ASCEnD

Aripiprazole Sertraline Combination Effectiveness

CLINICAL TRIAL PROTOCOL

Full Title:	**A**ripiprazole/**s**ertraline **c**ombination: clinical and cost-**e**ffectiveness in comparison with quetiapine for the treatment of bipolar **d**epression. An open label randomised controlled trial.
Short Title/Acronym:	ASCEnD
Protocol Version Number and Date:	V3.0 11/09/2024
Previous Versions:	N/A

RESEARCH REFERENCE NUMBERS

IRAS Number:	1007468
NHS Research Ethics Committee (REC) Reference:	23/NE/0132
Research Registry and References:	ISRCTN63917405

RESEARCH SPONSOR

Sponsor Name:	Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust (CNTW)
Sponsor Reference:	RES-20-032

RESEARCH FUNDER

Funder(s) Name**:**	National Institute for Health and Care Research. Call: 19/130 Bipolar Disorder National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) Programme. REWARD (Optional Mechanistic) Study is funded by an internal PhD scholarship awarded from Newcastle University.

This project is funded by the NIHR HTA Programme (project reference number NIHR132773). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

This protocol has regard for the Health Research Authority (HRA) guidance.

PROTOCOL APPROVAL SIGNATURE PAGE

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

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

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

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Short Study Title: ASCEnD

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TRIAL SUMMARY

Title (acronym)	**A**ripiprazole/**s**ertraline **c**ombination: clinical and cost-**e**ffectiveness in comparison with quetiapine for the treatment of bipolar **d**epression. An open label randomised controlled trial (ASCEnD).
Trial Design	Phase III, prospective, two-arm, open label, superiority, individually 1:1 randomised, controlled, pragmatic, parallel group, type A clinical trial.
Population	Adults (aged 18 years and over) with bipolar disorder who are experiencing a depressive episode.
Planned Sample Size	270 participants.
Treatment Duration	6 months.
Planned Trial Period	A total of 48 months, starting from 01/Sept/2022.
Investigational Medicinal Products	Aripiprazole/sertraline combination versus quetiapine. Medication to be taken orally. Exact formulation and dosages will be informed by clinical response and tolerability.
Primary Objective	To determine whether the improvement in depression will be greater in participants randomised to aripiprazole/sertraline combination than those randomised to quetiapine.
Primary Outcome Measure	The Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR) reported weekly, 12 to 16 weeks after randomisation in the two arms analysed as repeated measures, adjusted for baseline, using intention to treat principles.
Secondary Objectives and Outcome Measures	To compare the impact of aripiprazole/sertraline combination vs quetiapine on: • The trajectories of symptom change, measured via the QIDS-SR reported weekly from screening. • Treatment satisfaction, measured via the Treatment Satisfaction Questionnaire for Medication (TSQM) at baseline and weeks 4, 14 and 24. • Tolerability, measured via the Glasgow Antipsychotic Side-effect Scale (GASS) at baseline and weeks 4, 14 and 24. • Pattern of medication adherence, measured via weekly questions in the study database regarding dosages of study medications taken on each of the preceding 7 days. This will be supported by use of the Medication Adherence Rating Scale (MARS) at baseline and weeks 4, 14 and 24. • Pattern of non-randomised antidepressant/antipsychotic medication use, measured via analysis of concomitant medications weekly from screening. • Change in anxiety symptoms, measured via the General Anxiety Disorder-7 (GAD-7) scale weekly from baseline. • Change in manic symptoms and rates of relapse to a hypomanic or manic episode, measured via the Altman Self-Rating Mania Scale (ASRM) weekly from baseline. • Psychosocial functioning, measured via the Work and Social Adjustment Scale (WSAS) at baseline and weeks 4, 14 and 24. • Health-related quality of life, measured via the EQ-5D-5L questionnaire weekly from baseline. • Capability well-being, measured via the ICEpop CAPability measure for Adults (ICECAP-A) and the Oxford CAPabilities Questionnaire-Mental Health (OxCAP-MH) at baseline and weeks 4, 14 and 24. • Costs and incremental cost-effectiveness, based on the Health Economics Questionnaire (HEQ), measured at baseline and weeks 4, 14 and 24. • Informal carers' health-related quality of life, capability well-being and costs of caring measured via the EQ-5D-5L, ICECAP-A, OxCAP-MH and Caregiver Indirect and Informal Care Cost Assessment Questionnaire (CIIQ) at baseline and weeks 4, 14 and 24.
Exploratory REWARD study	• Changes in reward and punishment sensitivity, from baseline to week 14 post initiation of IMP, measured via the PILT and the BIS/BAS scales.

CONTENTS

GLOSSARY OF TERMS AND ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AR	Adverse Reaction
Antidepressants	Used to cover drugs listed in the BNF (British National Formulary) as antidepressant drugs (1). It includes selective serotonin reuptake inhibitors (such as sertraline), tricyclic antidepressants, monoamine oxidase inhibitors, vortioxetine and tryptophan.
Antipsychotics	Used to cover drugs listed in the BNF as antipsychotic drugs (1). It includes quetiapine and aripiprazole.
ASR	Annual Safety Report
ASRM	Altman Self-Rating Mania Scale
BAP	British Association for Psychopharmacology
BAS/BIS	Behavioural Approach System / Behavioural Inhibition System
Bipolar depression	A depressive episode in someone with bipolar disorder.
BNF	British National Formulary
BPoR	Be Part of Research
CA	Competent Authority
CAPA	Corrective and Preventative Action
Concomitant medication	Any prescribed medication other than the IMP
CI	Chief Investigator
CIIQ	Caregiver Indirect and Informal Care Cost Assessment
CWLY	Capability-Weighted Life Years
CNTW	Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust
CPRD	Clinical Practice Research Datalink
cRA	Central Research Assistant
CRN	Clinical Research Network
CSO	Clinical Studies Officer
DMC	Data Monitoring Committee
DoB	Date of Birth
DSM-5-TR	Diagnostic and Statistical Manual-5-Text Revision
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ePRO	Electronic Patient Reported Outcomes
EQ-5D-5L	The 5 Dimension 5 Level version of the standardised health-related quality of life measure developed by EuroQol.
GAD-7	General Anxiety Disorder-7 scale
GASS	Glasgow Antipsychotic Side-effect Scale

GCP	Good Clinical Practice
GP	General Practitioner
HEQ	Health Economics Questionnaire
HRA	Health Research Authority
HTA	Health Technology Assessment
IAPT	Improving Access to Psychological Therapies
ICECAP-A	ICEpop CAPability measure for Adults
IMP	Investigative Medicinal Product
ISF	Investigator Site File
ITT	Intention To Treat
LEAP	Lived Experience Advisory Panel
PILT	Probabilistic Instrumental Learning Task
MARS	Medication Adherence Report Scale
MDQ	Manic Depression Questionnaire
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
NCTU	Newcastle Clinical Trials Unit
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
OxCAP-MH	Oxford CAPabilities Questionnaire-Mental Health
PHQ-9	Patient Health Questionnaire-version 9
PCN	Primary Care Networks
PI	Principal Investigator
PIS	Participant information sheet
QA	Quality Assurance
QALY	Quality Adjusted Life Years
QIDS-SR	Quick Inventory of Depressive Symptomatology–Self Report
REC	Research Ethics Committee
RSI	Reference Safety Information
R&D	Research and Development
R+Me	Research + Me
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SCID-5-RV	Structured Clinical Interview for DSM-5-TR Disorders-Research Version
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group

TSC	Trial Steering Committee
TSQM	Treatment Satisfaction Questionnaire for Medication
UKCRC	UK Clinical Research Collaboration
USM	Urgent Safety Measure
WOCBP	Women of Childbearing Potential
WSAS	Work and Social Adjustment Scale

1. BACKGROUND

1.1. The size of the problem

Bipolar disorder is diagnosed on the basis of a current or previous episode of mania or hypomania. It is usually a lifelong relapsing and recurring illness (2). It has a prevalence of at least 1.4% (2, 3), is associated with reduced life expectancy of 8 to 12 years (4) and has estimated UK costs of £6.43B annually, with 68% of the total costs attributed to lost productivity and informal care and 31% to health care costs (5). People with bipolar disorder are symptomatic around half of the time, the vast majority of which is depression (6-9). Depressive episodes in bipolar disorder ("bipolar depression") are often intransigent with 50% of people remaining depressed at six months (10). Depressive episodes exert a greater burden on caregivers, quality of life, education, occupation, economic costs and suicide than manic episodes (9, 11-17). Wider social and environmental determinants of poor health impact onset, prevalence and severity of bipolar disorder (18).

1.2. Current treatment

Depression in bipolar disorder responds differently to depression in people who have never had an episode of mania or hypomania. For instance, in contrast to major depressive disorder, there is limited evidence of effectiveness of psychological interventions for bipolar depression (19). With regards to medication for bipolar depression, National Institute for Health and Care Excellence (NICE) recommends just quetiapine, olanzapine (with or without fluoxetine) and lamotrigine (19). This obviously differs from major depressive disorder recommendations which include a range of antidepressants.

There is extremely limited evidence regarding the effectiveness of antidepressants in bipolar disorder. A few small studies have shown some evidence of efficacy for antidepressant monotherapy (20-22), however, the largest such trial (with paroxetine) (23) and overall meta-analyses of both monotherapy and combinations of antidepressants with mood stabilisers, such as lithium (24), suggests that antidepressants are ineffective. Moreover, antidepressant monotherapy carries possible risks in bipolar disorder including destabilisation of mood (25), chronic dysphoria (26) and switch to mania (27-35). The only evidenced (36, 37) and recommended (19, 38-44) use of antidepressants for bipolar disorder is when fluoxetine is combined with the antipsychotic, olanzapine. This combination has the largest effect size of any bipolar depression treatment (19). Despite this, 40% of bipolar patients in routine clinical care are prescribed an antidepressant, but only vary rarely is this an olanzapine/fluoxetine combination (less than 1%) (45).

This mismatch between the evidence base and practice relates to the limited tolerability and real-world effectiveness of the evidenced treatments (37, 46-51). Olanzapine and quetiapine commonly cause significant weight gain and sedation (36, 52) contributing to non-concordance, diabetes and obstructive sleep apnoea. Quetiapine (53) and to a lesser extent olanzapine (54) affect cardiac repolarisation which is reflected on the electrocardiogram (ECG) as heart rate corrected QT (QTc) prolongation. QTc prolongation increases the risk of the potentially fatal Torsades de Pointes. Quetiapine also commonly causes symptomatic orthostatic hypotension, such as dizziness on standing (55). The other NICE recommended drug treatment option, lamotrigine, is of only moderate efficacy (Number Needed to Treat = 11-13) (56, 57) and requires slow dose titration leading to delayed response.

This evidence-practice gap also illustrates the clinical uncertainty about the use of antidepressants in bipolar depression (58, 59) and has been highlighted as an area needing further research by both NICE and the James Lind Alliance (60). Aside from olanzapine/fluoxetine combination, other antipsychotic/antidepressant combinations have not been tested in adequately powered trials in bipolar depression. It is therefore unknown whether there is something unique about the specific combination of olanzapine with fluoxetine or whether alternative antidepressants and antipsychotics might also be effective when combined.

2. RATIONALE

2.1. Role of antidepressants

NICE guideline CG 185 has identified that the role of traditional antidepressants is the most important unanswered question in the treatment of bipolar depression. This study will help to address this and advance understanding of "core business" in the management of bipolar disorder. The study will show whether aripiprazole/sertraline combination offers superior clinical and cost effectiveness compared with current standard treatment.

2.2. Significance if superiority is shown

If superiority is shown, this combination has the potential to make a significant difference to practice and to improve the quality of life for patients with bipolar disorder and consequently for their informal carers such as family and friends. Aripiprazole and sertraline's safety, tolerability and side effect profiles are such that initiation in primary care would be appropriate (61, 62). This is important because whilst current formulary guidance requires that all existing NICE recommended bipolar depression treatments across most of the UK are started only after secondary care recommendation, a third of patients with bipolar disorder are only seen in primary care (63, 64). In addition, discontinuities between primary and secondary care include significant delays in the provision of secondary care input (65-67). A drug regime that General Practitioners (GPs) could initiate would allow effective treatment whilst waiting for secondary care response or for those patients who decline or do not need secondary care involvement, thereby reducing the impact of the primary/secondary care barrier and facilitating improved involvement, detection and management across the Integrated Care System (68).

Conversely, if quetiapine is shown to be superior to aripiprazole/sertraline combination, this would be further evidence in support of current guidance to avoid using antidepressants in bipolar disorder given their potential disadvantages (27-35) and would challenge their current high rate of usage (45).

2.3. Impact on practice

An increase in the number and quality of effective treatment options with better side effect profiles is desperately needed, given the limitations of the currently recommended treatments and the significant morbidity and mortality of bipolar disorder.

2.4. Choice of aripiprazole

Aripiprazole's ability to augment an antidepressant for the treatment of depression is suggested by its unique pharmacology. It enhances dopamine function, normalising a demonstrated deficit (69) thereby facilitating reward activation (70, 71). It increases 5-HT neuronal firing rate via 5-HT_{1A} agonism (72, 73) and noradrenalin release via 5-HT_{2A} antagonism (74, 75).

In major depressive disorder, atypical antipsychotics as a class augment antidepressants (49-51, 76-80). For aripiprazole specifically there have been four large studies, with a dose range of 2 to 20 mg and mean of between 7.75 and 11.2 mg (78-81), and a fifth study with two active treatment arms – a fixed dose of 3 mg and a flexible dose of 3 to 15 mg (mean 9.8 mg) (82). All five, including both the fixed and flexible dose arms in the latter study, showed a clinically and statistically significant difference on the primary outcome measure (the Montgomery-Asberg Depression Rating Scale) (83) of around 3 to 4 points in favour of aripiprazole.

In bipolar depression, the augmenting potential of atypical antipsychotics is supported by a large case note review (84), an observational study (85) and by the olanzapine/fluoxetine randomised control trials (36, 37). For aripiprazole specifically, there have been non-controlled studies with relatively high starting doses (86-90) and small chart reviews (91-93) which suggest augmentation efficacy in bipolar depression but reveal high rates of akathisia (a side effect which is characterised by subjective and objective restlessness). A later and larger chart review examining patients prescribed smaller doses (5 mg or less) of aripiprazole augmentation of antidepressants showed promising results and a relative absence of side effects (94). In the one small pilot randomised controlled trial of aripiprazole augmentation of antidepressants in bipolar depression (n=23) there was a clinically (95), but not statistically (the study was not adequately powered), significant 4 point advantage of aripiprazole over placebo on the primary outcome measure (96, 97). Aripiprazole's acute antimanic efficacy, including at a dose of 10 mg (98, 99) is predicted to prevent switch to mania.

The tolerability of aripiprazole compared with the existing drugs for bipolar depression can be estimated using the short-term (≤12 week) unipolar augmentation data. In the aripiprazole arm of the pivotal studies, average drop out because of adverse effects was 4.1% (78-80, 82) compared with 11.6% (49-51) for quetiapine (mostly sedation and somnolence) and 11.2% (46-48) for olanzapine. Aripiprazole, in contrast to quetiapine and olanzapine, does not increase QTc (100) giving a better cardiac safety profile (101). It also has a lower risk of causing hyperprolactinaemia than the other second-generation antipsychotics (such as quetiapine and olanzapine) and thereby a reduced risk of amenorrhea, galactorrhoea, hirsutism, gynaecomastia, impotence, loss of libido, infertility, osteoporosis and hip fracture (102).

2.5. Choice of sertraline

Sertraline has been chosen as the antidepressant to combine with aripiprazole since it has a good safety profile and tolerability in both bipolar (20) and unipolar (103) depression populations, a favourable pharmacokinetic profile, only limited interactions with most psychotropics and it does not carry a risk of cardiac arrhythmias (104-107).

2.6. Choice of comparator

Quetiapine is the preferred comparator because it has the most robust evidence-base (23, 108-110). Quetiapine is available both in an immediate release (IR) and an extended release (XL) formulation. Both are licenced for the treatment of bipolar depression and whilst the XL form has a longer half-life, in bipolar depression, Summary of Product Characteristics (SmPC) instructions for both are to use a once daily dose (55). The IR form is approximately 25 times cheaper (111) and prescribed six times more frequently in primary care than the XL form (45). Relative tolerability of IR versus XL differs between individuals. As per LQD (112), choice between IR and XL will remain a clinical decision in participants randomised to quetiapine.

3. RISK ASSESSMENT

This trial is categorised as:

Type A = no higher than the risk of standard clinical care

For the purposes of this trial, quetiapine, sertraline and aripiprazole are classed as Investigative Medicinal Products (IMPs). All IMPs have marketing authorisation and extensive safety data:

- Sertraline has Medicines and Healthcare products Regulatory Agency (MHRA) marketing authorisation for depressive illness, obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder, and social anxiety disorder.
- Aripiprazole (oral) has MHRA marketing authorisation for schizophrenia and for treatment and recurrence prevention of mania.
- Quetiapine has MHRA marketing authorisation for schizophrenia, for the treatment and prevention of mania and depression in bipolar disorder and for adjunctive treatment of major depression.

All IMPs are generally well-tolerated, but potential participants will be informed of anticipated side effects and risks by their clinician and via the study participant information sheet (PIS). Clinicians are expected to make a collaborative decision with their patient with regards to the ongoing use of any of the IMPs where side effects are experienced (see section 13.4). The IMPs carry a risk of medication misuse and overdose. Clinicians will be alerted to cases of overdose (see section 16.12) and are encouraged to consult the SmPCs for the IMPs in these cases.

All trial outcomes will be measured via patient-completed or informal carer-completed online questionnaires. The central Research Assistants (cRAs) will support participants in the completion of questionnaires, including offering options to complete assessments via telephone or videoconference if participants experience difficulties in accessing or using the online system (see section 16.1).

3.1. Suicide

The eligible population for this study is at increased risk of suicide compared with the general population. In the ASCEnD study, the risk is managed by both primary and secondary care clinical teams. There is evidence that the IMPs reduce suicidality in the study population (113) and participation in the study, confers additional risk mitigation via the involvement of research personnel and the research process. Within the study, participants will complete a QIDS-SR (Quick Inventory of Depressive Symptomatology – Self-Report), weekly. Question 12 relates specifically to suicidality, and an answer of 3 '*I think of suicide or death several times a day in some detail, or I have made specific plans for suicide or have actually tried to take my life'* will trigger an automatic email alert from the study database to the ASCEnD NCTU inbox, the cRAs and the site team, including the site PI. The alert will not be triggered at Baseline because the questionnaire is reviewed by someone at site before being inputted into the database, so the alert will be at follow-up weeks 1 to 24.

The purpose of email alerts is to inform the site team that the participant has responded '3' to item 12. This is not necessarily a call to action; rather, site teams will use this information to exercise their clinical responsibility for the participant and respond to the alert as they deem clinically appropriate.

In response to the alert and/or if suicidal ideations are disclosed by the participant in any other manner, cRAs will screen the participant for new or escalating suicidal ideations during the next study phone call. Study calls are scheduled to occur weekly. As per the cRA working instructions, if new or escalating risk is established, cRAs will confirm whether the participant has already discussed this with

the site team or the care team. If the event has been discussed, cRAs will record this response and continue with the remainder of the study activities. If the event has not been discussed, cRAs will gather more information and relay this to the responsible clinician and healthcare professionals listed in the participant's Contacts Form, which includes the participant's site study team. cRAs have the option of emailing or telephoning healthcare professionals listed on participant Contacts Forms, depending on the more appropriate mode of communication in these instances. cRAs also have the flexibility to contact site teams and care teams if they feel any concern about the participant, irrespective of whether disclosures meet the parameters outlined above. cRAs will maintain documentation to confirm that communication with site has taken place in accordance with the protocol. If cRAs are concerned about the immediate safety of the participant, where possible they should stay on the phone and ring 999 from another line. On rare occasions it may also be necessary to inform next of kin of cause for concern and participants would be informed of this break of confidentiality. cRAs will receive training in dealing with emergency situations, will have regular supervision from a clinician, and can contact their clinical supervisor or the trial CI in case of concern.

To maintain the integrity of this communication plan, cRAs are required to maintain up to date records of the contact details of all site PIs and sites are required to send up-to-date contact details and/or inform cRAs of any changes related to healthcare professionals associated with the participant.

Prior to qualitative interviews, the qualitative researcher will ask cRAs if the participant has already been flagged as at risk for suicidal ideation, so that the qualitative researcher is aware of any risk prior to the qualitative interview.

If participants disclose risk of self-harm or suicide during a qualitative interview, a separate risk protocol will be in place which mirrors the above escalation procedure; the responsible clinician and healthcare professionals listed in the participant's Contacts Form, which includes the participant's site study team (and GP if applicable) will be notified and are then responsible for ensuring a plan for the ongoing care. The researcher may also contact the qualitative study lead, Professor Chew-Graham, (CCG) who is a GP (with clinical experience managing people who are distressed) and clinical academic. If the researcher feels it is appropriate or necessary, CCG will speak to the study participant whilst the researcher is still with the study participant or soon after.

3.2. Domestic Violence

Participants will complete the OxCAP questionnaire at Baseline, Follow-up weeks 4, 14 and 24. Question 7 reads: Please indicate how likely you believe it to be that you will be assaulted in the future (including sexual and domestic assault). The possible responses are: *Very likely*, *Fairly likely*, *Neither likely nor unlikely*, *Fairly unlikely*, and *Very unlikely*.

An email alert is set up to be triggered by the responses *Very likely* and *Fairly likely*, which will be sent from the database system to the ASCEnD NCTU inbox, the cRAs, and the site team, including the site PI. The alert will not be triggered at Baseline because the questionnaire is reviewed by someone at site before being input into the database, so the alert would only be at follow-up weeks 4, 14 and 24.

The purpose of email alerts is to inform the site team that the participant has responded 'Very likely' or 'Fairly likely' to item 7. This is not necessarily a call to action; rather, site teams will use this information to exercise their clinical responsibility for the participant and respond to the alert as they deem clinically appropriate.

In response to the alert and/or if safeguarding concerns are disclosed by the participant in any other manner, cRAs will confirm whether the participant has already discussed this with the site team or the care team. If the event has been discussed, cRAs will record this response and continue with the remainder of the study activities. If the event has not been discussed, cRAs will gather more information and relay this to the responsible clinician and healthcare professionals listed in the participant's Contacts Form, which includes the participant's site study team. cRAs have the option of emailing or telephoning healthcare professionals listed on participant Contacts Forms, depending on the more appropriate mode of communication in these instances. cRAs also have the flexibility to contact site teams and care teams if they feel any concern about the participant, irrespective of whether disclosures meet the parameters outlined above. cRAs will maintain documentation to confirm that communication with site has taken place in accordance with the protocol. If cRAs are concerned about the immediate safety of the participant, where possible they should stay on the phone and ring 999 from another line. cRAs will receive training in dealing with emergency situations, will have regular supervision from a clinician, and can contact their clinical supervisor or the trial CI in case of concern.

To maintain the integrity of this communication plan, cRAs are required to maintain up to date records of the contact details of all site PIs and sites are required to send up-to-date contact details and/or inform cRAs of any changes related to healthcare professionals associated with the participant.

Prior to qualitative interviews, the qualitative researcher will ask cRAs if the participant has already been flagged as at risk for domestic violence, so that the qualitative researcher is aware of any risk prior to the qualitative interview.

If participants disclose risk of domestic violence during a qualitative interview, a separate risk protocol will be in place which mirrors the above escalation procedure; the responsible clinician and healthcare professionals listed in the participant's Contacts Form, which includes the participant's site study team (and GP if applicable) will be notified and are responsible for ensuring a plan for the ongoing care.

3.3. Pregnancy

Information pertaining to reproductive safety of trial medication comes from the register-based cohort studies (114-116). Notable amongst them is the Massachusetts General Hospital National Pregnancy Registry (117), and the Medicaid registry (118). Reproductive risks associated with medication have been reviewed and published as BAP guidance (119). Risk of events is reported as odds ratios which may – or may not- be adjusted for confounding variables, including smoking, substance use and psychiatric diagnosis.

3.3.1. Antipsychotics

Studies that have used a comparison group of women with psychiatric illness but unexposed to antipsychotics (114-116, 120) or studies that adequately controlled for confounding variables (121), report few associations between antipsychotics and adverse maternal or infant outcomes. Existing evidence suggests that antipsychotics are not major teratogens (120, 122, 123). There is an association with cardiac defects (124) but this may be attributable to detection bias (119) and, after adjustment, the data suggests that the risk of cardiac malformation is not meaningfully increased for women exposed to atypical antipsychotics (*n*= 9258) (118).

Withdrawal symptoms have been described in neonates following late pregnancy exposure to antipsychotic medication, however, studies that adequately controlled for confounding did not find a specific association between antipsychotic exposure and poor neonatal adaptation (116, 119, 121).

3.3.2. Aripiprazole

The aripiprazole SmPC section 4.6 regarding the use of drug during pregnancy states that aripiprazole should not be used in pregnancy unless the expected benefit clearly justifies the potential risk to the foetus.

The Massachusetts register had (April 2020) data on 848 women who had taken aripiprazole in pregnancy and delivered infants. The risk of major malformations in the 158 women who took aripiprazole in the first trimester was 4.29%. This compares with 1.99% in the unexposed group. After adjustment for confounding variables, the risk of major malformations after first trimester exposure to aripiprazole was not significant compared to controls (odds ratio = 1.35 (95% confidence interval= 0.43, 4.20)(125). The US Medicaid sample, including 1756 first trimester exposures to aripiprazole showed a non-significant adjusted relative risk of 0.95 (95%CI= 0.76 to 1.19) for congenital malformations(118). Aripiprazole is not a major teratogen. The available data does not support a strong association between foetal exposure to atypical antipsychotics and an increase in the rates of major malformations (118, 119, 125).

3.3.3. Quetiapine

The quetiapine SmPC section 4.6 regarding the use of drug during pregnancy states that Quetiapine should only be used during pregnancy if the benefits justify the potential risks.

There is a concern that antipsychotics, such as quetiapine, that are associated with metabolic disturbance may increase the risk of gestational diabetes mellitus, obesity and gestational hypertension, conditions which are in turn associated with adverse maternal and neonatal outcomes such as foetal growth abnormalities, preterm birth and congenital malformations (119).

The Massachusetts register (n= 264 for quetiapine) reports an adjusted odds ratio comparing quetiapine with controls for congenital malformation was 1.04 (95%CI=0.38-2.85) (126). The US Medicaid sample consists of over 4,000 first trimester exposure to quetiapine with an adjusted relative risk for congenital malformation of 1.01 (95% CI =0.88 to 1.17) (118). Quetiapine is not a major teratogen (126), it does not meaningfully increase the risk for congenital malformations overall or cardiac malformations in particular (118, 119)

Maternal quetiapine produces doses in milk that are less than 1% of the maternal weight-adjusted dosage and a systematic reviews of mood stabilisers and second-generation antipsychotics concluded that quetiapine is be the first-choice agent during breastfeeding (127).

3.3.4. Sertraline

Sertraline's SmPC section 4.6 regarding the use of drug during pregnancy states that Sertraline is not recommended in pregnancy, unless the clinical condition of the woman is such that the benefit of the treatment is expected to outweigh the potential risk.

There are no data suggesting antidepressants impact on the ability of women to conceive (119). Drugs that block serotonin uptake, such as many antidepressants, are associated with increased risks of bleeding (128). There have been reports of particularly third trimester exposure to antidepressants being associated with an increased risk of postpartum haemorrhage (129, 130).

Large studies which adjust for confounding factors have not found an increased risk of teratogenesis or cardiac malformations with antidepressants (131, 132), There is a numerically small and statistically not significant adjusted increased risk of Persistent Pulmonary Hypertension of the Newborn in women who took antidepressants in pregnancy(133).

A neonatal behavioural syndrome following in utero exposure to antidepressants, which includes irritability, crying, jitteriness, vomiting, shivering, increased tone, and eating and sleeping difficulties has been convincingly reported (119). Data on long-term effects of antidepressant exposure in utero are sparse and do not convincingly show any long-term impact (119).

Sertraline is the preferred antidepressant for women who are breast feeding (119), levels in breast milk are low (134) and serum levels in babies are usually undetectable (135) (136).

3.3.5. Risks of untreated illness in pregnancy

Pregnancy is not protective against bipolar disorder or other mental illness(119). Very high rates of relapse of depression (70%) have been found in studies of women with histories of recurrent depression (137, 138). This finding wasn't replicated in a study recruiting from obstetric settings, likely to include women with milder forms of depression (139).

Maternal antenatal depression and anxiety symptoms are reported to be associated with an increased risk of neurodevelopmental and psychopathological consequences for the offspring spanning into childhood and adolescence(140). These include depression, emotional problems, symptoms of attention deficit hyperactivity disorder (ADHD) and conduct disorder, impaired cognitive function and schizophrenia (141, 142). Antenatal depression also increases the risk of the offspring being exposed to maltreatment in childhood, by approximately four-fold (143). A large cohort study found that the behavioural problems in children aged 7 born to women with prenatal depression wasn't seen in the children whose mothers took antidepressants in pregnancy (144). Women with bipolar disorder who are medication-free during pregnancy have a significantly higher risk of postpartum relapse (approximately 65% vs 25%) than those who were taking prophylactic medication (145).

3.3.6. Relevant definitions

For the purposes of this trial a woman is considered of child-bearing potential (WOCBP) i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

Effective methods of contraception are combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, a vasectomised partner, sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments).

A highly sensitive urine test is defined as a urine beta-HCG pregnancy tests conducted in line with local clinical policies, either by sending the urine sample to the local clinical laboratory or by a suitably trained individual using a clinically approved pregnancy test strip.

4. OBJECTIVES AND OUTCOME MEASURES

4.1. Aim

To determine the clinical and cost effectiveness of aripiprazole/sertraline combination in the treatment of depressive episodes in people with bipolar disorder.

4.2. Primary objective

To determine whether the improvement in depression will be greater in participants randomised to aripiprazole/sertraline combination than those randomised to quetiapine.

4.3. Primary outcome

The QIDS-SR reported weekly 12 to 16 weeks after randomisation in the two arms. Randomisation is measured as day 0 for follow up for the main trial.

4.4. Secondary objectives and outcomes

Trial secondary objectives will compare the impact of aripiprazole/sertraline combination versus quetiapine on the endpoints indicated in the table below over a 24-week follow up period:

Endpoint	Measure
The trajectories of symptom change	QIDS-SR reported weekly from screening.
Treatment satisfaction	TSQM at baseline and weeks 4, 14 and 24.
Tolerability	GASS at baseline and weeks 4, 14 and 24.
Pattern of medication adherence	Weekly questions in the study database regarding dosages of study medications taken on each of the preceding 7 days. This will be supported by use of the MARS at baseline and weeks 4, 14 and 24.
Pattern of non-randomised antidepressant/antipsychotic medication use.	Analysis of concomitant medications weekly from screening.
Change in anxiety symptoms	GAD-7 scale reported weekly from baseline.
Change in manic symptoms and rates of relapse to a hypomanic or manic episode.	ASRM reported weekly from baseline.
Psychosocial functioning	WSAS at baseline and weeks 4, 14 and 24.
Health-related quality of life	EQ-5D-5L questionnaire weekly from baseline.
Capability well-being	ICECAP-A and OxCAP-MH at baseline and weeks 4, 14 and 24.
Costs and incremental cost-effectiveness	HEQ at baseline and weeks 4, 14 and 24.
Informal carers' health-related quality of life, capability well-being and costs of caring	EQ-5D-5L, ICECAP-A, OxCAP-MH and CIIQ at baseline and weeks 4, 14 and 24.

4.5. Exploratory Objective and Outcome Measure (Optional REWARD Study)

Changes in reward and punishment sensitivity, from baseline (prior to IMP initiation) to week 14 post initiation of IMP, measured via the PILT and the behavioural inhibition (or avoidance) system (BIS) and behavioural approach system (BAS) scales.

Endpoint	Measure*
Reward and punishment sensitivity	PILT and BIS/BAS prior to IMP initiation (baseline), at IMP-weeks 3-4 (first follow-up), and at IMP-weeks 13-14 (second follow-up).

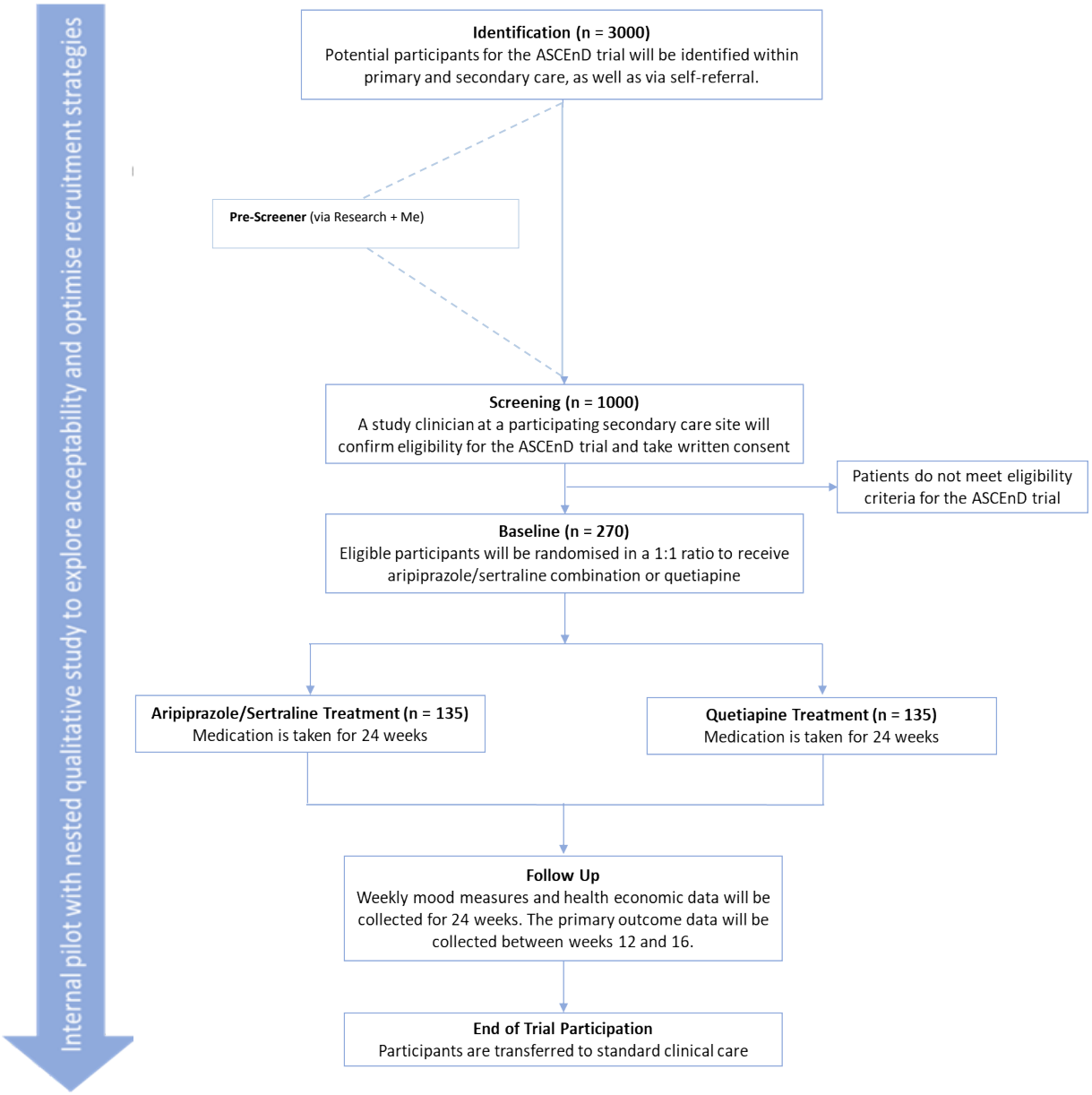
* 1st exploratory (3-4 week) and 2nd exploratory (13-14 week) follow up measured from the IMP start date and not from the date of randomisation.

Choice accuracy in win trials of the PILT and the total score on the BAS Reward Responsiveness subscale of the BIS/BAS will provide measures of reward sensitivity. Choice accuracy in loss trials of the PILT and the total score on the BIS subscale of the BIS/BAS will provide measures of punishment sensitivity.

5. TRIAL DESIGN

The ASCEnD trial is a prospective, two-arm, open label, superiority, individually 1:1 randomised, controlled, pragmatic, parallel group, type A open label clinical trial. It aims to determine whether a sertraline/aripiprazole medication combination is an effective treatment for bipolar depression.

The trial will be carried out at UK sites including primary, secondary and tertiary care mental health services. A target of 270 patients will be randomised (1:1 ratio) to receive either sertraline/aripiprazole combination or quetiapine. The effectiveness of sertraline/aripiprazole combination in reducing depressive symptoms will be assessed 12-16 weeks after randomisation. Patients and their main informal carer will continue to be followed up for 24 weeks. Over this period, the cost effectiveness and the effect of sertraline/aripiprazole combination on symptoms of depression, anxiety and mania will be assessed. Assessments will be completed by participants and their main informal carer online using electronic Patient Reported Outcomes (ePRO) or, for participants where this is not possible, via telephone or videoconference with a cRA.



5.1. Schedule of Events

Procedures	Screening	Baseline	Follow-up Week																							Trial Completion
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	
Site team activities																											
Informed consent	X																										
Eligibility assessment	X[a,b]																										
Pregnancy testing (if applicable)	X[g]																										
Demographics	X																										
Medical history	X																										
Review of current medications	X																										
Randomisation		X																									
Prescribe trial medication		X																									
Participant Recompense		X[c]														X[d]											X[c]
cRA activities																											
cRA contact			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Participant activities (assessments to complete on the ePRO system)																											
QIDS-SR	X[b,e]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
GAD-7, ASRM, EQ-5D-5L		X[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Review of current medications			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
GASS, MARS, WSAS, TSQM, ICECAP-A, OxCAP-MH, HEQ		X[e]				X										X										X	
Informal carer activities (assessments to complete on the ePRO system)																											
EQ-5D-5L, ICECAP-A, OxCAP-MH, CIIQ		X[e,f]				X										X										X	
Participant activities (optional exploratory assessments to complete on the Gorilla™ system)																											
PILT, BIS/BAS	X[h]			X[j]										X[j]													

(a) Includes completion of the Structured Clinical Interview for DSM-5-TR Disorders-Research Version (SCID-5-RV).
(b) To be completed within 7 days preceding randomisation.
(c) Participant to be recompensed £15.
(d) Participant to be recompensed £20.

(e) The QIDS-SR at screening, and baseline questionnaires, should be completed on paper to avoid delays to randomisation.
(f) To be completed within 14 days of the primary participant's baseline assessments.
(g) Pregnancy tests are done for women of childbearing potential not using effective methods of contraception (as defined in section 3.3.6)
(h) Optional baseline exploratory assessment to be completed prior to IMP initiation (for exploratory assessments only, IMP start date is defined as day 0).
(i) Optional follow up exploratory assessments to be measured post IMP initiation date. 1st follow-up to be completed between week 3-4 and 2nd follow up between week 13-14 post IMP initiation.

6. RECRUITMENT

The study will recruit patients with a pre-existing diagnosis of bipolar disorder, as well as those whose bipolar disorder is not yet recognised. The Clinical Research Networks (CRNs) will support recruitment via a number of routes. The Research+Me (R+Me) consent for contact registry (see appendix 2) is available, as well as the Be Part of Research registry (BPoR) (see section 6.2.4), to support recruitment.

6.1. Hard to reach groups

It is acknowledged that there is a differential in participation in clinical research across the population according to socio-demographic characteristics. Those living in socio-economically disadvantaged circumstances, and those from certain ethnic and marginalised groups are known to experience more barriers to accessing research opportunities and as a result are underrepresented in clinical research. The recruitment strategy for the ASCEnD study aspires to minimise this impact.

6.2. Participant Identification and initial contact

6.2.1. Identification via secondary care

Identification via secondary care mental health services will combine electronic patient record review (supported by the Clinical Record Interactive Search (CRIS) System where available (146)) and opportunistic approaches. It will be supported by flags in electronic notes where possible and by study profile raising. Initial contact will be from the patients' clinical team or local CRN delivery team who will facilitate consensual sharing of contact details with the site team. The site team will provide the patient with the study PIS and organise a screening appointment.

6.2.2. Identification via primary care

NHS primary care sites within a LCRN will be set up as Patient Identification Centres (PICs) to allow patient identification and invitation to the ASCEnD trial. Recruitment via primary care health services is described in sections 6.2.2.1 and 6.2.2.2 and will utilise opportunistic electronic health record alerts, active record and register searches and local Improving Access to Psychological Therapies (IAPT) services.

6.2.2.1. Opportunistic approaches

Alerts in electronic records will serve to remind GPs and other primary care health care professionals about the study when seeing patients who are currently being treated for depression or who have a pre-existing diagnosis of bipolar disorder. In order to encourage the identification of depressive episodes in patients with bipolar disorder, the alert will include either the Patient Health Questionnaire-version 9 (PHQ-9) or NICE recommended Whooley screening questions (147) for a current depressive episode: "during the past month, have you often been bothered by feeling down, depressed, or hopeless?" and "during the past month, have you often had little interest or pleasure in doing things?" (148, 149). In patients with a diagnosis of depression, but not bipolar disorder, the alert will also include the question: "has there ever been a period of time when you were not your usual self and thoughts raced through your head or you couldn't slow your mind down?". This is the most sensitive question from the manic depression questionnaire (MDQ) (150). Primary Care health care professionals will ask those identified as potential participants for their permission to be contacted by an ASCEnD site team and will provide a link to the ASCEnD website, which includes the study PIS.

For patients who give verbal permission to be contacted by the ASCEnD site team, patient details will be sent to the local ASCEnD trial site team by phone or secure email. This will include patient identifiers (name, NHS number, DoB) and contact details. On receipt, a member of the trial team will contact the potential participant to further discuss the trial and potentially invite to a screening visit.

6.2.2.2. Record searches and IAPT

Primary care electronic patient record and register searches will be used to identify people with recorded diagnoses of bipolar disorder or of depression. Identified patients will be contacted by their usual care team or the CRN delivery team by text, e-mail or letter (depending on local practice).

Patients with mood disorders, who are currently depressed, and who have been referred into IAPT (via self-referral or GP-referral) will be identified using the PHQ-9 (151) depression rating scale. This is routinely completed at first IAPT assessments. Initial contact will be from the IAPT team and potential participants will provide a link to the ASCEnD website, which includes the study PIS.

As per the current NIHR funded BASIL study (152), we will look to utilise a follow up call to a sample of potential participants during the internal pilot. We will determine the broader cost per participant of this technique and determine whether there are any predictors of its success in recruitment (e.g. pre-existing diagnosis of bipolar disorder) to allow the strategy to evolve over the course of the recruitment period. The call will be made by the practice team or CRN delivery team members who have the appropriate access permissions.

6.2.3. Identification via self-referral

Self-referral into the trial will be supported by a content-led digital media campaign organised by the digital advertising company Just-R, and posters. This aims to raise the profile of clinical research and the opportunity to participate in ASCEnD. Just-R will advertise the study across a limited number of geographic regions at any one time. In addition, the study will be advertised via the charity Bipolar UK (who are funded through the application), the CRN, the associated Universities, and NHS trusts on relevant websites (including the Northern Centre for Mood Disorders and ASCEnD websites) and via engagement with third sector organisations (e.g., at peer support meetings, conferences and via publications).

The ASCEnD website (www.ascendtrial.co.uk) will include details of how potential participants can self-refer to the trial, including contact details for recruiting sites and how to register interest by completion of the Research + Me pre-screening assessment (section 6.2.66).

6.2.4. Be Part of Research (BPoR)

The trial will utilise recruitment via the NIHR BPoR registry. Volunteers who have consented to this registry are invited to take part in relevant trials by an email from BPoR. An email will be sent inviting BPoR volunteers to take part in ASCEnD, which will include a link to the trial website and how to register interest by completion of the pre-screening assessment (section 6.2.6).

6.2.5. Research plus Me

The trial will utilise the Research+Me (R+Me) recruitment platform, hosted by the Newcastle upon Tyne Hospitals NHS Foundation trust. R+Me has HRA REC favourable opinion for standard procedures (REC REF NE/23/0090) and a Data Protection Impact Assessment (DPIA).

At a rate determined by sites, R+Me registrants from the sites nearest relevant geographical locality will be sent information about the trial by email from R+Me. Registrants who do not respond to the initial invitation will be sent a limited number of reminders.

6.2.6. The Research plus Me Online Pre-Screening Assessment

R+Me has the functionality to support online pre-screening assessments for trials. As detailed in section 23.2 (Appendix 2) potential participants may access the ASCEnD study R+Me online pre-screener in different ways.

Potential participants may access the ASCEnD online pre-screener via an email invitation, after registration onto the R+Me registry and following their agreement to a consent statement and privacy notice.

If the potential participant does not want to register for R+Me but wants to complete the ASCEnD pre-screening assessment, they may alternatively access the pre-screener directly without the need to register onto the registry (e.g. directly from the trial website or via one of the other referral pathways described). The potential participant will be required to agree to a 'pre-screener without registering for Research+Me' consent statement and privacy notice.

Participants will be supported to complete the pre-screener with a short video which will be available to view prior to completing.

Those undertaking the pre-screening assessment will be informed of the outcome of the assessment (potentially eligible or not eligible) and will receive an automated email including signposts to sources of appropriate additional support (for example their GP, Samaritans etc).

Registrants who are potentially eligible will receive an automated email containing the e-mail contact details of their local site team, as well as a link to the ASCEnD website that contains the study PIS. A data sharing conditions agreement will be completed between participating sites and R+Me, allowing delegated site staff access to the contact details of those potentially eligible participants who have consented for their contact details to be shared. This data will be shared by secure email and will include the potential participant's contact details and the details of the pre-screening assessment. Site staff will contact these patients on up to three occasions to see if they are interested in arranging a screening appointment. This contact may also serve to consider appropriateness for inclusion in the trial. The data sharing conditions agreement outlines that site teams should not keep or use the contact details for any other purpose and the details should be deleted once they are no longer needed (by the end of the study recruitment period at the latest).

7. ELIGIBILITY CRITERIA

Eligibility criteria for this trial are pragmatic, in line with UK clinical practice. There is no upper or lower limit of bipolar disorder treatment-resistance, duration of current depressive episode, time since initial symptoms or time since the diagnosis of bipolar disorder. Patients will *not* be excluded if they are receiving, planning to receive or have recently received psychological or digital therapies.

7.1. Inclusion criteria

Patients must fulfil all of the following criteria to progress to randomisation:

1. Aged 18 or over at the point of consent.
2. Able to provide written informed consent.
3. A current (i.e., within 7 days) Diagnostic and Statistical Manual-5-Text Revision (DSM-5-TR) (153) confirmed diagnosis of a major depressive episode within bipolar disorder. This will be confirmed using the SCID-5-RV (153).
4. A current (i.e., within 7 days) QIDS-SR greater than 10.
5. Clinical uncertainty regarding the next course of treatment and judgement that the sertraline/aripiprazole combination and quetiapine treatment arms are both clinically appropriate and represent equipoise. This judgment includes consideration of reproductive risks.
6. In the opinion of the clinician, the participant is able to follow trial prescription instructions, complete weekly questionnaires and engage in weekly telephone calls with the cRAs throughout the 24 week follow up period of the trial.

7.2. Exclusion criteria

Any of the following criteria prevent progression to randomisation:

1. Currently participating in any other interventional clinical trial that may affect the outcome of ASCEnD.
2. DSM-5-TR defined severe substance use disorder (153).
3. Any known contraindications to aripiprazole, sertraline or quetiapine.
4. Currently pregnant, planning to become pregnant during the trial and/or breastfeeding.

8. ePRO, SCREENING AND CONSENT

8.1. ePRO

The electronic data capture system used in ASCEnD is Red Pill. ePRO is a function of the data capture system that allows participants to enter questionnaire responses directly into the clinical trial database (see section 18.1).

Participants will be encouraged to complete questionnaires weekly via ePRO throughout the study via email or text prompts. If a participant does not have access to the internet or is otherwise unable to enter data directly into ePRO, this process will be supported by the cRAs or site staff who will complete the questionnaires by telephone or videoconference with the participant and enter data on their behalf directly into the appropriate electronic Case Report Forms (eCRFs).

The PILT and BIS/BAS measures for the exploratory outcome (REWARD study) will be collected via the online platform "Gorilla™". If a participant does not have access to the internet or is otherwise unable

to access this online platform, they do not have to take part in this part of the trial. Capture of these exploratory measures are optional.

8.2. Screening and consent

The screening and consent appointment will be conducted by the site PI, or delegate, who is a GMC registered doctor. The site PI, or delegate, will discuss the trial with the potential participant, encourage them to ask questions about the trial and inform them of their right to withdraw at any time without any impact on the standard of care they will receive or their legal rights.

The appointment serves to:

(i) Enable the potential participant to make an informed and capacious decision about whether to participate in the study. This includes the potential participant having a full understanding of the risks of trial participation, including the risks associated with the trial drugs. This risk includes risks associated with pregnancy that are set out in section 3.1 of this protocol and in the patient information sheet. Any reproductive risk- and its mitigation via effective contraception (see 3.3.6) should be considered at screening and consent. All WOCBP, as defined in protocol section 3.3.6, who are not using highly effective contraception should be given a highly sensitive pregnancy test to confirm they are not pregnant.

(ii) Formally take and record study consent.

(iii) Confirm all eligibility criteria for study participation are met. This includes completion of the SCID-5-RV diagnostic interview and QIDS-SR on paper, and entry of this information into the appropriate eCRFs by delegated site staff.

(iv) Collect relevant study information including method of identification, current concomitant medications, recent (within 6 months) current and planned psychological therapy, medical history (time since diagnosis) and demographic details (including initials, age, sex at birth, gender, highest level of education, family status (single/divorced/married), ethnicity and post-code), This information may be entered directly into the appropriate eCRFs by delegated site staff, or documented on paper worksheets and later entered into the appropriate eCRFs.

(v) Collect the potential participant's email address, register them to complete self-service questionnaires (ePRO) and support with completion and use of the system. If a participant has given consent to take part in the optional REWARD study, support to access the Gorilla™ platform will be given.

8.2.1. Consent

Consent for trial participation must be sought by the site PI, or delegate, who is a GMC registered doctor. The original signed consent form must be filed in the Investigator Site File (ISF), a copy must be filed in the participant's medical records, and another copy given to the participant. Copies of the PIS used must be filed in the ISF and participant's medical notes. Participants will specifically consent to their GP (and referrer where applicable) being informed of their participation in the trial. Consent to the nested Qualitative pilot study and the REWARD study are both optional.

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

A copy of the completed consent form and QIDS-SR must be sent by site to the secure NCTU email address nctu.ascend.conf@nhs.net – this is for central monitoring purposes. Sites must send these documents using either an nhs.net account or a similar secure method which has been agreed by the NCTU Trial Manager(s). For participants who do not consent to sharing of their consent form, the study

consent proforma must be completed by site staff and sent to NCTU instead, via the same method. The proforma will enable NCTU Trial Manager(s) to assess the accuracy of completion of each consent form without sight of a participant's personal details.

8.2.2. Eligibility

Eligibility for the ASCEnD trial must be assessed by GMC registered doctor after receiving written informed consent from a patient to take part in the study. This assessment must be documented in the participant's medical records. Only personnel formally delegated by the local PI to assess eligibility may perform this task. If it is determined that a patient does not meet the trial's eligibility criteria, they will be considered a "screen failure", continue with their standard treatment pathway, and medical delegates will collect no additional data except to record the reason for non-progression (where provided) on the study screening log.

If eligibility is confirmed, the PI (or delegated clinician) will inform the participant, the participant's GP (and referrer where applicable) via the study GP letter, the cRAs by the study Contact Form (sent by secure email to ASCEnD@cntw.nhs.uk) and a copy of the completed eligibility proforma must be sent by site to the secure NCTU email address nctu.ascend.conf@nhs.net for central monitoring purposes.

Enrolling a patient onto the trial who does not meet the inclusion/exclusion criteria is considered a protocol waiver and is in breach of Regulation 29 (SI 2004/1031) of the Medicines for Human Use (Clinical Trials) Regulations 2004. Protocol waivers are not permitted.

8.2.3. Screening and recruitment of informal carers

We are using the term "informal carer" to define a spouse, family member or friend who provides support in an unpaid capacity. All participants should be asked who, given this definition, they would consider to be their main informal carer and asked if they agree for contact between that person and the study team. If so, the site's contact details should be given to the participant for them to pass to their informal carer (if the informal carer is not present at the participant's screening/baseline visit). The informal carer must then contact the site team to arrange a face-to-face consent appointment. This must take place no later than 14 days after the primary participant's baseline appointment. At the carer's consent appointment, the nature, use and identifiable nature of any information that will be asked of the informal carer (see below) should be explained. The informal carer can only participate in ASCEnD if:

(i) the primary participant gives written informed consent for contact between the site team and their informal carer.
(ii) the informal carer is considered likely to be able to provide written informed consent.
(iii) the informal carer is at least 18 years of age.
(iv) the informal carer is able to access and use the online ePRO system.

Consent for informal carer participation must be sought by an appropriately trained and delegated member of the site team. The original signed consent form must be filed in the ISF, and another copy given to the informal carer. Copies of the PIS used must be filed in the ISF. In the case of protocol amendments or information becoming available which may affect informal carer's willingness to continue in the trial, it may be necessary to re-consent informal carers on an updated consent form (after necessary regulatory approvals are obtained). Copies of informal carer's consent forms do not need to be sent to NCTU for central monitoring purposes.

Following consent, demographic details (specifically initials, age, sex at birth, gender, highest level of education, family status (single/divorced/married), ethnicity and post-code) will be collected and access to ePRO arranged. Site staff should support informal carers with use of ePRO and if required, help them to register their email address to support with completion of self-service questionnaires and use of the system. Informal carers will be prompted after their first login to change their password to something that only they know.

Only one informal carer may be consented and recruited per ASCEnD participant.

9. BASELINE AND RANDOMISATION

Once a participant is confirmed as eligible to take part in the study, a baseline appointment will be arranged. The screening and baseline appointments are likely to occur during the same visit.

The baseline appointment serves to:

(i) Collect baseline measures (including issuing the optional exploratory REWARD study task log-on instructions if a participant has provided consent).

(ii) Randomise participants to either aripiprazole/sertraline combination, or quetiapine.

(iii) Prescribe trial medication or communicate the randomisation to the clinical team, if the site team is not the same as the clinical team.

9.1. Baseline measures

Baseline measures will be completed on paper and include the GAD-7, ASRM, EQ-5D-5L, GASS, MARS, WSAS, TSQM, ICECAP-A, OxCAP-MH and HEQ. Baseline measures for informal carers will be completed on paper and include the EQ-5D-5L, ICECAP-A, OxCAP-MH and CIIQ. This will be supported by paper questionnaire booklets for participants and their informal carers. Delegated site staff will enter this information into the appropriate eCRFs and copies of participant- and carer-completed questionnaires are to be kept with participant trial documents for monitoring purposes.

The following optional exploratory outcome measures will also be completed prior to IMP initiation, if a participant has consented to take part in the REWARD study:

(i) measurement of the probabilistic instrumental learning task (PILT)

(ii) measurement using Behavioural Inhibition System/Behavioural Approach System (BIS/BAS)

These measures will be captured by the participant using the online Gorilla™ platform. **The IMP start date will be defined as day 0 for exploratory outcome measures only.**

The optional exploratory outcome measure tasks should be completed anytime before IMP initiation (i.e., even on the same day, but before) with the recommendation to complete the task as close as possible to IMP initiation.

9.2. Randomisation

Eligible participants will be randomised in a 1:1 ratio to aripiprazole/sertraline combination or quetiapine. Randomisation will incorporate block stratification using three variables (being in mental health secondary care services at screening (y/n), being prescribed antidepressants at screening (y/n), being prescribed an antipsychotic at screening (y/n)). Randomisation will be conducted by a delegated and trained member of the site team at each site using Red Pill (a central, secure, 24-hour web-based

randomisation system, which is owned by Sealed Envelope™). Randomisation should take place as soon as possible and no more than one week after a participant has been confirmed as eligible.

Randomisation system URL: https://www.sealedenvelope.com/access/

This system is available 24 hours a day, seven days a week. In the event that the online system is not accessible at site, NCTU can liaise with Sealed Envelope Support to investigate the cause. Site staff should contact NCTU Database Support during normal working hours:

Email: nctu.database.support@newcastle.ac.uk **Telephone**: 0191 208 8211

9.3. Prescription of study medication

Prescriptions for study medications will be written by the participant's clinical team, which may include non-medical prescribers where this is standard procedure at site for these medications. Sometimes the clinical team will not overlap with the research team. If this is the case, efficient communication between the site team and the clinical team is important to avoid any delays in treatment onset. The randomisation email sent to site PIs (or their nominated delegate) following randomisation will serve to remind the site team to either write a prescription or contact the participant's clinical team to do so.

10. TREATMENT AND FOLLOW UP

All participants are followed up for 24 weeks while taking trial medication.

10.1. Research measures

Weekly measures to be completed through to week 24 include:

(i) participant completion of the QIDS-SR, GAD-7, ASRM and EQ-5D-5L via ePRO.

(ii) participant review of current medications during weekly telephone or videoconference calls with the cRAs. Participants will be asked to confirm:

a. whether there have been, and the nature of, any changes to their concomitant medications.

b. whether they have started taking either aripiprazole/sertraline or quetiapine.

c. what dose of either aripiprazole/sertraline or quetiapine they have taken on each of the previous 7 days.

d. Whether the risk of pregnancy of any participants has changed (eg via change in sexual activity of contraception) or if any WOCBP are, or could be, pregnant. If appropriate, the cRAs will share this information with the site team and/or recommend that participants contact their site team.

Participants will be supported in this process by a paper patient diary. The cRAs will enter the information provided by participants into the participant monitoring spreadsheet and then into the appropriate eCRF. To assist with the accurate collection of concomitant medication information, the ePRO system will generate a list of the medications and dosages the participant indicated they were taking the week prior. The list of concomitant medications taken by the participant at screening will have been entered previously by the site team (see section 8.2).

cRAs or site staff where there is appropriate resource will also support participants in the completion of questionnaires by phone and by email and by posting paper copies out where appropriate, and will especially prioritise calls between weeks 12 and 16 to facilitate data completeness for the primary outcome.

At weeks 4, 14 and 24, additional measures to be completed include:

(i) participant completion of the GASS, MARS, WSAS, TSQM ICECAP-A, OxCAP-MH and HEQ via ePRO. HEQ data will be triangulated with information from patient records requested from treatment teams if necessary and collated by cRAs (see section 16.1).
(ii) informal carer completion of the EQ-5D-5L, ICECAP-A, OxCAP-MH and CIIQ via ePRO.

10.2. Optional Exploratory Outcome Measures (REWARD Study)

For those participants who have consented to the REWARD study, the participant ID, partial DoB (MM/YYYY), date of randomisation, and participant IMP initiation date will be shared with the REWARD study team via email in order to schedule exploratory follow-up measurements and email/text reminders to participants.

Follow up optional exploratory outcome measures will be completed at weeks 3-4 (1st follow up) and weeks 13-14 (2nd follow up) after IMP start date (IMP start date defined as day 0 for exploratory outcome measures), only if a participant has consented to take part in the REWARD study:

(i) measurement of the Probabilistic Instrumental Learning Task (PILT)
(ii) measurement using Behavioural Inhibition System/Behavioural Approach System (BIS/BAS)

These measures will be captured by the participant using the online Gorilla™ platform.

An instruction sheet and video will support participants to complete the exploratory measure on the Gorilla™ platform and provide more information on the REWARD study and a working instruction made available to sites.

Taking part in the REWARD study is only available to participants who are not randomised to continue the same medication (quetiapine and aripiprazole only) and who complete the baseline measure prior to initiation of either quetiapine or aripiprazole. For the purposes of inclusion in the REWARD study, timing of starting or continuation of sertraline is irrelevant.

10.2.1 PILT (REWARD Study)

The PILT consists of a 2-arm bandit decision-making task. On each trial, patients are presented with two abstract shapes (letters selected from the Agathodaimon font). In "win" trials, symbols within each pair are associated with reciprocal probabilities (0.7 vs 0.3) of a "win" outcome (+20 points) or a "no win" outcome (0 points). In "loss" trials, symbols within each pair are associated with reciprocal probabilities of a "loss" outcome (-20 points) or a "no loss" outcome (0 points). Patients are instructed to choose one of the symbols, after which they receive visual feedback (e.g., "+20 points") alongside their current total points. Across testing sessions, patients are instructed to learn which symbol in each pair leads to the best outcome more frequently, and to consistently select this.

10.2.1 BIS/BAS (REWARD Study)

The BIS/BAS scales are a 24-item self-report measure of sensitivity. The scales are composed of four subscales, including BIS responsible for promoting negative affective states and avoidance (7 items),

the BAS responsible for promoting positive affective states and approach behaviour, Fun Seeking (4 items), Drive (4 items), and Reward Responsiveness (5 items). Four additional items are fillers. Participants are asked to rate each item on a four-point Likert-type scale (1 = Very true for me; 4 = Very false for me).

10.3. Clinical measures

Clinical teams are encouraged to follow the NICE recommended monitoring of trial medication throughout the treatment and follow up phase of the study.

11. TRIAL COMPLETION

11.1. End of trial participation

After 24 weeks of follow up, participants who are being seen in research clinics will be transferred to standard clinical pathways. The study will not prompt change in ongoing drug treatment and study medication will not stop because the study has ended. Participants will be contacted and thanked for their participation.

11.2. Withdrawal criteria

Participants have the right to withdraw from the trial at any time without having to give a reason. Investigator sites should try to ascertain the reason for withdrawal and document this within the appropriate eCRF and participant's medical notes, and also notify the cRAs and NCTU. NCTU will inform the REWARD and Qualitative study teams. Participants who withdraw from the trial will not be replaced. *Discontinuation of trial medication is not synonymous with trial withdrawal.*

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

- Participant withdrawal of consent.
- Significant protocol deviation or non-compliance.
- Investigator's discretion that it is in the best interest of the participant to withdraw.
- Loss of mental capacity to participate in the study. In these cases, the PI must perform a best interest assessment as per the Mental Capacity Act (154) to determine whether continued data collection is in the best interest of the participant.
- An adverse event that renders the participant unable to continue in the trial.
- Termination of the clinical trial by the Sponsor.

Participants who have consented to the nested qualitative study will have the option to continue to take part in the qualitative study, or also withdraw from this part of the study.

11.3. End of trial

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

12. PARTICIPANT RECOMPENSE

Participants will receive recompense for time and inconvenience on a pro-rata basis. It has been agreed with the charity, Bipolar UK, that a level of £50 per randomised participant (£15 from identification to randomisation, £20 from randomisation to week 14 and a further £15 from week 14 to completion) is appropriate to recompense for inconvenience and time (this may be gift voucher or

money depending on local site). A further £25 gift voucher recompense for participants who consent to take part in the nested qualitative study will be paid for their time. All GPs who consent to take part in the nested qualitative study will be paid £88 gift voucher recompense for their time, in accordance with guidance issued by the British Medical Association. Reasonable travel expenses and any directly identifiable costs will also be paid.

13. TRIAL MEDICATION

13.1. Name and description of IMP

For the purposes of this trial, quetiapine, sertraline and aripiprazole are classed as IMP.

- Quetiapine is an antipsychotic drug and is licensed for the treatment of depression in bipolar disorder.
- Sertraline is a selective serotonin re-uptake inhibitor and is licensed for the treatment of depression.
- Aripiprazole is an antipsychotic drug and is licensed for the treatment of schizophrenia and treatment and recurrence prevention of mania.

Quetiapine is being used within its licensed indication in this study. Sertraline and aripiprazole are being used outside of their licensed indications.

13.2. Drug storage and supply

IMP will be provided, open label, by local pharmacies according to their usual prescribing practices. Any brand of study medication may be used. No specific storage instructions arise as a result of this study and no temperature monitoring or accountability of the products is required to be carried out by sites. Storage should be in line with the product SmPC being utilised for the treatment.

13.3. Preparation and labelling of IMP

Labels and packaging will follow local usual clinical and dispensing practices, which may differ between sites. As study medication will be provided open label, annex 13-compliant labelling is not required on the products at the point of dispensing.

13.4. Dosage schedule and modifications

The study does not mandate use of specific medication dosages or dose escalation procedures. Instead, clinicians are encouraged to use their judgement in accordance with clinical guidelines and the BNF dose schedule. Dosage decisions and decisions regarding the ongoing use of study medications taken during the study remain the responsibility of the prescriber but are informed by a participant's weekly clinical scale scores and reported side effects. Further guidance is provided in appendix 1.

13.5. Known drug reactions and interactions

For a full list of side effects and safety information, refer to the relevant SmPC and BNF.

13.6. Concomitant medications

Local site teams should follow their usual clinical practice and consult the BNF to review cautions and contra-indications (see appendix 1).

13.7. Assessment of compliance

Participants will report compliance weekly to cRAs, and cRAs will record this information in the appropriate eCRF. Participants will also complete the MARS at baseline and weeks 4, 14 and 24.

13.8. Discontinuation of IMP

Participants who discontinue trial medication will be encouraged to remain in the trial and to continue to provide outcome data.

14. INTERNAL PILOT

The trial includes an internal pilot which will run for 9 months from the start of the recruitment period. It will incorporate a nested qualitative study and evaluation of study progress.

14.1. Nested qualitative study

A nested qualitative study will be conducted within the internal pilot with the aim of informing recruitment strategies and optimising training for the participating sites. We will explore the acceptability of the intervention and trial participants' reasons for withdrawal and completion. We will also explore perspectives of diagnosis and management of bipolar disorder and attitudes to medication combinations. The nested study will follow a fully detailed pre-specified qualitative analysis plan that is reviewed by the trial oversight committees.

14.1.1. Participant recruitment to qualitative study

The site name, participant ID, date of randomisation, date started and stopped medication, and (for those who assert their right to) date of withdrawal will be shared with the Keele qualitative research team for those participants who have consented to the qualitative study. For those participants selected for interview, contact details for the participant, their next of kin and their site and care teams, as well as participant DoB, will be shared via the cRAs using the study Contacts Form. A qualitative research associate at Keele University will contact the participant(s) and ask to participate in a semi-structured interview. If the participant is happy to proceed, verbal consent will be taken and documented by the qualitative research associate prior to the interview. A copy of this consent form will be shared with the participant by post or email. Up to 25 people with bipolar disorder who consented during the internal pilot, will be invited to interview (15 people who complete the trial and ten who withdraw). It is anticipated that this number of participants will be sufficient to achieve data saturation (155). From those who give consent, a range of people based on age, gender, ethnicity, and area of work (deprivation indices) will aim to be sampled.

14.1.2. Staff recruitment to qualitative study

Psychiatrists in participating trial sites (but not PIs), as well as GPs, will also be interviewed to explore the acceptability of the recruitment procedures and of trial drugs. Staff members may hear about the opportunity to take part in a qualitative interview by attendance at study meetings, networks, snowballing, or social media and will be provided with the relevant staff PIS prior to consent to take part. The name and contact details of staff members who agree (verbally or by email) to be contacted to be interviewed, will be shared with the Keele qualitative research team along with their PI's contact details. If the staff member is happy to proceed, verbal consent will be taken and documented by the qualitative research associate prior to the interview. A copy of this consent form will be shared with the participant by post or email. We will interview up to 15 GPs and 15 Psychiatrists or until data

saturation is achieved. Purposive sampling of GPs and Psychiatrists will ensure sampling across the sites and aim for a range of clinicians based on age, gender, ethnicity, and area of work (deprivation indices).

14.1.3. Qualitative study procedures and data protection

Interviews will be conducted by a qualitative research associate, either by telephone or using a virtual platform, in line with COVID-19 restrictions and to reduce costs and participant burden. If a participant requests a face-to-face interview, this will be accommodated in line with COVID-19 guidance. Interviews will be digitally recorded with consent, transcribed verbatim (as per Keele University policy using an approved transcription company under a data processing agreement) and pseudo-anonymised using participant ID. The transcripts will form the data to be analysed. Personal data will only be accessible to the research team during the data collection phase of the study and stored on Keele University's secure network in a password-protected folder. Personal data and interview recordings will be kept for up to six months after the end of the pilot phase of the study, this will be password protected and stored in a different file to the transcripts. The transcripts of the recordings will be kept for up to 5 years.

If a participant consents to be informed of findings of the qualitative study, then contact details will be kept on Keele University's secure network in a password-protected folder until the end of the study. This data will be deleted once findings have been disseminated.

If a participant or member of staff chooses to withdraw their consent before an interview, their personal data including the study contact form received from cRAs (but excluding their consent form), will be permanently deleted from Keele University's secure network. If a participant or member of staff chooses to withdraw their consent during or after an interview, their personal data including the study contact form received from cRAs (but excluding their consent form), will be permanently deleted from Keele University's secure network. The interview recording and pseudo-anonymised transcript will be retained unless the participant requests that the recording is destroyed prior to transcription. Withdrawals from the qualitative study will be fed back to both the cRAs and the site PI.

A qualitative risk protocol is in place to ensure the site PI is notified if intent to harm, suicidal ideation, domestic violence or a safeguarding concern is disclosed by a participant during an interview (see sections 3.1 and 3.2 for further details). As per section 14.1.1., the qualitative research team will obtain a copy of the contact form for participants prior to their interview, which include contact details for their site and care teams and next of kin, should these be required in case of cause for concern. Prior to interviews, the researcher will also speak to the cRAs to see whether the participant has already been flagged as at risk for self-harm, suicidal ideation, or domestic violence.

14.1.4. Qualitative study topic guide

Topic guides will explore the acceptability of the intervention and trial participants' reasons for withdrawal and completion. As well as current difficulties in making a diagnosis and management of bipolar disorder, attitudes to medication combinations, challenges in accessing or delivering specialist opinion within current NHS systems, and possible change in workload will be explored in order to help inform potential future implementation of the use of aripiprazole/sertraline combination into clinical practice. The topic guides will be developed with reference to the existing literature, and with input from the study team and LEAP (Lived Experience Advisory Panel) (see section 20.3) and will be modified iteratively as data generation and analysis progresses.

14.1.5. Qualitative study analysis

An inductive approach using thematic analysis (156) will be conducted, looking for connections within and across interviews, and across codes, highlighting data consistencies and variation. A sample of initial transcripts will be independently coded by members of the qualitative site team to develop categories and themes to be discussed at team and LEAP meetings. Analysis will be an iterative process, carried out in collaboration with the study LEAP, with emergent findings used to further refine topic guides for subsequent interviews. The thematic analysis within datasets will be followed by a framework analysis based on the Theoretical Framework of Acceptability (157) across the datasets.

The findings of the qualitative study will be discussed in a LEAP meeting and at Trial Management Group (TMG) meetings (see section 16.8) to inform refinement of recruitment procedures and other aspects of the trial.

14.2. Evaluation of study progress

Data relating to overall site opening, recruitment and retention rates will be reviewed on an ongoing basis by the TMG (see section 16.8). Recruitment at individual sites will also be reviewed so that lessons from high recruitment sites can be applied to any site recruiting at a rate of <0.75 randomised participants/month.

We will also consider the utility of R+Me in recruitment to ASCEnD. Depending on the method of identification used, patients will receive distinct web links with which to access R+Me (see section 6), allowing an evaluation of the efficacy of recruiting participants to ASCEnD via the registry. A DPIA between Newcastle University and R+Me will be arranged as the study progresses to allow sharing of information relating to participants who were successfully recruited into ASCEnD via R+Me.

14.3. Progression criteria

ASCEnD has clear progression criteria (158). These will be assessed against the categories green/amber/red (see table below) from month 10 of the study. We anticipate 54 participants (20% of the overall total) to have been recruited and 8 sites (80% of the overall total) to be open to recruitment by this time. If 20% or fewer participants drop out of the study, this will mean that the study will proceed to the full trial as all green criteria have been met. If any one category meets amber criteria, this will trigger the instigation of a recovery plan, which will be supported by the trial oversight committees and proposed to the Funder. If any one category meets red criteria, study closure options will be discussed with the Funder. The Funder will have the final decision regarding study progression.

The progress of the study will be continually monitored by the study team and Funder. Recruitment and trial procedures will continue during the decision-making process.

	Green % (n)	Amber % (n)	Red% (n)
Total number of participants recruited	100% (54)	75-99% (41-53)	<75% (<41)

Total number of participants who drop out before week 16	≤20% (≤11)	21-30% (12-16)	>30% (>16)
Number of sites opened	100% (8)	75-99% (6-7)	<75% (<6)
Related actions/outcomes	Proceed with the main trial.	Consider mitigations with oversight groups and propose a recovery plan to Funder.	Closure options to be discussed with Funder.

15. PHARMACOVIGILANCE

15.1. Definitions

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

15.2. Recording and reporting AEs and SAEs

AEs occurring from randomisation to the end of study participation will be recorded by participants using the GASS. This will collect only a sub-set of adverse events which will not be reviewed for severity

or causality; this is appropriate given study medications already have marketing authorisation and extensive safety data for all study medications are already available.

SAEs will be identified by site teams and, occasionally, cRAs via telephone or videoconference calls with participants. All SAEs occurring following randomisation to the end of study participation must be reported to NCTU on the ASCEnD SAE form and also recorded in the appropriate eCRF page.

All SARs occurring from randomisation to the end of study participation must be reported to NCTU on the ASCEnD SAE form and also recorded in the appropriate eCRF page. Following this defined active monitoring period for SARs, investigators are still required to report any SARs or SUSARs they become aware of.

All SAEs/SARs must be reported to NCTU on the ASCEnD SAE form by email (nctu.ascend.sae@nhs.net) within 24 hours of research staff becoming aware of the event (see appendix 3).

Preliminary reporting to NCTU via email is acceptable in order to meet the 24-hour reporting timeline, where circumstances do not allow for immediate completion of the SAE form. However, the SAE form should be completed and submitted as soon as possible after the initial notification in order to comply with reporting timelines.

For each SAE the following information will be collected:

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

Any change of condition or other follow-up information should be submitted to NCTU using secure email to nctu.ascend.sae@nhs.net as soon as it is available, or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

15.3. Recording and reporting SUSARs

All SUSARs occurring from randomisation until 28 days post a participant's 24-week follow up visit must be reported to the MHRA and REC. The Sponsor will perform this reporting.

The assessment of expectedness will be performed by the CI against the approved RSI for the trial. As medication doses will differ amongst participants and the manufacturer of study medications used will vary across participating sites, we will use the most common brand of each of the study medications as the relevant RSI for the purposes of this trial. We are using section 4.8 of the relevant SmPC as the RSI for this trial.

Medication	Section 4.8 of SmPC
Aripiprazole tablets	Abilify 30 mg tablets
Sertraline tablets	Lustral 100 mg film-coated tablets

Quetiapine tablets	Seroquel 300 mg film-coated tablets

Fatal and life-threatening SUSARS must be reported no later than 7 calendar days after the Sponsor has first knowledge of the event. Any relevant follow-up information must be sought and reported within a further 8 calendar days.

Non-fatal SUSARs must be reported no later than 15 calendar days after the Sponsor has first knowledge of the event. Any relevant follow-up information should be sought and reported as soon as possible after the initial report.

As soon as a site suspects that a SAR may be a SUSAR they must contact the CI, the Sponsor representative and the NCTU Trial Manager(s) immediately. The reporting timeframe starts at day 0 when the Sponsor is in receipt of a minimum set of information:

- Sponsor trial reference and trial name (Sponsor reference)
- patient trial number and DoB
- name of IMP(s)
- date of notification of the event
- medical description of the event
- date and time of the onset of the event (including event end date, if applicable)
- causality assessment
- seriousness of the event, particularly if life threatening or fatal
- an identifiable reporter (e.g., PI).

This information must be provided on the ASCEnD SAE reporting form (see appendix 3). The site is expected to fully cooperate with the Sponsor in order that a full and detailed report can be submitted to the MHRA and REC within the required timelines.

PIs will be informed of all SUSARs by the Sponsor.

16. ROLES AND RESPONSIBILITIES

Embedding research into the NHS and it being delivered by clinicians across primary and secondary care raises potential challenges regarding responsibilities. These challenges and the response to them will differ between sites and over time.

16.1. Central RAs

The cRAs are responsible for contacting participants throughout the study, via telephone and/or videoconference. This will take place weekly from week 1, with calls that inform the primary outcome during weeks 12-16 prioritised. Whether calls have taken place will be recorded in the appropriate eCRF, with reasons for missed calls documented.

cRAs will:

- Collect concomitant medication information and details of IMP start and adherence directly into the appropriate eCRFs. The cRAs will enter the information provided by participants into the participant monitoring spreadsheet and then into the appropriate eCRF. Participants will communicate this information to cRAs during each weekly contact and will be supported in doing so via a paper patient diary.

- help participants complete questionnaires in ePRO. This may involve completing questionnaires on behalf of participants who themselves are unable to access or use the ePRO system; this can be done via a telephone call, videoconference or by sending a paper copy of the questionnaire to the participant where site do not have this capacity. For sites that have capacity, they will assist in completion of questionnaires.
- monitor the completeness of participant's entries in ePRO. If there are missed entries, the cRA will attempt to schedule an ad-hoc contact with the participant to provide additional assistance. The cRA will contact the site team if there are concerns regarding engagement.
- contact the site PI (or nominated delegate) if any signs of deterioration (e.g. suicidal ideation, overdose etc.) are either disclosed during a call with a participant or are identified (see section 3). cRAs have the option of emailing or telephoning healthcare professionals listed on participant Contacts Forms, depending on the more appropriate mode of communication in these instances.
- maintain up to date records of the contact details of all site PIs.
- maintain up to date records of the contact details of study participants via an appropriate contact form.

16.2. Site team

The site team comprises the PI, staff from the Mental Health and Primary Care CRN and other support staff as appropriate and delegated at participating sites. The PI (or appropriate delegate within the site team) will be responsible for:

- identifying participants, at times liaising with colleagues within primary and secondary care to provide education with regards to the study.
- confirming participant consent and eligibility for the study.
- collecting information relating to demographics, medical history and concomitant medications at screening, and entering this information into the appropriate eCRFs.
- Entering data from participant and carer-completed paper questionnaires from screening and baseline into the appropriate eCRFs.
- randomisation of participants.
- contacting the participant's clinical team to prescribe study medication. Where responsibility for a participant's clinical care sits with the site team, the site team can themselves prescribe study medication.
- contacting the participant's clinical team in cases of participant deterioration. Where responsibility for a participant's clinical care sits with the site team, the site team can themselves develop a plan to ensure the ongoing safety of the participant.
- documenting any discussions with study researchers in medical records where relevant.
- ensuring that participants receive appropriate recompense.

With regards to safety reporting, the PI will:

- assign causality to all SAEs.
- ensure that all SAEs/SARs, including SUSARs and pregnancies, are recorded and reported to NCTU within 24 hours of becoming aware of the event and provide further follow-up information as soon as it is available.

16.3. Clinical team

Participants' clinical care in relation to the study will be managed by either their primary or secondary care team. These teams have responsibility for the ongoing clinical care of the patient which may involve developing a plan to ensure the ongoing care of a study participant if any signs of deterioration

are identified during the study, and the prescribing of study medication. This may include non-medical prescribers where this is in line with the usual local prescribing processes.

16.4. National clinical support team

Newcastle-based psychiatrists with adequate understanding of the ASCEnD study (including the CI and deputy CI) will offer an out of hours (5pm – 9am) national on-call clinical support rota for primary and secondary care clinicians with study responsibilities. The team will provide support for the study and advise on uncertainty and equipoise decisions. Clinicians on the on-call rota will not make decisions about clinical care, which will remain the responsibility of the participant's clinical team.

16.5. Chief Investigator

The CI is responsible for:

- clinical oversight of the safety of trial participants, including an ongoing review of the risk/benefit profile of the study.
- assigning expectedness to SARs in line with the RSI.
- immediate review of all SUSARs.
- review/assignment of Medical Dictionary for Regulatory Activities (MedDRA) or body system coding for all SAEs and SARs.
- preparing the clinical sections and final sign off of the Annual Safety Report (ASR)

16.6. Sponsor

The Sponsor is responsible for:

- data collection and verification of AEs, ARs, SAEs, SARs and SUSARs onto a database (may be delegated to NCTU).
- reporting safety information to the independent oversight committees for the ongoing assessment of the risk/benefit ratio throughout the life of the trial (may be delegated to NCTU).
- assessment of expectedness of any SUSARs (may be delegated to the CI).
- expedited reporting of SUSARs to the CA and REC within required timelines.
- notification of all investigator sites of any SUSAR that occurs (may be delegated to NCTU).
- reviewing RSI at least annually and notification to PIs of any required updates (may be delegated to NCTU).

16.7. Trial Oversight Committees

The Data Monitoring Committee (DMC) is responsible for reviewing all trial safety data. They will meet at least annually throughout the trial and will make recommendations to the Trial Steering Committee (TSC) regarding trial progress. The TSC has the authority to recommend changes to the protocol and/or ongoing progress of the study. Membership of both committees has been agreed by the trial Funder.

The TSC consists of an independent chair with at least two other independent members, an informal carer representative, the CI and co-CI. Meetings may be attended by nonvoting observers including representatives from NCTU, Sponsor and Funder.

The DMC consists of an independent chair, an experienced independent statistician and at least one independent psychiatrist with an interest in bipolar disorder. The CI, co-CI and NCTU personnel will attend DMC meetings.

16.8. Trial Management Group

A TMG will be responsible for the day to day running of the study and will consist of the CI, co-CI, NCTU personnel, trial statisticians, health economists and as required other members of the co-applicant team. The TMG will meet on an approximately monthly basis.

16.9. Clinical Trials Unit

NCTU, a UK Clinical Research Collaboration (UKCRC) registered Clinical Trials Unit, will oversee study governance and delivery. NCTU is responsible for:

- methodological input into study design.
- creating monthly TMG reports and maintaining communication across the TMG.
- identification and mitigation of risks.
- contracting and financial management of the study.
- reporting to and communicating with the Sponsor and Funder.
- submission of trial documents for regulatory approvals at trial set-up and on an ongoing basis via amendments.
- site set-up, training and monitoring (onsite, remote and central).
- site close down and archival.
- design and building of the study database and randomisation system.
- day-to-day management of trial conduct, regularly liaising with trial sites.
- responding to data queries and data cleaning.
- administrative support, including minuting of meetings.

With regards to safety reporting, NCTU is responsible for:

- review and reconciliation of all SAEs, SARs and SUSARs reported by sites.

16.10. Notification of deaths

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

16.11. Pregnancy reporting

In the event of a study participant becoming pregnant on study, the site must notify NCTU within 24 working hours of becoming aware of the pregnancy using the pregnancy reporting form. Completed pregnancy reporting forms should be sent to NCTU by secure email to nctu.ascend.sae@nhs.net. Preliminary reporting to NCTU via email is acceptable in order to meet the 24-hour reporting timeline, where circumstances do not allow for immediate completion of the pregnancy reporting form. If cRAs become aware of a study participant becoming pregnant, they will alert the site PI.

Site teams must approach the study participant to obtain consent to follow the pregnancy until the outcome of the pregnancy is known. A copy of the completed pregnancy follow-up consent form must be sent by site to nctu.ascend.conf@nhs.net via secure email (for example, an nhs.net account or a similar method that has been agreed by the NCTU Trial Manager(s)). This is for central monitoring purposes. For participants who do not consent to sharing of their consent form, the study pregnancy follow-up consent proforma must be completed by site staff and sent to NCTU instead, via the same method. The proforma will enable NCTU Trial Manager(s) to assess the accuracy of completion of each pregnancy follow-up consent form without sight of a participant's personal details.

Follow up of any pregnancy will comprise regular telephone or videoconference calls to the participant, and documentation of the outcome of the pregnancy, and any AEs, in the participant's medical notes.

16.12. Overdose

BNF-recommended maximum daily dosages of study medications are 30 mg aripiprazole, 200 mg sertraline and 800 mg quetiapine (159). If a participant reports that they have taken more than any of these dosages of study medication during their weekly calls with a cRA, the cRA must email or telephone site PIs as soon as possible. Site teams should consult the SmPC of trial medications for advice on the management of overdose. Any instance of a trial participant taking more medication than prescribed should be reported as a protocol deviation by the site team and the PI (or appropriate delegate) should assess whether participant is suitable to stay in the study. More than one known instance of overdose would be assessed by the trial Sponsor as to whether they constituted a serious breach.

16.13. Reporting Urgent Safety Measures

An Urgent Safety Measure (USM) is an action that the Sponsor or an Investigator may take in order to protect the participants of a trial against any immediate hazard to their health or safety. Upon implementation of an USM by an Investigator, NCTU must be notified immediately and details of the USM given. NCTU must inform the MHRA and the REC within 3 days of the USM taking place in accordance with NCTU's SOPs.

16.14. Annual Safety Reports

A short version Annual Safety Report (ASR) will be submitted to MHRA once a year on the anniversary of the CTA date. NCTU must ensure that the report is submitted within 60 days of the end of the reporting period. NCTU staff will prepare and submit the ASR for the trial, in accordance with NCTU SOPs. The CI must review and authorise the final report before it is ready for submission. The ASR should also be reviewed by the NCTU Quality Assurance (QA) Manager and Sponsor representative prior to submission.

17. STATISTICAL CONSIDERATIONS

17.1. Analysis population

The primary analysis population will be the intention to treat (ITT) population (i.e. participants analysed according to randomisation allocation).

17.2. Analysis overview

The analysis will follow a fully detailed pre-specified statistical analysis plan (SAP) that is reviewed by the trial oversight committees.

17.3. Analysis of the primary outcome

The primary analysis will be on the ITT population and will use mixed effects linear regression to account for the repeated measurements. The analysis will compare the weekly repeated 12-16-week QIDS-SR scores in the two arms adjusted for baseline QIDS-SR score and all stratification factors. The statistical analysis will use all weekly measurements available between 12 and 16 weeks.

17.3.1. Sensitivity analyses on the primary outcome

One sensitivity analysis will adjust for the stratification factors as in the ITT analysis but be conducted on the per protocol population which is defined in the SAP.

A second will repeat the primary analysis but include outcomes for all randomised participants by using appropriate multiple imputation techniques to infer values for missing data.

17.4. Primary outcome period

The primary outcome period for analysis is 12-16 weeks because data from other studies of quetiapine in bipolar disorder (52, 108, 109, 160), and of sertraline (161-163) and aripiprazole (78, 79) in unipolar depression studies, show that the point of maximum separation will occur 6-8 weeks after dose escalation. The 12–16-week period allows time for medication transition to the IMP and for response to optimised doses for each individual in the study in both treatment arms. Twelve weeks is also the time point used for assessment of acute efficacy in previous CEQUEL and PAX-BD studies in bipolar depression.

17.5. Power

We will use a minimum clinically important change in QIDS-SR of two points which has been previously established in two clinical trials (110, 164) and will use design parameters calculated from PreDiCT (165) and CEQUEL (110); specifically a standard deviation of the QIDS-SR outcome of 5.4 and a correlation of 14 week QIDS-SR with baseline of 0.5. Based on PreDiCT (165) and CEQUEL (110), we further assume a conservative estimate of 0.9 correlation between 2 post randomisation measures observed between 12 and 16 weeks to power the trial. The sample size calculation assumes an average of 2 (of the total 5) measurements will be available. We conservatively have assumed an attrition rate (defined as dropping out of the trial outcome follow up between randomisation and week 12) of 20% for the primary outcome point, based in part on CEQUEL (110). 270 participants randomised will provide 90% power using 5% two-sided significance testing.

Including two or more weekly measurements for the repeated measures design increases power. The trial therefore becomes more efficient and less costly without losing robustness of the evidence of effect size because of the need for a smaller sample size.

17.6. Analysis of secondary outcomes

Secondary analyses allow examination of trajectories of symptom change and the pattern and cause of drug discontinuation over 24 weeks.

17.7. Analysis of Exploratory outcomes (REWARD Study)

Exploratory analyses will allow examination of reward processing changes over 14 weeks following IMP initiation (IMP initiation date defined as day 0 for the exploratory outcome). Further analyses will allow examination of reward processing changes over 14 weeks following IMP initiation and their association with trajectories of symptom changes over the full 24 weeks. These analyses will follow a fully detailed pre-specified REWARD study plan that will be reviewed by the trial oversight committees.

17.8. Health economic analysis

A prospective, within-trial economic evaluation will be conducted primarily from the health and social care perspective with secondary analyses incorporating wider societal costs (e.g. lost productivity, informal care) for the ITT sample over 24 weeks. Costs will be calculated by multiplying collected

resource use information with matching UK national-level unit costs from routine sources (e.g. 166). Quality-adjusted life years (QALYs) derived from the EQ-5D-5L will be assessed as the main outcome. With concerns about the responsiveness and comprehensiveness of the EQ-5D-5L in BD (167), alternative capability well-being outcomes (OxCAP-MH, ICECAP-A) and derived capability-weighted life years (CWLY) will be also measured. Missing cost and outcome data will be handled using multiple imputation methods. Differences between the two arms will be investigated within an incremental cost–effectiveness/cost-utility framework with extensive uncertainty and sensitivity analyses including per protocol and complete samples.

In addition, the effects on informal carers' health-related quality of life, capability well-being and their time and costs (based on the EQ-5D-5L, ICECAP-A, OxCAP-MH and the CIIQ completed by informal carers at baseline and weeks 4, 14 and 24) will be analysed, and also taken into consideration together with information from participants to investigate the cost-effectiveness jointly for the patient/informal carer dyad.

17.9. Equity analysis

The impact of socioeconomic status, age, gender and ethnicity (characteristics identified by the PROGRESS framework (168) as being important to consider in terms of equity of inclusion in health research) on recruitment, participation and the clinical and cost effectiveness of the study treatments will be determined. This will be examined by comparing these characteristics in populations eligible for and engaged in the trial at different points in the trial pathway. Relevant populations include the screening and randomisation populations for each site and patients who click on social media advertisements organised by Just-R, register with R+Me, are invited to complete the initial eligibility assessment, complete the initial eligibility assessment, appear eligible following the initial eligibility assessment, successfully contact sites to arrange a screening appointment, consent to participate, remain in the study until the primary outcome point and complete the study. All demographic details received from patients within the R+Me system will be anonymous.

Where possible, and with due accord to clinical governance pertaining to identifiable data, Clinical Practice Research Datalink (CPRD) (169), Primary Care Networks (PCN) and individual primary care centre records will be utilised to examine the impact of deprivation and ethnicity on primary care recruitment.

17.10. Interim analyses

There are no formal interim analyses planned except for snapshots reported to DMC, and therefore no criteria for the premature termination of the trial.

18. DATA HANDLING

18.1. Data collection tools

Clinical and safety data for trial participants will be recorded by local site staff and Clinical Studies Officers (CSOs)/equivalent in the appropriate eCRFs of the established clinical data management system (Red Pill), which is owned by Sealed Envelope™. Participant identification on the eCRFs will be through a unique trial ID number.

Trial participants will enter data from study questionnaires directly into ePRO, when prompted by email and/or text message throughout the study. There is the option for cRAs or site staff to help enter

participant data directly into the appropriate eCRFs during videoconference/telephone conversation with a participant, where participants cannot access or use the ePRO system. cRAs will also receive patient identifiable details on a study contact form which will be used to help support participants to complete data entry, enable risk procedures to be implemented when appropriate (see section 3.1 and 3.2) and enable the sharing of relevant study data with the Qualitative team.

Data from PILT and BIS/BAS as part of the optional REWARD study will be collected by participants entering data directly into the Gorilla™ platform, when prompted by email and/or text message. Data will be stored on Gorilla™ and Newcastle University OneDrive. Participant identification will be through a unique trial ID number and the month and year of birth of the participant as a second identifier, to add a further layer of data protection.

18.2. Data handling and record keeping

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

Potential participants registering with the Research+Me registry will follow the usual REC-approved processes, with appropriate consent and provision of a approved privacy statement (see appendix 2). The data controller will be Newcastle Hospitals. For those in the 'ASCEnD only pathway', the Research+Me platform acts as a data processor, whilst the study sponsor acts as the data controller.

18.3. Access to data

Staff involved in the conduct of the trial at participating sites will have access to an ISF. NCTU will have access to all ISFs from all sites for monitoring purposes.

The trial data and patient medical records may be looked at by monitoring or auditing personnel from the REC or MHRA, or the Sponsor.

Password limited access, restricted to a particular role and site, to the trial's Red Pill™ database will be granted to site PIs and their delegated data entry personnel. cRAs will have access to the trial's Red Pill ™ database for all sites for data entry purposes. The NCTU trial management team will also have access to the trial's Red Pill™ database for all sites for monitoring purposes. For the REWARD study, data on participant IMP initiation date will be shared via email alongside the participant study ID unique trial ID number, in order to schedule follow-up measurements, as well as partial DoB (see section 10.2 for further details). For the nested qualitative study, contact details for the participant will be shared via the cRAs using the study contact form (see section 14.1 for further details).

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

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

Access and management of the ePRO system will be controlled and monitored by the online platforms' provider. The NCTU Data Management team will have administrative access to the Sealed Envelope ePRO system. The REWARD study team will have administrative access to the Gorilla™ platform.

18.4. Archiving

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

18.5. Data handling within the nested qualitative study

Data storage procedures for the nested qualitative study will follow Keele University's SOPs for research. Personal data will only be accessible to the research team during the data collection phase of the study. A study database containing participant information will be housed on Keele University's secure network in a password-protected folder. Personal data will be kept for up to six months after the end of the study.

There are secure physical storage arrangements for hard copies within the School of Medicine in lockable filing cabinets. The School of Medicine building operates a key-code entry system to ensure only appropriate persons can enter the building. In addition, any hard copy research data that has been printed for checking will be destroyed by shredding.

Research data will be pseudo-anonymised prior to analysis through the use of a unique study code; only members of the study team will have access to the link to identify data. Electronic copies of anonymised transcripts will be stored for five years on a secure university network to be accessible for future research (where participant consent has been obtained).

Transcription of interviews may be sent to The Transcription Company (UK), a Data Processor. Keele University has a Data Processing Agreement (DPA) in place with the company who may use SendThisFile as a Sub-Processor to assist with the transcribing process. SendThisFile is registered and complies with the EU-US Data Privacy Framework and the UK Extension to this under Article 45 of the UK GDPR.

For archiving at the end of the study, all data will be maintained in such a form that they cannot be linked with identifiable participants and will be anonymised in the reports.

19. MONITORING, AUDIT AND INSPECTION

A trial monitoring plan will be developed prior to recruitment, based upon the trial risk assessment, and agreed by the TMG, NCTU QA representative and the Sponsor.

All monitoring activity will be detailed in the monitoring plan. Monitoring of trial conduct and data collected will be performed by a combination of central review and on- and off-site monitoring visits, to ensure the trial is conducted in accordance with GCP and appropriate regulations. Site monitoring will be undertaken by NCTU personnel.

All monitoring findings will be reported and followed up with the appropriate personnel in a timely manner. Sites will be expected to assist the Sponsor in monitoring the trial e.g. by hosting monitoring visits, providing information for on- and off-site monitoring and responding to monitoring findings within the timeframes requested.

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

20. REGULATORY CONSIDERATIONS

20.1. REC review and reports

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

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

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

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

20.2. Peer review

The trial has undergone peer review through the process of grant application and funding award by the NIHR HTA Panel. The REWARD (Optional Mechanistic) Study is funded by an internal PhD scholarship awarded from Newcastle University.

20.3. Public and patient involvement

A study LEAP has been organised by the McPin Foundation, a mental health research charity specialising in promoting patient involvement within mental health research trials (www.mcpin.org). The LEAP has provided input to the protocol and to patient-facing study documents. The group will meet regularly throughout the study to review progress and provide recommendations to the trial oversight committees. At trial end, the LEAP group will be involved in the dissemination of study findings to patient groups.

The former head of public involvement at the McPin Foundation was a co-applicant for the study and is a current member of the TMG. The TSC also includes an informal carer representative.

20.4. Regulatory compliance

The trial will be conducted in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments. All parties must abide by these regulations and the ICH GCP guidelines. NCTU will obtain a CTA from the MHRA prior to the start of the trial and will notify

the MHRA of any substantial amendments that require review by the CA. These substantial amendments will not be implemented until the MHRA have issued an acceptance of the amendment. The Sponsor will notify the MHRA of any serious breaches of GCP or the protocol, USMs or SUSARs that occur during the trial. The ASR will be submitted each year to the MHRA by NCTU until the end of the trial. NCTU will notify the MHRA of the early termination or end of trial in accordance with the required timelines.

20.5. Protocol compliance

It is the responsibility of the CI to ensure that the study is run in accordance with GCP and the protocol. Study tasks may be delegated to a suitably qualified or experienced member of the site team, but the CI and PI at site will retain overall responsibility for adherence to the protocol and to GCP.

The study will be monitored by NCTU staff, to measure protocol compliance and manage deviations. Protocol deviations, non-compliances, violations or breaches are departures from the approved protocol. Deviations that could impact the outcome of the study or the safety or rights of participants will be classed as violations. Deviations that are found to frequently recur at a site are not acceptable. These will also be classified as violations and could also be classified as serious breaches (see section 20.6.). Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used.

Site staff and cRAs are responsible for compliance with the protocol in their everyday trial activities and must report anything that they feel constitutes a SAE, SUSAR, protocol deviation, protocol violation, serious breach or anything that requires an USM. Deviations from the protocol and GCP occur in clinical trials and the majority of these events are technical deviations that are not serious breaches. These events must be documented by site on the protocol deviation log, with details of the relevant Corrective and Preventive Action(s) (CAPA) included. These will be reviewed by NCTU and the Sponsor in accordance with the NCTU SOP.

20.6. Notification of serious breaches

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

(i) the safety or physical or mental integrity of the subjects of the trial; or
(ii) the scientific value of the trial

The Sponsor must be notified immediately of any incident that may be classified as a serious breach. NCTU will notify the MHRA and the NHS REC within the required timelines in accordance with the NCTU SOP.

20.7. Data protection

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

20.8. Indemnity

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

20.9. Amendments

It is the responsibility of the Sponsor to determine if an amendment is substantial or not and study procedures must not be changed without the mutual agreement of the CI, Sponsor and the TSC.

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

Non-substantial amendments will be submitted to the HRA and will not be implemented until authorisation is received.

Substantial amendments and those minor amendments which may impact sites will be submitted to the relevant NHS Research and Development (R&D) Departments for notification to determine if the amendment affects the NHS permission for that site. Amendment documentation will provide to sites by NCTU.

20.10. Final trial dataset

In accordance with CNTW, Government and NIHR policies, non-identifiable research data may be shared with researchers in other Universities and organisations (including those in other countries), for research in health and social care. If there is a need to share identifiable information, explicit consent will be sought from participants. Appropriate safeguards will be in place where any identifiable information is transferred to other countries, in particular those countries with different data protection laws to the UK.

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

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

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

21. DISSEMINATION POLICY

Dissemination will include a final report to the NIHR.

Findings will be disseminated to the academic and clinical community via conference presentation and publication in peer review journals. Every effort will be made to include people with lived experience (such as LEAP members) as co-authors in all study publications. The study LEAP will be acknowledged in all study publications.

A plain English ‘lay’ summary of the findings will be disseminated to patients and their informal carers via social media and presentation at Bipolar UK meetings. A graphical summary of the results (an infographic) will also be produced by the McPin Foundation and will be made publicly available.

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23. APPENDICES

23.1. Appendix 1 – Trial medication guidance

Clinicians are encouraged to use their own judgment with regards to the dosages of sertraline, aripiprazole and quetiapine prescribed to participants of ASCEnD. The following guidance has been written in accordance with SmPC and BNF guidance, but clinicians should be informed by a participant's weekly clinical scale scores and reported side effects.

Sertraline/Aripiprazole

The BNF recommends a dose range of 50-200 mg sertraline daily for individuals experiencing depression and 15-30mg aripiprazole daily for individuals with bipolar disorder. However, for aripiprazole, research evidence suggests effectiveness of lower doses up to 10mg daily for antidepressant augmentation (see section 2.4).

As a result, starting daily dosages of 50 mg sertraline and 2.5 mg aripiprazole are recommended for participants for ASCEnD with dose increases, if lack of clinical response suggests and tolerability allows, of 50 mg sertraline or 2.5 mg aripiprazole (alternating) to a maximum of 150 mg and 10 mg daily, respectively.

Quetiapine

The BNF recommends a dose range of 300-600 mg quetiapine daily for individuals experiencing bipolar depression. Quetiapine daily doses in clinical trials typically start at 50 mg and increase to 300 mg. ASCEnD will rely on guidance from the CEQUEL study which achieved a dose of 300 mg by day 7 (50 mg by days 1 and 2, 100mg by days 3 and 4 and 200mg by days 5 and 6) in order to minimise the risk of side effects[1].

Quetiapine is available in an immediate release (IR) and in an extended release (XL) formulation. The choice between IR and XL will remain a clinical decision in participants randomised to quetiapine.

Contraindications

A study-specific supportive document is available as a ready reference guide for concomitant cautions and drug interactions with IMPs. However, clinicians should refer to the most recent SmPC and BNF for guidance regarding safe prescribing.

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

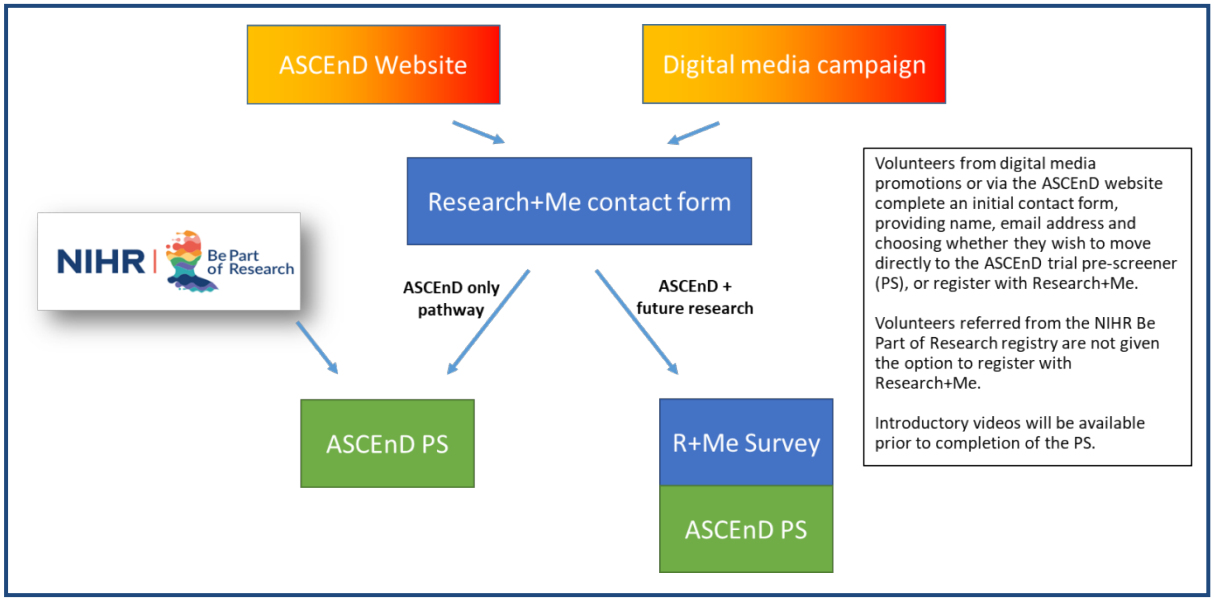
23.2. Appendix 2 – Research+Me

The Research+Me registry is an NHS-owned recruitment platform developed to empower patients (and healthy volunteers) to access research available via the following link: https://newcastlejro.com/take-part/researchplusme/.

The platform has approval from the Health Research Authority Research Ethics Committee (REC Ref. 23/NE/0090), has a robust infrastructure and governance protocols, and an excellent track record. There is synergy and joint working with the NIHR Be Part of Research (BPoR) registry. The Research+Me registry stores data securely and has mechanisms for inviting patients and healthy volunteers in an efficient manner, utilising detailed pre-screening surveys. This provides a steady flow of potential participants to sites at a level that maximises delivery capacity.

The platform is able to invite registrants to participate in trials, perform online eligibility assessments, assess the outcome of those assessments to determining eligibility and direct eligible participants to their nearest recruiting site.

The platform will process potential participants from within the registry itself, from external promotions (social media campaign, GP PIC sites, posters etc) and from the NIHR BPoR registry. Potential participants coming from BPoR should not register with the registry part of Research+Me as this might cause future confusion. Some of the volunteers from external promotions may also prefer not to register with Research+Me, all will have a choice on initial contact with the platform as shown in the figure below.

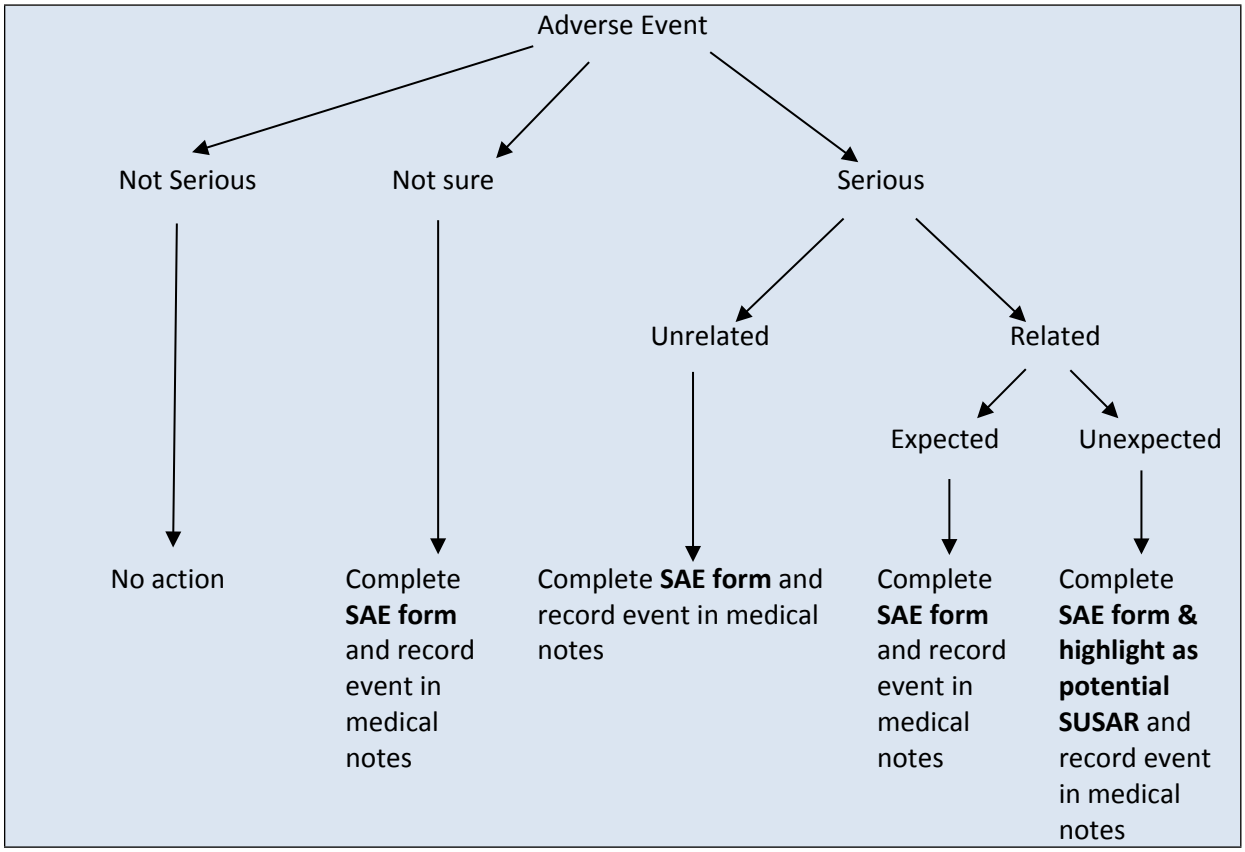


Those individuals registering with the Research+Me registry will follow the usual REC-approved processes, with appropriate consent and provision of privacy statement. In these cases, the data controller will be Newcastle Hospitals. For those in the 'ASCEnD only pathway', the Research+Me platform acts as a data processor, whilst the study sponsor acts as the data controller which will have a separate consent form and privacy statement.

Volunteers who complete the online eligibility assessment will be informed of the outcome (potentially eligible or not eligible) and will receive an automated email containing signposts to sources of additional support.

Eligible participants will be provided with contact details of the nearest research site (determined by postcode tagging) and, if they have agreed, their contact details will be passed on to that research team. A data protection impact assessment (DPIA) will be executed to describe the data flows. Sites receiving data will need to confirm they have read and understood the DPIA and abide by appropriate data sharing conditions.

23.3. Appendix 3 - Safety reporting diagram



Send completed ASCEnD SAE reporting forms to nctu.ascend.sae@nhs.net.

23.4. Appendix 4 – Amendment history

Amendment number	Protocol version	Date	Author(s) of changes	Details of changes made
SA02	V3.0	11/09/2024	ASCEnD trial management group members	Minor typographical errors throughout Updates to Key Trial Contacts Update to Glossary of Terms and Abbreviations Addition of exploratory REWARD study throughout Section 3.1 Update to procedure in relation to suicide risk Section 3.2 New section relating to procedure in relation to domestic violence risk Section 4.2 Clarification of primary objective to avoid confusion related to hypothesis testing language Section 4.3 Clarification of primary outcome baseline timepoint Section 4.5 Addition of new exploratory objectives and outcome measures relating to REWARD study Section 5 Update to diagram Section 5.1 Update to Schedule of Events to add REWARD study assessments and clarify that participant recompense will be provided by sites in line with site agreements Section 6 Removed diagram, addition of further details around self-referral to the trial and online pre-screening assessment provided by Research Plus me Section 8.1 Addition of Gorilla ePRO for exploratory REWARD study Section 8.2 Clarification that sites may use paper worksheets as source data Section 8.2.1 Clarification around consent to inform GP and refers around participation in the trial, and around optional consent for REWARD and qualitative studies Section 8.2.2 Addition of details of actions post-confirmation of eligibility Section 8.2.3 Change of time period for informal carer recruitment from 7 to 14 days Section 9 and 9.1 Addition of exploratory REWARD study baseline measures

				Section 9.3 Clarification that prescribers may include non-medical prescribers where this is standard procedure at site for these medications Section 10.1 Update that cRAs will use a spreadsheet as source data, and that cRAs or site staff may support in questionnaire completion Section 10.2 Addition of exploratory REWARD study measures Section 11.2 Clarification around communication pathway of withdrawals Section 12 Additional details around participant recompense Section 14.1 Expanded details around qualitative study including recruitment, data protection and withdrawals Section 16 Clarification of roles and responsibilities Section 16.14 Update that a short form annual safety report will be submitted in lieu of a DSUR Section 18 Additional details around data handling, including in relation to Research+Me, qualitative and REWARD studies Section 20.3 Change of institution for PPI member of team Appendix 2 Addition of further details relating to recruitment via Research+Me Removal of previous Appendix 3 (summary of NICE monitoring recommendations)