs, follow-up to 12 weeks, follow-up to 52 weeks.

Barriers to recruitment of patients

1. Expression of depression symptoms

Presentation, endorsement and impact of depression symptoms or other BD symptoms.

2. Risk of trial to mental health

Participation would be depressing or anxiety provoking, make depression or other bipolar symptoms worse, withdrawal of antipsychotic or introduction of mood stabiliser risky, titration too slow, denial of other treatment approaches while involved in trial.

3. Stigma

Perceived stigma, self-stigma – weakness or vulnerability associated with mental illness, moral judgement, for example 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 study.

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, for example placebo, 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, concern over technology and data security.

Facilitators of recruitment of patients in depression randomised controlled trials

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.

Appendix 6 Patient and public involvement report

Background

Public involvement is generally accepted to be a key component of health and care research as it makes it more relevant to the people who will ultimately benefit from it. It is requested by most funders as a part of their study design in the UK. However, this has the potential to lead to tokenism and several reviews of PPI have concluded that evidence of impact is weak.

There have been a number of tools and guidelines created for researchers to assess and review the public involvement within their studies, with some arguing that PPI impact is difficult to assess, other than documenting contributions, due to its complexity. Others have argued that PPI can be diminished through professionalisation of public contributors. Experience and confidence can lead to improved contributions; thus, experienced public contributors can positively impact a study. However, to address this concern, a mixture of PPI experience can be beneficial to a study to gain a diversity of opinion through lived research experience as well as focusing on ensuring a representative group factoring in equality, diversity and inclusion.

More evidence is required of public involvement in research in order to identify challenges, barriers and methods to overcome these to ensure appropriate and impactful public involvement throughout the research process. This will support researchers and public contributors to be more effective in their roles, create innovative and inclusive involvement within studies and be able to measure the impact of public involvement.

The NIHR HTA Panel-funded PAX-BD study was a multicentred RCT with the primary outcome of evaluating the clinical effectiveness of pramipexole versus placebo alongside mood-stabilising medication, over 12 weeks, in the management of patients with TRBD. The trial design included an economic evaluation as well as a qualitative section exploring the acceptability and experiences of the trial for the participants and the researchers involved.

This paper has been written by the PAX-BD PPI group to add to the growing evidence identifying the impact, challenges and successes of public involvement in research. The aims of this paper are to answer the following questions:

- What impact did PPI have on the PAX-BD trial?
- How did the researchers respond to the PPI input?
- What have we learnt from the PPI on the PAX-BD trial?
- What would we do differently if we could re-do the trial?
- How can these learnings support future researchers and PPI within trials?

This paper will review the PPI from question to dissemination during the PAX-BD RCT. We will look at the development of the PPI within the study, its natural expansion and depth of inclusion during the study duration. We will discuss the impact that PPI voices had on the study design, its implementation and ultimate early closure. We review the feelings of the PPI members as well as those of the study team on how PPI was integrated within this study, what worked well, what could have been done differently and how PPI can be embedded within trials for the future.

This was a complicated trial with a number of challenges due to participant recruitment, the study population itself, amendments being implemented throughout the trial, the pandemic restrictions, personnel changes at the NCTU, the passing of our PPI lead and the early closure of the trial. This all led to us being able to assess the public involvement in the trial through the lens of facing and overcoming challenges as well as more generalised public involvement in a RCT.

Methods

The nature and design of the PAX-BD trial are described in a separate publication.[57] The trial funding began in April 2018, first site was opened in November 2019 and first patient was recruited December 2019. The trial was closed due to COVID-19 restrictions from March to October 2020, and ultimately closed early in 2022 (last participant recruited April 2022, last participant visit October 2022) due to funders decisions around time extensions, costs and recruitment issues. The trial recruited 51 participants of whom 39 were randomised, 36 reached the primary outcome time point and X completed the full 52 weeks of the study.

The core methodology used in the analysis of PPI involvement in the PAX-BD study has used the GRIPP2 tool which aims to improve reporting of PPI within research. The GRIPP2 checklist, however, does not take into account the quality and impact of PPI on a study, so we also reviewed our evidence following the work of Wilson *et al.*[125] in their realist evaluation which concluded that six actions are required for positive outcomes of public involvement:

- Researchers and public contributors share an understanding of the goal and methodological purpose of PPI.
- A dedicated individual to co-ordinate PPI.
- Public contributors have a strong connection with the target study population.
- The whole research team is positive about PPI input and fully engaged with it.
- Efforts to develop relationships of trust and mutual respect established and maintained over time.
- PPI is evaluated in a proactive and systematic approach.

We have also reviewed our contributions utilising the dialogue and change award criteria designed by Investing in Children and the ARC NENC. This method of assessment is focused on the voices and experiences of the public contributors involved in the research project and provides an alternative view to that of the researchers themselves.

We have completed a retrospective review of all documentation relating to the public involvement within the trial as well as holding a meeting with the public contributors and members of the trial team to get their views on the impact. Evidence was collated from TMG and the PPI group meeting minutes, e-mail chains between members of the PPI group and the trial team as well as questionnaires completed by the members of the PPI group and the trial team.

A meeting was held with the PPI group and key members of the trial team to discuss these changes and gain in-depth understanding of the groups attitude towards their input and impact and questionnaires reviewing the PPI within the trial were completed by the members of the PPI group and the trial team.

All five members of the PPI group and seven members of the trial team either completed a questionnaire or attended and contributed to the final PPI group meeting, to discuss the impact of PPI within the PAX-BD trial. Thematic analysis was undertaken.

The evidence was analysed by the lead author of the paper and reviewed by members of the PPI group and the trial team (names, number of contributors).

Results

Patient and public involvement before the PAX-BD study

In 2016 and 2017, prior to funding being secured, the first public involvement lead (SH), patients and carers, including from a Bipolar Support Group, gave feedback on the funding application and study design, and contributed to the selection of the outcome measures used in the study. This was expanded throughout the application and funding process to the group of 5 who were ultimately involved in the PPI group for the duration of the trial.

The initial PPI budget was £950 for the duration of the trial within a £1.8 million application, 0.05%. We received an additional £1600 in closedown costs but gave Funder back £54,544.28 of total award so total provisions for PPI was £2550, 0.14% of our final budget (£1,817,144.90).

The patient and public involvement group and its operation

There were no formal criteria for the PPI group membership other than having lived experience of depression, bipolar disorder or major depression, as either a patient or carer. The group was made up of five people with lived experience of depression (two), bipolar disorder (two) and carers of people with bipolar disorder (one and one additional member joined in 2022). We came from a range of backgrounds with diversity of age (approximately 41–65), socioeconomic status, disability (visual, physical and mental) and sex (two male and three female) as well as a range of previous experience with public involvement in research. The PPI lead had extensive experience of public involvement, two members had some experience and two had no previous experience.

The PPI lead attended monthly TMG meetings and bi-weekly CI catch-up meetings over the course of the trial. Sadly, the PPI lead passed away in September 2021 and the lead author (VB) took over this role from October 2021 continuing to attend all TMG and CI meetings. One new member was subsequently recruited to the PPI group who joined us in April 2022 maintaining the membership numbers.

The PPI group met eight times over the course of the trial, once in 2019 pre-funding, once in 2020 prior to COVID-19 lockdowns, three times in 2021 and three times in 2022 as well as attending the final results reveal meeting in January 2023. Meetings were ad hoc depending on the needs of the trial and the feedback from the PPI lead during any TMG or catch-up meetings when areas for PPI input was identified. There was a large gap between meetings in February 2020 and February 2021 due to COVID-19 lockdowns delaying the start of patient recruitment. The PPI group were consulted on reopening the trial and were also involved in reviewing documents and providing role-play training calls with the RAs via phone and e-mail between meetings. We were all group members for the duration of the trial and averaged four to five attendees at each meeting.

Meetings were in person until 2020 due to COVID-19 lockdowns and PPI group members were compensated for their time with Love2Shop vouchers and travel expenses. From 2021 meetings were held online and group members received £20 Love2Shop vouchers for their attendance and input at the meeting. No payment was given for any preparation or work completed in between meetings. This was changed to £25 per hour plus £5 virtual meeting expenses as per NIHR guidelines from October 2021. The original PPI lead did not take payment for her involvement. The replacement PPI lead, from October 2021, was paid via BACS at the rate of £25 per hour for all activities.

In-person meetings were held at an accessible venue with refreshments provided. After changing to online meetings adjustments were made after feedback from the group to ensure meetings included comfort breaks when over 1 hour, conversations avoided triggering topics and that documents were sent in formats accessible to our group member with visual impairments.

The Trial Manager attended the majority of the PPI meetings along with the trial administrator. Other members of the research team and the CI attended when required or requested by the PPI group. The trial RAs also regularly attended the meetings to discuss the details of the participants and their interactions with them gaining PPI perspectives on this and addressing any potential issues.

Meeting minutes were sent out and reviewed by the attendees following every meeting, and from October 2021 the PPI lead e-mailed a summary of the TMG and catch-up meetings on an ad hoc basis to keep the PPI group updated on any issues or changes with the trial.

Patient and public involvement was a standing agenda item for all TMG and CI catch-up meetings and the PPI lead was included in all decisions regarding the trial.

Impact of the patient and public involvement group

The PAX-BD application stated the following aims of PPI within the study:

- To have two PPI representatives on the TSC.
- Involved in dissemination to relevant groups.

- Review both the quantitative and qualitative data from the internal pilot study.
- Provide an opinion and recommendations to the TSC and DMC.
- Hold three PPI group meetings to review the findings of the internal pilot.
- Any change of patient-related material will be reviewed by the PPI representatives on the TMG and the fuller group as needed.

All of these aims were achieved with the exception that only one PPI representative was appointed to the TSC by the funder (NIHR HTA Panel). Indeed, the impact of the PPI group was wider than these a priori aims, as detailed in *Appendix 1*.

The majority of impact from the PPI group centred around trial methodology. At the trial design stage, PPI group input led to the addition of a measure of anxiety to be included with the weekly measures of mood that participants completed. There was substantial involvement in the form of feedback given on participant-facing documents which were amended after PPI feedback, but also included training of RAs. We completed role-play calls prior to the study going live to support the training of the RA's which they found beneficial. 'Feedback helped RAs to make calls more personal, and it was good to practice the difficult questions' (RA1). The PPI group also assisted in the recruitment of a third RA. An amendment to the eligibility criteria for participants, removing the need to stop taking any antipsychotics, was implemented following PPI feedback, and we contributed to revised recruitment plans which were not implemented due to the early study closure.

The PPI group also impacted on the analysis, conclusions and dissemination of the study. We contributed to the funders report in 2021 requesting an extension to the study, and to the proposal submitted regarding the closure options for the early end of study. In addition, the group contributed to the end-of-study results meeting, reviewing and inputting to, the qualitative data obtained from participants and research staff taking part in the trial, and to this paper.

Two changes were made to the PPI plan within the trial after feedback from the group: deciding on Love2Shop vouchers and requesting further funding for PPI for the extension of the trial.

The findings from the evidence collected regarding the impact of the PPI group have been grouped into themes of: 'importance of PPI within the trial'; 'equality of PPI and researchers'; 'value of PPI to the trial team'; 'depth of PPI engagement with the study'; and the 'personal benefits for the PPI contributors'. Additional theme of 'PPI Group functioning' and 'challenges' were also included.

Importance of patient and public involvement within the trial

Both the researchers and the public contributors felt that the PPI within the trial was very important and had a measurable impact on the trial itself:

> *The benefits of PPI into the trial are undeniable and numerate.*
>
> *RA1*

> *I think the strength of us is on lived experience, and it's the patient and public side of it that we are putting over isn't it. How would you do if you were part of the trial? How would you do if you had to read this? Does this make sense? what would be the obstacles. How can we keep you on board? You know all of these kind of practical things.*
>
> *PPI 3*

> *I believe that as laypeople (though with direct or indirect experience of depression), we could take an objective view of the trial and specifically of the communications with those undertaking the trial.*
>
> *PPI 4*

Patient information documents were greatly impacted by the feedback from the PPI group with the trial team having to spend time reviewing and rewriting the documents, but ultimately seeing the value in this:

> *[O]ne of the key benefits was amplification of the patient voice in everything we do . . . PPI helped to make the trial design, resources and amendments as patient centered as possible.*
>
> *RA1*

> *[I]t was the PPI group that basically said, Look, strip this down so people can actually understand it.*
>
> *RA2*

Due to having a member of the PPI group with visual impairment, accessibility was highlighted to the entire team and all documents, and the website, were worked on to try and make them accessible to a range of disabilities:

> *I can remember making a comment from my perspective about it not being very accessible, for disabled people like me.*
>
> *PPI 3*

> *It's made a massive difference, and it's made me think about that just in my life more (accessibility).*
>
> *PPI 5*

We had two public contributors who were carers and this also became a vital component to the PPI input as we were continually thinking about the participant's support network, how they would manage the demands of the trial and how their family and friends would also be impacted by their participation:

> *[I]nvolving the family, is important, involving the network.*
>
> *PPI 2*

Thus, the carers voice was continually front and centre alongside that of the people with direct lived experience of BD as we concluded that having someone to support you as a participant in a drug trial like this would be essential:

> *[I]f you want to be part of something, (like a trial) it's the support you need to do all of these things.*
>
> *PPI 2*

The members of the PPI group also commented that they felt that the patient was always at the heart of this trial, that the researchers were focused on supporting participants and ultimately finding out if pramipexole would be helpful to patients with BD:

> *I felt the whole way through this, that the patient's always been a priority for the study team.*
>
> *PPI 5*

> *Oh, I think that's got to be true. Yeah.*
>
> *PPI 4*

> *Yeah, I wouldn't be part of something if I felt it wasn't.*
>
> *PPI 2*

As there had not been a comprehensive PPI plan for the trial this led to it being more reactive and driven by the members of the PPI group rather than following a set structure of involvement. This was a positive and negative, in that it allowed the PPI group to be involved where they wanted to be, and allowed for creative and alternative inputs, but could also have been challenging for the trial team as they had to identify areas for PPI involvement as the study was progressing:

> *I feel that sometimes researchers struggle to know what tasks to ask of PPI members. They can seem a bit hesitant to ask for our input in case it's too much, or not something that is usually done.*
>
> *PPI 5*

Equality of patient and public involvement and researchers

All of the members of the PPI group felt listened to by the research team, that our input was valued, useful and did actually instigate changes being made to the study design, patient information documents and the ethical concerns around the trial:

> *[T]he fact that they've taken our thoughts into consideration, all the way through, is made me really quite proud of this study.*
>
> *PPI 5*

> *[T]hat's right*
>
> *PPI 3*

The CI was seen to be fully engaged with the PPI, leading by example his attitude towards the public contributors was always inclusive, open and professional:

> *I think something that really impressed me about him it was, you know. He's a pretty big light in the mental health. Well, you know, and my psychiatrist speaks very highly, and yet, you know he was humble enough to answer my really rubbish questions, and and I really I really admired him for that. Actually.*
>
> *PPI 3*

The PPI voice was included in the TMG as an equal member. This was accepted by the rest of the trial team and seen to be beneficial:

> *This (integrated PPI) was facilitated by inclusion of PPI in the TMG which meant that representatives were constantly part of discussions and changes.*
>
> *RA1*

By including the PPI lead in all TMG meetings and CI catch-up meetings for the duration of the trial PPI has truly been integrated into the study:

> *[T]he public involvement voice has really been listened to in this.*
>
> *PPI 3*

The PPI group meetings were felt to be inclusive and beneficial to the researchers:

> *Because, if you ask some kind of basic simple question then I think that informs the researcher as well. They know their subject so well, and they haven't even considered this very basic issue.*
>
> *PPI 4*

Concerns in the literature around public involvement possibly being tokenistic or a tick box exercise was very much not the case in this trial. The PPI meetings were driven by a desire to gain the public perspective from the researchers on aspects of the trial with specific areas requiring review and feedback discussed at each meeting.

> *The team have always been very open to working with the PPI group and been, eager to get their input and make use of recommendations. They actively requested PPI input and have always been able to attend PPI meetings when requested.*
>
> *PPI 5*

The PPI group were kept informed of developments in the trial by the PPI lead as she attended all trial meetings and was fully involved in all decisions made. Feedback was given to the PPI group following any changes that had been made after their previous comments maintaining our commitment and inclusion within the trial:

> *I have always felt fully part of the study and my views as a PPI member were valued and appreciated and very much welcomed.*
>
> *PPI 2*

All of this, having a feeling of true involvement, being included in the decision-making and being treated with respect and appreciation by the trial team led to a strong bond between the PPI group members and the trial.

Depth of patient and public involvement engagement with the trial

With this being a randomised controlled drug trial for patients with BD the ethical issues surrounding the trial were complex. As a PPI group we had many concerns around a variety of issues which were listened to by the researchers. Sometimes amendments to the trial could and were made, and on other occasions we influenced the patient documents, recruitment of participants and even checked that the RAs were being fully supported in their roles as they were contacting the participants regularly with in depth and personal questionnaires to be completed to track the trial outcomes.

Concerns around recruitment were based on what capacity the patient would have to engage with the trial. We were concerned about numbers of patients with BD who were ill enough to require treatment, but well enough to be able to manage the burden of participating in the trial. The participants were required to complete weekly questionnaires online, engage with the RA phone calls and manage the medication titration which was quite complicated.

> *You know that they were always going to find it very difficult to join a trial, because I mean when I was ill earlier in the year between March and June. very poorly, and yes . . . while I was poorly there's no way I would have joined the medical trial.*
>
> *PPI 3*

> *Yeah, I agree. when you're in that kind of state you don't want to do anything*
>
> *PPI 4*

> *When the patients are poorly with bipolar. I think about my own case, which is all I can think about, all I've got experience of. There's no way I'd have joined the trial.*
>
> *PPI 3*

> *Well, this Isn't going to be for everybody with Bipolar, but certainly in my case at the minute, (caring for her daughter) . . . Things wouldn't happen without a lot of support from me.*
>
> *PPI 2*

The removal of the eligibility criteria that participants had to be withdrawn from antipsychotics, if they were on them, prior to randomisation was an important amendment. We were very pleased that this was approved to support inclusion of participants without causing them any detrimental effects from having to stop taking their antipsychotics.

> *I think about my own case, there's no way my psychiatrist would have let me stop taking anti psychotic, insisted on me carrying on with them. So I think that was a very important change.*
>
> *PPI 3*

> *I was very worried about that, because this study, can do no harm, so it can't make people worse. And I remember that being one of my big concerns*
>
> *PPI 2*

Concern for the participants centred around the calls with the RAs, which were adjusted after the role-play calls were completed with the PPI group

> *(The RA's were) talking to patients about hospitalisation and (I was) thinking that would really scare them.*
>
> *PPI 3*

The inclusion of the anxiety questionnaire alongside the weekly mood rating scales was a contentious issue:

> *[P]eople to keep the questions to the minimum in all parts. But I think the PPI group said, actually given the rates between depression and anxiety that felt really important to monitor this.*
>
> *RA*

Ultimately it was the PPI voice that was the deciding factor in this decision and anxiety questionnaires were included to monitor patient symptoms, even though it added to the number of questionnaires being completed by participants.

There were also concerns around the end of the trial, participants being unblinded and their potential feelings if they found out that they were on the placebo drug.

> *Exit strategies are a huge thing. Because . . . you can't just sort of leave somebody cold and say right? Goodbye . . . it's been part of your life . . . And you feel like, there's a big hole, and you have lost something.*
>
> *PPI 2*

> *Yeah, the participants will have created relationships, (with the RA's) and it's like part of that support network.*
>
> *PPI 5*

> *I was concerned about the psychological impact of the patient finding out. (If they were on the placebo or active drug.)*
>
> *PPI 3*

> *I think, for me, if I was feeling better, and I was on the placebo, I might feel like I have been tricked or something.*
>
> *PPI 2*

These concerns led to the addition of a final RA call with the participant and highlighting the importance of a discussion with their local clinician around the end of the trial and their medications going forward.

We had personal concerns for the RAs completing the phone calls to participants:

> *[T]he phone calls they terrified me, thinking that, like [RA1] and [RA2], they're gonna be in that offices at this point in time, because this was before the lockdown, like in your offices, ringing people all day every day talking through these questions and things. It sounded like so draining*
>
> *PPI 5*

> *I was worried about you guys.*
>
> *PPI 3*

We were reassured that they had support from each other as well as by the CI with weekly supervision meetings, and planned their days so that the patient contact calls were spread out to lessen their emotional impact.

Value of patient and public involvement to the trial team

The researchers involved in the PAX-BD study often commented on the importance of the PPI input to the trial which was reiterated to the PPI group at every meeting and seen in the level of importance placed on PPI within the TMG meetings and attitude of the researchers. Retrospectively the researchers who completed the PPI questionnaire and participated in the PPI review meeting commented that the PPI group added to the trial, as well as to their own views of PPI within research:

> *My expectations . . . were certainly surpassed by the ongoing enthusiasm and invaluable contributions from the group. I would say that this made me think more about how to involve PPI members in things I was working on beyond the initial expectations.*
>
> *RA 1*

The PPI group were not restricted by existing dynamics within research infrastructure and were able to highlight areas which should and could be challenged, while maintaining a professional and evidence-based approach to challenges and questions:

> *The group additionally highlighted where we should push back against funder requirements and study closure, as well as providing robust justifications and support to do so.*
>
> *RA1*

The RAs who were involved in the role-play calls found the experience beneficial:

> *We've spoken to pretty much everybody (in the PPI group) at one time or another on the on the phone going through the questionnaires. Yeah, they were very, very useful. I mean just from a training aspect . . . getting it getting a feel for how it's going to sound on the other end of the phone. So when we finally did get our participants on board, it became more of a conversation . . . So that was really really useful on our personal level.*
>
> *RA 2*

> *PPI members supported the training of RAs via role play phone calls, which was extremely helpful in providing constructive feedback, fine-tuning the prompts and reconciling clinical and/or potentially alarming questions with a personal/reassuring touch. The role plays also helped RAs practice study phone calls, familiarise with the prompts and put them at ease when the initial participant calls began.*
>
> *RA 1*

> *[J]ust learning how to make it sound more relatable, and not as they were just reading off the sheet. and you know more of the sort of human touch like the personal touch around it. So actually reassuring people before asking questions, particularly for the first time, and around hospitalisation or side effects. Anything like that. That was super helpful. and and also just establishing some transparency like explaining why we're asking questions, and just how it would work weekly.*
>
> *RA 1*

The PPI group recalled creating challenging scenarios for the role-play calls to challenge the RAs:

> *I gave them a hard time. I was suicidal . . . I thought. Like with the worst case scenario. And then you'll be prepared for anything.*
>
> *PPI 5*

Which, although challenging, proved to be useful:

> *Yeah, it was appreciated. Actually, the curve balls . . . You expect one thing, and it did happen once or twice, speaking to the participants. So you know, had you not done that, I would have been even more on the back foot.*
>
> *RA 2*

However, there were also negative views of this experience which highlights a lack of planning and possibly training for the PPI group prior to completing this exercise:

> *This was helpful to RAs in terms of practicing how to speak to prospective participants with those preferences, but when it came to overall feedback, it could have been helpful to balance the subjective experience with a generalised view of others, that is distinguishing nice-to-haves/personal preference suggestions vs. serious concerns that could adversely impact participant wellbeing and/or hinder ability to carry out the role – safety monitoring and data collection. Also, to consider RA individualism as a factor when reflecting on interactions and advising changes, e.g. feedback on voice-pitch as an amendable attribute seemed unconstructive.*
>
> *RA 1*

The research team also noted that the time taken to include the feedback from the PPI group was factored in and adapted to as often as possible, but it was a challenge:

> *We went back and forth a few times on the information sheets, we'd start them, and then you (the PPI group) had to look at them and tweak them for us, and then I think it was a couple more bits of back and forth, just to get them to get them right.*
>
> *TM1*

The RA who was recruited during the trial was interviewed by a panel and also completed a role play call with the PPI lead as part of the interview process. The PPI lead completed the role play with all of the interview candidates with RA 1 present taking notes. RA 1 and the PPI lead then discussed each candidate's performance and feedback was given to the CI when deciding on which candidate to offer the job to. This process was seen as positive by the RA who was recruited:

> *I remember when I got the call from Hamish, when he was offering me the job, one of the things that really swung It was how I performed in the role play. To hear that feedback, I think it was a really nice way to do the interview.*
>
> *RA3*

Personal benefits of patient and public involvement contribution

We became personally emotionally engaged with the trial due to the many challenges that we faced, the COVID-19 pandemic, having to delay the start of the trial, recruitment challenges, moving all communications online, extending the trial date, early closure and losing our PPI lead which impacted us all.

The early closure was very disappointing:

> *It was really upsetting wasn't it. It was upsetting and unsettling times.*
>
> *PPI 2*

> *I think the expectations was a bit unrealistic, really, because it was always going to be very difficult to get bipolar patients who were treatment resistant to go on the trial.*
>
> *PPI 3*

> *[I]t just felt very unfair, like, after we were still in COVID-19 restrictions.*
>
> *PPI 5*

> *[A]nd recruitment's been the big issue, as far as I'm concerned.*
>
> *PPI 4*

We all felt personally let down by the trial's early closure, and some felt it represented the attitude towards mental health in this country:

> *[A]nd it's hard not to take that personally, like I know it was a business decision and a financial decision. But it was yeah for me. It was really emotional.*
>
> *PPI 5*

> *I just felt it reflected attitudes towards mental health.*
>
> *PPI 4*

> *I realise this is cynical, but I do feel that there are some real big political, hot potatoes in health care like you know, cancer treatment and heart treatment, and so on. And that's good that those things are important because they are important. But I think mental health is very underrated, and I think it's, certainly my mental health has contributed to a lot of my other physical ailments, you know, and I think that's that's overlooked.*
>
> *PPI 3*

Losing a group member was possibly the most challenging aspect of being part of this trial:

> *[I]t's difficult and sad times isn't it, with what happened to Sandy and everything, and we miss her, and it was such a shock to me. It was very traumatic losing our PPI lead. Very raw and sad.*
>
> *PPI 2*

VB (PPI 5) took over as PPI lead in October 2021.

> *[A]s a close personal friend of Sandy, and her being the reason I became part of the trial it was a big loss which was felt by the entire team, but also I felt fully supported in my new role*
>
> *PPI 5*

> *I think you've done really well, because I think taking over the lead from Sandy was always going to be really hard. I think, if you if you did it from the beginning it would have been easier. And we understand why this has happened, and it's really terrible and sad. So I think you did a great job of taking over. I really do.*
>
> *PPI 3*

However, overall, PPI group members found the experience of being involved with the PAX-BD study positive:

> *For me this has been an entirely positive experience, largely because of knowledge gained from others in the group and their own experience of bipolar/ depression. I continue to feel that the treatment of mental health in the UK is poor at best and if I can continue to make even the smallest contribution, I feel privileged to do so.*
>
> *PPI 4*

> *We've all got different reasons perspectives for being on it. So I was glad to be included in something that I thought was important. Gains from my perspective are mainly altruistic as my daughter could not benefit directly but others possibly could.*
>
> *PPI 2*

> *I felt empowered and valued in my role as a PPI group member and even more so as a PPI lead.*
>
> *PPI 5*

Patient and public involvement group functioning

The PPI group felt that training was not an essential factor in our ability to participate in the PPI within the trial,

> *I don't even know what kind of training would they do to make anything any better, We got trained through the meetings. Really. But I think that's been a successful strategy actually and I think it's the meetings for us as held everything together.*
>
> *PPI 4*

Training was seen to be through the research team presenting at PPI meetings, providing an overview of the trial and detail on the aspects that we discussed and provided feedback on.

> *[I]n each meeting you asked questions you discovered about it. The whole of the project was outlined. We discussed it all. We looked at the materials. I mean, I don't think we need to be experts in like data analysis . . . I need the human side of it.*
>
> *PPI 2*

This implies that although training is important in ensuring effective public involvement, it can take many forms. Completing an induction, online or in person training is not always necessary and needs to be tailored to the PPI group and its individual members. This includes supporting an open dialogue between researchers and public contributors during meetings and through any contact between meetings, and recognising the needs and experiences of the individual, either through lived experience of the study condition, previous research involvement and knowledge, or personal skills and abilities:

> *Having never taken part in anything similar, I was initially apprehensive about taking part. I doubted the value of my contribution at first but as we progressed, I realised that the group as a whole were making an incisive and valuable input.*
>
> *PPI 4*

The PPI within this trial developed from its initial modest plan to more integrated inclusion by the end of the trial shown from the differences in the expectations of the researchers at the start of the trial,

> *I hadn't worked on a trial with PPI input before, so my expectations when I joined the trial extended to input on the trial design and patient-facing resources, i.e. information sheets, consent forms, patient diaries and so on.*
>
> *RA 1*

and their final conclusions of PPI:

> *From successful collaboration, the trial team and PPI's desire for more involvement increased, e.g. qualitative study input. Given that this was unplanned, we did not obtain input into the topic guide and it was also too late for interviews and analysis due to the study report deadlines . . . This is a huge disappointment considering we have seen how much insight and value PPI can bring.*
>
> *RA1*

Occasionally feedback was requested from the PPI lead only due to time restraints and mainly occurred when reviewing patient document amendments with hard deadlines for submission. The challenges in balancing the preferences of the PPI group and the requirements and conditions that had to be followed due to ethics or funder requirements was also identified by the researchers:

> *[A]t times it felt difficult to mitigate strong PPI interest with bureaucratic requirements, predominantly 1) Various conditions set by the funder, and 2) RA training – there was a slight disconnect in terms of the standard being satisfactory for safety monitoring and data collection vs. the PPI point of view. At times, there was focus on individualistic preferences which were different across the members, and it was challenging to satisfy disparate inclinations under time constraints.*
>
> *RA 1*

We attempted to ensure all PPI meetings were held on dates and times suitable to all group members, but this was not logistically possible, so occasionally people missed a meeting; however moving to online meetings did facilitate attendance as one PPI contributor was able to attend the meeting from France, and others were able to attend when unwell which would not have been possible had the meetings been held in person.

> *I think we've all adapted to zoom and felt supported with it, and it's been a new way of life that we've all like to adapt to.*
>
> *PPI 2*

Challenges

While overall PPI group members found the experience of working on the PAX-BD trial a positive one, some challenges were also identified. Working through the COVID-19 pandemic, losing our PPI lead in 2021 and trial staff changes which created additional challenges for our PPI group.

Our PPI group felt supported by the PPI lead and the trial team throughout the process; however, the turnover of staff meant that we had three Trial Managers and two administrators throughout the trial, which made it difficult to know who to contact and become familiar with new procedures.

> *Support was given to me when I took over as PPI lead. I spoke to the trial manager and requested cash payments, also discussing which meetings I would attend and which I wouldn't. The decisions were down to me and they took my preferences and requests into account and amended their ways of working to accommodate me.*
>
> *PPI 5*

The recruitment of a new member of the PPI group fell at the same time as the early study closure and a new Trial Manager starting which impacted the process:

> *When recruiting a new PPI group member I was sent the (training) information I requested, unfortunately her first meeting coincided with the early trial closure and the existing trial manager leaving her post and a new person starting so it felt a bit messy. I didn't feel as if I/we gave the new PPI member a proper introduction to the trial, the group and the impact that she would be able to have.*
>
> *PPI 5*

Communication was occasionally hindered by the health conditions of the PPI lead. Both PPI leads had/have chronic fatigue and pain conditions as well as lived experience of mental health which restricted their ability to respond quickly to contact from the other members of the PPI group or the trial team. Occasionally meeting minutes took an extended amount of time to be completed and forwarded to the PPI group and an agenda for the meeting often arrived late, and not at all on one occasion.

> *I didn't send out an agenda for today, because I haven't been very well, and then I was panicking about that all last night.*
>
> *PPI 5*

This was a challenge for myself and my predecessor which on reflection could have been mitigated by us requesting further admin support from the trial team, but was not seen to be a big issue for the PPI group:

> *I was like, you know what I don't have an agenda, but I knew roughly.*
>
> *PPI 2*

Not having a consistent dedicated person leading PPI was challenging in terms of communication as e-mails were often copied to multiple members of the team in order to reach the appropriate person. Having a number of Trial Managers was also challenging as working relationships had to be reestablished with new colleagues and ways of working reviewed.

Communication was also challenging due to the second PPI lead having apple technology which was not compatible with the documents sent out by the trial team. This meant that all attachments had to be sent individually to the PPI lead as well as being sent to the trial mailing list, creating more work for all involved.

Having a member of the group being visually impaired meant that some documents were incompatible with his software and had to be read to him by his wife, or copied onto compatible formats, again creating more effort for those involved. Reflecting on this highlights the need for accessibility to be considered for all communications at all times to minimise additional effort and potentially embarrassing or uncompleted requests for accessibility from individuals.

The payment process was challenging for both the PPI group and the trial team.

> *Reimbursement was challenging at times, firstly because I get the impression we didn't have the funding we needed due to expected vs. actual PPI input . . . Secondly, vouchers were often delayed due to various reasons related to internal processes – I was cognisant that this felt unfair given the tremendous contributions from the group, and did not want the delays to poorly reflect on how we valued the members' time and effort.*
>
> *RA1*

As described, the methods of ordering vouchers were often challenging and time consuming so there were delays in the PPI group receiving them leaving people feeling a little under appreciated.

> *I think that the challenges of getting them out (Vouchers), this has been a bit discouraging. You kind of feel is your input valued?*
>
> *PPI 3*

The type of voucher was an issue for some of the PPI group members, but they had to all receive the same type thus restricting the ability to pay to individual preference.

> *I can't go out on my own. So it was difficult, having vouchers just that could only be used offline and actually my wife had to do all that for me. So that was quite tricky.*
>
> *PPI 3*

> *I know the love to shop . . . you know it is tricky trying to get it printed out and get the bar codes, and do it all. And you think, oh, man! And then remember you've got it, and not losing it, and everything like that in some ways I would quite just like the money to just go straight in my bank account, and then I don't have to worry about trying to find where takes the voucher, remember, that I've got it.*
>
> *PPI 2*

The initial limited budget for PPI was challenging due to the actual level of PPI involvement and resulted in additional communications between the PPI group members, the PPI lead and the trial team which could have been avoided if appropriate funds had been requested in the initial application and the payment process had been set up in advance. Expenses procedures also had not been established causing some concerns:

> *I remember a meeting with Hamish. I feel embarrassed about it now, actually paying cash out of his own pocket for our traveling expenses. And . . . I don't think it had been costed in properly, and there was hiccups at the beginning.*
>
> *PPI 2*

The second PPI lead requested cash payments for her involvement when she took the role in October 2021 which was authorised by the Trial Manager of the time and a system for claiming was later established with the Trial Manager who took over the role. A new PPI budget was created by the second PPI lead and included in the extension funding application to cover predicted costs of PPI from 2022 until the end of the trial.

> *[M]y personal opinions (about PPI payments) have changed throughout the study, because at the start I was volunteering . . . then, as my health has got better, and I've kind of turned public involvement into a job and as I took on the PPI lead after Sandy passed away I requested payment for it, and that was sorted out, but it was like quite a big thing, and I don't know if a PPI payment was written into the funding application in the first place.*
>
> *PPI 5*

Having a clear, organised system for public contributors' payments and expenses claims is clearly an important factor in establishing trust and respect between the PPI contributors and the research team:

> *I think when you've given up all your time and doing this stuff then the principle of PPI, you should reward people in the way they want to be rewarded.*
>
> *PPI 2*

If payments and procedures are explained at the outset and any delays, issues addressed immediately then people will be understanding and able to decide for themselves how to proceed.

> *I think that's fine as long as people knows that there is a delay, and you will get them (vouchers/payments) at some point. People don't worry about it.*
>
> *PPI 2*

We also had to adapt to online meetings following the COVID-19 lockdowns:

> *[D]ifficulty of COVID-19 meant that we were obliged to hold many meetings on Zoom. Not my first choice, but this approach was surprisingly effective.*
>
> *PPI 4*

The data collection of this paper was difficult as the PPI was not planned to be evaluated and thus some documents and communications had not been actively stored for the purpose of review. Also the PPI lead and the Trial Manager were not involved from the start of the trial and found it difficult to locate some information, occasionally having to ask other colleagues as seen in e-mails and conversations between the PPI lead and Trial Manager:

> *I'm finding difficult at the minute, writing this paper and looking through it all. I haven't been involved all the way from the start.*
>
> *PPI 5*

> *I'm struggling with this one a little. Eva has helped me out massively and I think found what you're looking for.*
>
> *TM 1*

Discussion

Six actions have been identified by previous research as being required for positive outcomes of public involvement and echo the findings of the RAPPORT study:

- Support – including compensation and individual requirements.
- Capacity building – training for PPI contributors and researchers.
- Proportional – involvement is tailored to the needs of the research and public advisers, and pragmatic decisions are made to balance contradicting demands and limited resources.
- Communication – consistent, responsive and proactive and in a format suitable to the individual.
- Involvement throughout the research.
- Evaluation.

With three main barriers to involvement being identified as:

- Time – things take longer when you are running them past a group of public contributors.
- Communication – understanding the terminology, hierarchy barriers to questioning researchers and asking for clarification, challenges when people don't have the confidence to ask for what's they need, including explanations. Academic language and PPI terminologies can cause confusion for example, the term 'layman' is not deemed acceptable to some PPI members as it has a religious undertone, and plain English is the preferred term for accessible language.
- Funding – paying for PPI time, input and what is available in budgets. To include diverse and relevant representation you need a larger number of PPI members, but this is costly to fund.

Although we can find evidence of all of the six actions for positive public involvement within the PAX-BD trial, we have identified both positive and negative aspects to the majority of them, as well as finding the same barriers to involvement as previously identified along with our own of

Payments in PPI are a contentious issue with lots of work being done to minimise disruption to public contributors in terms of it possibly affecting benefit claims, pensions and tax returns. This is a barrier to public involvement in research and needs to be addressed on a national scale. For individual trials, our recommendation is to appropriately cost PPI activities within the funding application, allow extra funds for additional input and reactive involvement as the trial progresses and relationships and individual skills are developed and included if possible, and ensure that payment systems are in place and fit for purpose prior to involving public contributors. This will reduce any teething problems and provide physical proof that their time, effort and opinions are valued by the team. Considering PPI contributors as equal partners within research means ensuring payments are as professional as you would expect your own salary to be. Communication around payment is also vital in maintaining trust and relationships between researchers and public contributors.

However, on reflection, some training for the PPI contributors on providing feedback to the RAs when completing the role-play calls would have been beneficial in ensuring that appropriate and implementable feedback was provided.

I have heard anecdotally, and have personal experience of researchers being driven to tears by aggressive PPI members questioning their work, or bullying behaviours from one public contributor to another. Inappropriate behaviour is unacceptable in any situation and requires effective management which may not be included in researcher training. Training for researchers is vital in areas such as facilitation of PPI meetings, communication, influencing and group management skills to ensure all voices are heard, behaviours are managed and research questions are addressed within the allocated timescale.

Additionally, PPI members need to be able to communicate their lived experience while staying on track with the question being asked, being respectful and being acknowledged and for their input and expertise. Pre-existing skills of PPI contributors need to be drawn upon and feedback on contributions made to establish a professional working relationship and enable personal development and self-awareness. Confidence can be an issue with many PPI contributors, possibly feeling as if academics are intellectually superior and would not want to hear their opinions or that their questions may be obvious or silly. Effective facilitation of meetings and one-to-one discussions could help increase confidence levels as well as building trust and respect between researcher and PPI contributor.

This integration and successful collaboration were probably due to the inclusion of the PPI lead on the TMG and CI catch-up meetings, which enabled us to identify areas of the trial for PPI input and proactively create opportunities for the group. The requests of the PPI lead were never refused, which could be seen in a negative light, as PPI involvement demanded extra time of the researchers, additional meetings and costs not budgeted for. However, the positives were that the PPI group were able to be included in more aspects of the trial than initially planned, for example, the qualitative paper, the end-of-study results meeting, and this paper was also an additional requested action for the trial which was approved by the CI and the TMG.

Opportunities for involvement were available throughout the duration of the trial, from initial feedback and assessment of the funding application to involvement in the dissemination of the findings and creation of this paper. PPI contributors were able to be involved when they wanted to, and declined aspects of involvement that they did not want to participate in, or have capacity to do (e.g. one member of the PPI group did not take part in the RA role-play calls).

Our evaluation of the public involvement within the PAX-BD trial has been led by well-known PPI evaluation tools and frameworks. We have identified areas of PPI impacting the study as well as discussing the process of PPI integration within the trial and the personal impacts to the public contributors and the researchers. We have answered the research questions identified and created a list of recommendations to support future public involvement in research.

Conclusion

Our evaluation of the public involvement within the PAX-BD trial has been led by well-known PPI evaluation tools and frameworks. We have identified numerous areas of PPI impacting the study as well as discussing the process of PPI integration within the trial and the personal impacts to the public contributors and the researchers. We have answered the research questions identified and created a list of recommendations to support future public involvement in research. The PPI within this trial was largely developed as we progressed which had both positive and negative impacts for the trial, the researchers and the PPI contributors and with hindsight there are some changes that we would make.

Some limitations of this review are that we did not have the aim of writing this paper until towards the end of the trial, so some information may have been lost due to not being aware of the need for PPI record keeping. The original PPI lead sadly passed away in September 2021. She had been involved from the initial study design and unfortunately was not able to participate in this assessment of the overall involvement which would have added more depth to our evaluation. A different PPI lead taking over created new ways of working which may have affected the views of and created a ‘before and after’ attitude towards PPI from the other PPI members and the researchers, possibly impacting the involvement from the group. The second PPI lead was not involved from the outset of the trial so has no reference

for the period prior to funding being received and her joining the group in March 2019. There have been a number of different Trial Managers which could have impacted the level of PPI involvement in the study.

On the whole, the PPI has been relevant, beneficial and impactful to the trial, the researchers and the public contributors, with one PPI group member with no previous research experience stating:

> *Actually, I've really enjoyed it. It's been so interesting to listen to. So I mean the upshot of all that is that I would definitely volunteer for a similar thing in future for sure.*
>
> *JA (PPI 4)*

Which I find to be an endorsement of our contribution and conclude that our PPI was successful. This detailed report of the positive and negative aspects of PPI within a RCT will hopefully help others to design and carry out effective and inclusive PPI to ensure that research is focused on creating improvements for the patients and public affected by the issues being investigated.

Recommendations

What worked well

- Positive attitude of trial team to PPI led by the CI.
- Flexibility for PPI members to be involved where they wanted to.
- Integration into the TMGs – status of PPI lead was never questioned as an equal partner in the group.
- Prioritising PPI as an agenda item for every TMG and CI catch-up meeting.
- Utilising people's different expertise.
- Listening to carers as well as people with lived experience of the condition.
- Reactive PPI for changes to patient documents, study amendments and recruitment.
- Using PPI voices to challenge the funders re recruitment and trial amendments.
- Feedback actioned and changes made to anything that the PPI group reviewed or discussed.
- Feedback on changes made after PPI feedback was given to the group at the next PPI meeting keeping us informed of our impact.
- There was diversity of gender, lived experience of depression and BD and carers of people with BD, age, disability and research experience within the group providing a range of perspectives.

What not to do

- Create the PPI as the trial goes along. Having a plan and some structure would have been beneficial to getting PPI involved in the appropriate places. Having a PPI member at the TMG and catch-up meetings did go some way to addressing this, but it still could have been more organised and streamlined.
- Missed opportunities for PPI input, for example designing the qualitative questions and themes and analysis.

What would we do differently next time

- Involve PPI in more aspects of the trial – qualitative planning, possibly use as peer researchers to complete qualitative interviews.
- Involve the PPI group at an earlier stage when drafting patient documents to reduce time spent redrafting.
- Due to COVID-19, many changes to the study had to be made very quickly and the PPI members were not involved in these as much as the study team would have liked.
- More in-depth planning for PPI activities, for example role-play calls, qualitative interviews to ensure appropriate involvement and inclusion of PPI in important study areas.
- Training on relevance when providing feedback for PPI group members.
- Have a dedicated PPI lead within the trial team.
- More admin support for PPI lead.

- More diverse PPI group members. We were all North East based, White British, mainly middle class.
- Larger PPI group – creates more opportunity for diversity, a range of voices and new ideas.
- PPI Funding – set up as part of the funding bid. Appropriate to the level of involvement expected, additional tasks, involvement etc., not just meetings. Enough to cover a larger and diverse group.
- Voucher payments made more timely. Cash payments available if preferred.
- Maintain PPI records with the goal of authoring a paper showing the impact and learnings for researchers to use to support more effective PPI in future trials.
- Funding applications need to allow room for innovation and flexibility in terms of PPI plans, inputs and altering trial design, outputs and dissemination. You don't know what you will produce until you have the conversations with people with lived experience.

Appendix 7 Discussion

Lessons for future research: issues identified in qualitative data – insights from the qualitative analysis

The following extends the qualitative analysis, specifically examining lessons that could be learnt for future similar research.

Organisational issues

Findings in the 'barriers' section of *Appendix 5* highlighted organisational issues associated with poor research prioritisation, lack of staff resources and limitations of the care pathway which made it difficult to access TRBD patients for the PAX-BD study. As such, HCP participants emphasised the importance of clinically driven research, whereby medical personnel integrate trials into treatment delivery practices to improve research visibility and recruitment. This could be achieved through compulsory GCP training, protected time for research and the requirement to inform patients about ongoing trials to facilitate informed choices about treatment.

> *It really needs to be medic led because it is the medics, it is the doctors that will say, 'Yes, I want to refer my patient', or, 'Yes, I will give them this information'.*
>
> *HCP Researcher 4*

> *. . . more people being involved in research and having their GCP would be helpful to increase the pool of doctors who are qualified to get involved in research . . . research champions embedded within teams . . .*
>
> *HCP PI 4*

> *. . . a certain NHS trust has research as something mandatory that clinicians have to ask their patients about. I think if that was implemented in all NHS places, that would help a lot.*
>
> *HCP Researcher 11*

Experienced HCPs additionally advocated the utilisation of primary care to broaden patient access, as well as the ability to use mass promotion strategies such as mail-outs. Recruiting from general practices and setting up Patient Identification Centres could therefore bypass barriers of patient gatekeeping and reliance on staff with low availability, as well as providing access to depressed patients who may otherwise remain without treatment or referral to secondary care.

> *[Y]ou could send a generic letter out to everybody with bipolar who have necessary depression in their lives and say, 'Would you be interested in trying this drug?' And you might get these responses back from all these people that no one had even thought about.*
>
> *HCP Researcher 6*

> *They have been getting the study teams to put it in their protocol to use GP services. So they get GPs to send out mail outs with their patient information sheets and then they just attach a reply slip if they'd like to be contacted . . . they have had so much response from that and they've been able to recruit really well. And I think it's just because it cuts out care coordinators, because they're really, really busy. Whereas GPs they obviously get a contract and they get paid X amount of money to do it. But once one mailshot has gone out, you do see more of a response . . . I think that does really help. Well, it has helped for their studies anyway. So if there is a way of doing that in the future, I think it would be a way forward.*
>
> *HCP Researcher 10*

One HCP suggested that simple improvements in record-keeping practices may facilitate the identification of eligible patients. In the PAX-BD study, site staff widely used patient databases for pre-screening, but often found them to be lacking in meaningful detail; clear information around diagnoses and treatment history could streamline this process, cease reliance on clinicians and prevent the erroneous exclusion of eligible patients.

> *. . . being able to access diagnoses and just being able to- without the clinician having to the remember their patient might be suitable . . . They must have been doing some kind of search on RiO and then came up with a diagnosis that looked . . . like it might have been a suitable candidate. I know that's another way of accessing patients . . .*
>
> *HCP PI 3*

Trial design

Some participants reported experiencing difficulties with the titration process. They expressed that additional support around managing titration would have been helpful, for instance providing more information, ready-filled dosette boxes and extended discussions with CSOs and/or RAs about medication as well as the involvement of carers in such conversations. This indicates some reliance on study documents and/or participants to reliably convey the intricate dosing information to carers, despite not managing their usual medication.

> *I used a Dosette box . . . being given in, like, a Nomad type box, so they were increased, might be helpful.*
>
> *Participant W12 > 2*

> *. . . a little bit more information for the first week. Because it's a trial and everything else, it had got my partner confused. Like I say, that first week it was confusing for her etc. so maybe a bit more information for that first week.*
>
> *Participant W12 > 10*

Patient participants additionally described challenges with the burden of dense study information and the volume of questionnaires during the trial. They indicated this would be easier to digest if spread across a number of days or weeks.

> *I did find it a little bit difficult. There just seemed a lot at once, sometimes, at the very beginning of the trial . . . I think maybe if it was broken down into two parts, so that you did some one day and some another day, then that might have been less daunting.*
>
> *Participant W12 > 3*

> *If we could have staggered those over a couple of weeks or something like that, then perhaps that would have been better rather than, yes, have to complete however many questionnaires it was in one go . . .*
>
> *Participant W12 > 4*

Some HCPs indicated that the option of face-to-face site training and participant visits would add a personal touch. This may have improved understanding of the study, connectivity to the trial and engagement from both research personnel and PAX-BD participants, all of which can have positive implications for recruitment and retention.

> *I think if there was a hybrid option of it can be done over the phone but if you want to come in we can do it person. Just so it gives patients that flexibility of them choosing . . . if they do want to come in it might, you know, make them feel more engaged and that they were getting that physical contact.*
>
> *HCP Researcher 10*

> *The training videos because you do them and then you start doing the study. Your learning just builds like with anything. It's like building blocks, isn't it? There is something about a practical application of learning or a face, which obviously we couldn't do because of COVID. There is something around that and a bit more of an interactive way of learning that, I think, would have helped me.*
>
> *HCP Researcher 6*

Trial processes

One HCP suggested that consulting experienced site teams on recruitment could lead to informed strategies based on local knowledge of feasibility factors such as resources, trust networks and the profile of patients in the locality.

> *. . . would be really good in the future when a study is started, if they asked us how we would recruit . . . If they ask us, we've got a lot of experience of recruitment of patients, and we kind of know what patients go for, or what would make it easier to recruit to a study, that would be helpful.*
>
> *HCP Researcher 8*

Collaboration between the central team and site staff was highlighted as a facilitator; sites benefitted from the CI and CI delegate presenting at their clinics and indicated they would welcome more of this support.

> *. . . come in and help us out with some of those talks, that would be great.*
>
> *HCP Researcher 7*

Central RAs also expressed they would value more site involvement with study participants in terms of encouraging engagement with safety monitoring and highlighting the importance of this. In future trials, introductions or handovers with all parties could be arranged to bolster the sense of collaboration and continuity in care.

> *. . . reiterating from the beginning to participants that one of the compulsory aspects of taking part in the study is engagement with the phone calls . . . introduction to the RAs from the site, so it feels like a bit of a handover . . . via video call or even on a group conference call.*
>
> *HCP Researcher 2*

Some patient participants similarly indicated that a stronger site presence during the trial may have been helpful, particularly from clinicians.

> *. . . there was less contact from the study doctors, from my team. So I did think there may possibly have been a bit more contact on that side.*
>
> *Participant W12 > 6*

As discussed under *Barriers*, some patient participants expressed feeling confused after reading the information sheet due to exclusion of active symptoms such as impulse control behaviours, as well as use of the term 'hospital'. It was suggested these sections could be re-worded for clarification, as one participant indicated that despite explanations from study staff, their queries remained somewhat unanswered.

> *I still wonder why that is, even though they've explained it to me. I still wonder why that is put in the information given and it's put very strongly. That would be one thing that definitely I would, well of course it needs to be there, but it needs to be in a better format.*
>
> *Participant W12 < 1*

Insights from central study team

Analysis of the barriers and facilitators, as well as 'Suggestions for future improvement' as an emergent theme and staff experiences precipitated much reflection on the successes and shortcomings of designing and implementing a semiremote, national multicentre Phase III CTIMP RCT. The lessons learnt are summarised to inform general considerations for similar studies in future.

Remote design

Remote designs can alleviate burden from busy site teams and optimise funding using central RAs. They are likewise appealing to participants with busy schedules who require flexibility to complete study activities, and also broaden the reach to include patients who have limited scope for in-person visits. However, RAs observed that for some participants, completing study tasks in their own time seemed to feel like an encroachment on personal life. As discussed previously, low mood can additionally impede engagement.

A hybrid design with the option of face-to-face appointments with research staff could mitigate these barriers to provide personalisation, separation from private life and elicit a higher rate of completion, as well as increasing patient satisfaction around clinical team involvement, and minimising participants lost to follow-up. Grounding research tasks in site visits may additionally establish stronger associations with clinical treatment, reinforcing the salience of safety monitoring and providing purpose. Expanding the range of choice would reinforce patient-centred values, and integrating some face-to-face visits can bolster the quality of safety monitoring with visual cues of well-being and medication adherence checks alongside participant reported symptoms.

As follows, the use of technology as the only means of data collection is inadvertently exclusionary. In addition, the choice of digital platform is also vital; issues with systems can be frustrating and demoralising for participants, as well as tarnishing trial credibility and stagnating data collection. RAs reported that such malfunctions significantly hindered participant engagement and crucially, this reliance on digital self-reported symptoms created blind spots in safety monitoring processes central to CTIMPs. It is recommended that researchers choose reputable platforms with reliable developers experienced in customising the system for trials, vigorously test the user-experience on multiple devices and ensure regular reminders can be sent to participants to prompt questionnaire completion. Likewise, comprehensive, accessible and established procedures for offline options (such as paper questionnaires and staff-assisted completion) are required to provide a contingency plan in case of technical failures, as well as expanding inclusivity of the trial.

Trial management

Reflections of trial management offered insights into key learnings in the areas of AE reporting, governance oversight and expectations based on site team experience.

Adverse events for the trial were collected by the RAs during weekly assessments with participants and recorded centrally. It was discovered at the end of the trial that some disparities existed between the data collected by the central team and those collected by clinicians locally. Future study design should build in ways of confirming local data collected in clinical consultations with those collected centrally to ensure the quality and completeness of data collected.

This review of data completeness stemmed from the experience of the trial management team regarding the expectations of research teams and variation of research experience across the country. It was found through the trial that psychiatric clinical teams were not as research experienced in running trials and this should be noted for future work in the speciality. Many sites needed support in completing routine research activities such as the upkeep of an ISF and paper archiving. It was noted that changes to ISF management and archiving came into place because of the pandemic but that considerations should be made for future research regarding the potential changes to protocol and sponsor governance regarding permissions of e-ISFs and e-archiving.

A final word regarding general oversight for local governance at sites would recommend an annual formal review of local site arrangements for upkeep of the ISF provided, planned archiving arrangements and provision of staffing to enable the adherence to legal research requirements. This will allow the harmonisation of local trust policies with sponsor and funder requirements in keeping with national and international research guidelines.

Central pharmacy

The study structure of a centralised pharmacy dispensing directly to participants provided a unique opportunity in trial management. From an oversight and governance perspective, a central pharmacy had a series of positives over dispensing at a local level. There were, however, some drawbacks to this approach namely around storage of stock, risk assessments and the need for clear study roles.

Regarding stock, the quantity of stock held at the sponsor central pharmacy provided a challenge in terms of logistics as well as monitoring. This trial was fortunate in that the storage requirements for IMP did not require temperature or other special environmental considerations which would have otherwise rendered the central storage impossible due to the quantity of IMP.

The additional consideration with a centralised pharmacy is that of the delivery itself. During the study, delivery was disrupted by the COVID-19 pandemic as well as postal strikes that, although did not result in direct difficulties for the trial, did nevertheless present a challenge in regards to considerations for timescales for follow-up. The role of the RAs in this regard was essential in keeping open lines of communication with participants during the weekly calls to ensure that IMP has arrived as well as the empty bottles being posted back to pharmacy. Future considerations should bear in mind national strikes affecting the national postal service and so should be factored into initial risk assessments.

The final point around the use of a central pharmacy should come with the considerations of the use of the sponsor organisation as a site as well as a sponsor. This requires the clear definition of trial roles to enable clinicians to also engage in additional roles on behalf of the sponsor and so not to create conflict of interest. This is particularly relevant when considering the role of clinicians as CI and PI, or as sponsor representative and Clinical Research Organisation at site.

The feedback from sites regarding the centralised pharmacy has been positive however as it took any potential burden away from the local sites which was particularly pertinent during COVID-19. As such, it meant that only one pharmacy organisation needed to enact amendments, whereas multiple organisations would be required to do so if prescribing at a local level. Key feedback for the trial and for setting up any future research would be to involve pharmacy from the very beginning of the trial in all areas to create a robust trial design and to reduce the need for amendments later on.

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