This protocol has regard for the HRA guidance and order of content.

FULL/LONG TITLE OF THE STUDY

Behavioural therapy for inter-episode bipolar symptoms: A multiple baseline case series evaluation

SHORT STUDY TITLE / ACRONYM

IEBS case series

PROTOCOL VERSION NUMBER AND DATE

Version 1.2, 27/4/23

RESEARCH REFERENCE NUMBERS

IRAS Number: 320627

SPONSORS Number: 2021-22-36

FUNDERS Number: NIHR302220

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

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 investigation without the prior written consent of the Sponsor

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

For and on behalf of the Study Sponsor:

Date: 27/04/2023

Signature:

Name (please print): Ms Pam Baxter

Position: Research Governance Manager (Health and Social Care)

(Sponsor's representative)

Chief Investigator:

Date:

Signature: 27.4.23

Name: (please print): Kim Wright

KEY STUDY CONTACTS

Chief Investigator	Kim Wright Email: K.A.Wright@exeter.ac.uk Tel: 01392 725227
Study Co-ordinator	To be advised
Sponsor	University of Exeter Contact: Pam Baxter Email: P.R.Baxter2@exeter.ac.uk Tel: 01392 726621
Funder(s)	This study is supported by an NIHR advanced fellowship (NIHR302220) awarded to Kim Wright (1/9/22 – 30/11/26)
Key Protocol Contributors	Kim Wright, Barney Dunn, Heather O'Mahen, Sandra Bucci,
Committees	Trial Steering Committee (subsuming DMEC functions), chair: Prof Fiona Lobban, Lancaster University

STUDY SUMMARY

Study Title	Behavioural therapy for inter-episode bipolar symptoms: A multiple baseline case series evaluation
Internal ref. no. (or short title)	STABILISE
Synopsis	Bipolar Spectrum Disorders typically involve periods of depression, and periods of very high energy and mood (hypomania or mania). Bipolar Disorders (BDs) are common, affecting around 1 in 20 people at some point in their lifetime. They can be very distressing and disruptive to the people who experience them, and for friends and relatives. Many people with these conditions have mood issues outside depressive or manic episodes. Often these issues include ongoing low mood, and/or frequent swings in mood or emotions. These are sometimes called "inter-episode bipolar symptoms" (IEBS). There are psychological (talking) therapies designed to help people with Bipolar Disorders, but these tend to be aimed at preventing a relapse of depression or mania, or they are aimed at helping people recover from a period of depression. There is no universally accepted talking therapy for helping people who have ongoing low mood or mood swings in between full episodes. The aim of this study is to provide an initial evaluation of a psychological therapy designed to address these ongoing symptoms. A total of 12 people, in two consecutive cohorts of six to allow refinement of the therapy in between, will be offered the therapy and will be randomly allocated to a waiting period of 3-5 weeks after their baseline assessment. They will then repeat some

	of the assessment measures and commence the therapy which will be delivered over a period of approximately seven months. At the end of therapy, they will complete the set of assessment measures again and complete a three week post therapy monitoring period. Throughout the baseline, therapy and post-therapy periods they will be invited to complete some brief measures of symptoms on a weekly basis. At two points (during the first two weeks of the baseline period and of the post therapy period) they will be invited to complete a block of mood and activity monitoring when they will be asked briefly about mood and key activities three times per day for 14 days. Views on the acceptability of the therapy will be collected from participants in terms of numerical ratings of acceptability, written feedback and through interviews.
Study Design	Two cohort randomised multiple baseline ABA case-series design
Study Participants	Participants will be adults who i) meet research diagnostic criteria for Bipolar I or II Disorder, Other Specified Bipolar Disorder or Cyclothymic Disorder; ii) do not meet criteria for a manic or severe depressive episode; iii) have IEBS, defined as at least mild depressive symptoms (Patient Health Questionnaire [PHQ9] >=5) or above-average bipolar mood instability defined as >=1.3 on the brief Affective Lability Scale (ALS) depression-elation scale; iv) are willing to engage in psychological work addressing IEBS or its impact on functioning; v) sufficient English to complete questionnaires without translation; vi) have completed the intake measures. Exclusion criteria include: i) current substance dependence according to ICD-11 criteria; ii) frequent and serious self-harm that cannot be safely managed in a community outpatient setting; iii) currently engaged in another psychological therapy for bipolar disorder.
Planned Size of Sample (if applicable)	12
Planned Study Period	21 months
Research Question/Aim(s)	i) To allow initial evaluation of intervention safety, feasibility and acceptability. ii) To investigate whether the pattern of change in symptoms is consistent with the potential of the intervention to deliver benefit. iii) To refine the therapy protocol and procedures for training and supervising therapists. iv) To develop an initial therapy competence and adherence measure.

FUNDING AND SUPPORT IN KIND

FUNDER(S) (Names and contact details of ALL organisations providing funding and/or support in kind for this study)	**FINANCIAL AND NON FINANCIAL SUPPORT GIVEN**
University of Exeter	The Chief Investigator is employed by the University of Exeter and will conduct this study as part of this employment.
National Institute for Health and Care Research	This study will be conducted within a programme of work funded by an NIHR advanced fellowship awarded to the applicant (NIHR302220).
Devon Partnership NHS Trust	This organisation will host the research associate delivering this study and will offer support to the running of the study from the Research and Development Office.

ROLE OF STUDY SPONSOR AND FUNDER

The study sponsor (University of Exeter) is legally liable for the overall conduct and management of the study. The sponsor will not influence study design, analysis, interpretation, manuscript writing or dissemination of results. The sponsor may influence the conduct of the study, and exercise a final decision with respect to its continuation, in accordance with their legal responsibilities.

The study funder (NIHR) will not influence the study design, conduct, data analysis, interpretation, manuscript writing or dissemination of findings.

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

The University of Exeter will act as sponsor for this study. The Chief Investigator (Wright) will be responsible for the day-to-day running of the study.

A Trial Management Group (TMG), consisting of the Chief Investigator and team members, will meet approximately weekly over the duration of the study to facilitate the day to day running of the study and to monitor study progress and manage overall study governance.

A Trial Steering Committee (TSC) has been convened including independent members. The TSC will be responsible for advising the TMG on the conduct of the study. Given the relatively small scale of the study, a separate Data Monitoring and Ethics Committee (DMEC) will not be convened. Instead the DMEC functions (reviewing data collected including adverse events and making recommendations for the future conduct of the study) will be included within the terms of reference of the TSC. All safety relevant events will be reported to the TSC and reviewed on an ongoing basis.

PROTOCOL CONTRIBUTORS

The protocol has been written by the Chief Investigator, Kim Wright, with contributions from co-investigators Barney Dunn and Heather O'Mahen. The protocol has been reviewed by an independent clinical researcher and modified in line with these comments. A subgroup of the study patient and public involvement panel have contributed to the development of this protocol.

KEY WORDS

Behavioural Therapy

Bipolar Disorder

Multiple Baseline

Case Series

STUDY FLOW CHART

Figure 1: IEBS GANTT chart

Dates (months) 1 =Jan 2023	Pre-start	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Ethics approval																						
Finalise treatment manual																						
Train therapists																						
Recruit patient: cohort 1																						
Baseline assessments: cohort 1																						
Pre-treatment assessments: cohort 1																						
Therapy: cohort 1																						
Post-therapy monitoring phase and interview: cohort 1																						
7 month follow-up assessments: cohort 1																						
Recruit patient: cohort 2																						
Baseline assessments: cohort 2																						
Pre-treatment assessments: cohort 2																						
Therapy: cohort 2																						
Post-therapy monitoring phase and interview: cohort 1																						
7 month follow up assessments: cohort 2																						
Analysis																						

GLOSSARY of Terms and Abbreviations

BA	Behavioural Activation
BD	Bipolar Disorder
DBT	Dialectical Behavioural Therapy
CI	Chief Investigator
GCP	Good Clinical Practice
PPI	Patient and Public Involvement
RC	Reliable Change
TSC	Trial Steering Committee
TMG	Trial Management Group
PHQ-9	Patient Health Questionnaire
GAD-7	General Anxiety Disorder Assessment
BRQ	Bipolar Recovery Questionnaire
QoL.BD	Quality of Life in Bipolar Disorder Questionnaire
ASRM	Altman Scale for Rating Mania
HAM-D	Hamilton Depression Rating Scale

Behavioural therapy for inter-episode bipolar symptoms: A multiple baseline case series evaluation

STUDY PROTOCOL

1. BACKGROUND

Bipolar Disorders (BDs: Bipolar I or II Disorder, Cyclothymic Disorder) result in substantial personal and societal costs and affect around 1 in 20 people across their lifetime (Pini et al., 2005). Compared to the general population people with BDs are over twice as likely to die prematurely, and up to 1/5 people with BDs die from suicide. In 2007 the societal cost of BDs was estimated at £5.2 billion, projected to rise to £8.2 billion in 2026 (McCrone et al., 2008).

In addition to major episodes of depression or mania, people with BDs can experience ongoing bipolar symptoms (inter-episode Bipolar symptoms: IEBS). With IEBS, depressive symptoms tend to be more frequent relative to hypomanic symptoms (Paykel et al, 2006) and instability of mood is common (MacQueen et al., 2003).

Treatments are needed for IEBS for three reasons. First, they are common: significant levels of ongoing Bipolar symptoms are experienced by up to half of those with Bipolar I or II Disorder who are not in a major episode (Gershon & Eidelman, 2015), and on average people with BDs spend around twice as long experiencing sub-clinical symptoms as they spend in acute episodes (Paykel et al., 2006). Second, they are associated with significant distress and impairment, including increased psychiatric comorbidity and poorer functioning (Gershon & Eidelman, 2015; Kochman et al., 2005MacQueen et al., 2003; Samalin et al., 2016; Stanislaus et al., 2020). Third, they are associated with risk of developing full depression and mania (Judd et al., 2008), which can be financially costly to the health service and wider society, and personally costly to patients and families.

Despite the impact of IEBS, and treatment of persisting BD symptoms being a U.K. research priority (James Lind Alliance, 2016), the evidence base for helping people with this disabling presentation is not well developed. Whilst some studies have examined the effects of pharmacological agents on residual symptoms (Alda et al., 2017), relatively few consider their impact upon mood instability and there is no established pharmacological strategy for IEBS as a whole (NICE, 2014).
Psychological therapies for individuals with BDs are valued by service users, and are a national priority (Mental Health Task Force, 2016), yet the extant literature does not provide direct guidance on the optimal psychological treatment for people with IEBS. Whilst three published studies (two single case reports and one small randomised controlled trial: Fava et al., 2011; Totterdell et al., 2008; Totterdell et al., 2012) report the effects of psychological therapy for adults with Cyclothymic Disorder, this study did not include those with Bipolar I or II Disorder with residual symptoms (mood instability or ongoing depressive symptoms). In a randomised controlled feasibility trial in people with type I, II or other specified bipolar disorder, whilst mood instability was included as a secondary outcome it was not an inclusion criterion (Steel et al., 2020). Finally a randomised controlled feasibility trial by Mansell and colleagues (2014) for people with bipolar disorder tested a therapy addressing mood instability but did not mandate this as an inclusion criterion or measure it as an outcome (Mansell et al., 2014). Thus we do not currently have a talking therapy that seeks to address the common ongoing mood

symptoms (low mood and mood instability) that people with BD or Cyclothymic Disorder present with, nor a therapy that has been tested across the bipolar spectrum with respect to these issues.

In previous work we have developed promising psychological treatments for both bipolar mood instability and bipolar depressive symptoms. This study represents a first step in bringing these together into a single approach that would apply across the full range of IEBS. This is necessary because we found the patients in our studies often presented with both, for example moving between periods of low mood and periods of mood instability, and rigidly following one single protocol made it difficult for therapists to address both issues. The two existing protocols are both behavioural in approach and our experience so far indicates they can be easily and successfully integrated.

In an NIHR RfPB funded feasibility RCT led by the current Chief Investigator (the ThrIVe-B trial: Wright et al., 2021) with input from patients and clinicians we adapted an existing, group-based therapy for emotion regulation in other patient groups, Dialectical Behaviour Therapy, to better meet the needs of people with Bipolar mood instability. This two-site trial examined the feasibility and acceptability of the research procedures, safety, and acceptability of the therapy. Recruitment and data completion rates (3.9 patients per month; 74% at 9 month follow-up) indicated feasibility of these aspects, and safety criteria were met. Qualitative feedback revealed many perceived benefits of the therapy, however therapy attendance was below our pre-specified criterion of >= 60% of participants attending at least 50% of sessions and feedback from participants indicated that this was in part due to the group nature of the intervention (e.g. inability to vary the day and time of sessions). A viable next step is to redesign this approach to maximise consistent attendance and individualisation of material through using one-to-one rather than group-based delivery of therapy.

Separately, Behavioural Activation (BA) is a parsimonious, straightforward intervention used in the treatment of unipolar depression, and was recently evaluated in U.K. primary care in the large, successful, NIHR-funded COBRA trial on which the current Chief Investigator was a co-applicant (Richards et al., 2016). With input from therapists and people with BD, we delivered an adapted version of this approach to 12 individuals with bipolar depression (ClinicalTrials.gov: NCT03658824, Wright et al., submitted). Attendance and feedback indicated high acceptability and reduction in depression symptoms, however the protocol does not contain techniques for managing mood instability, despite this characterising some of the participants in our sample.

2. RATIONALE

As part of an NIHR funded advanced fellowship a co-production approach is currently being used to formally integrate the ThrIVe-B and BT streams of work to develop an intervention for IEBS based on a simple, behavioural core approach but with the flexibility to use the additional techniques according to the patient's needs and capacity. As part of the development process, we plan to conduct a case series to allow us to refine the therapy protocol and procedures for training and supervising therapists, conduct an initial evaluation of intervention safety, feasibility and acceptability, develop an initial therapy competence and adherence measure, and explore proof of concept of clinical efficacy based on changes in symptoms from the baseline to the treatment and post-treatment phases.

The intention is to then progress to a randomised controlled feasibility trial of the intervention at the point where it meets minimum thresholds in terms of acceptability and clinical promise, as well as appearing safe. This trial is not the subject of the current HRA application.

3. THEORETICAL FRAMEWORK

Through a series of workshops and other communications the CI is developing and refining the therapy protocol with a panel of eight people with lived experience of bipolar disorder. There is also input from therapists familiar with the component therapies throughout. The approach taken is informed by Experience-Based Co-Design whereby a group of stakeholders identify uncertainties which are then prioritised, before being addressed collectively. This process extends before, alongside and after the case series and thus not all aspects of the therapy will be finalised until the case series is complete and learning has been taken from it. However, the theoretical framework and the concepts and techniques used are largely predetermined.

The therapy is based on the following principles:

- In line with the behavioural theory of depression, depression is hypothesised to be maintained at least in part by low rates of response-contingent positive reinforcement and an increase in negatively reinforced behaviour (e.g. relief from avoiding things that are distressing). In participants with depressed mood the therapy seeks to promote re-engagement with positively reinforced activity, aided by support in reducing barriers to these activities (avoidance, difficulties in problem solving, rumination).
- In accordance with a broader behavioural perspective, the goal is not to maximise activity or high-activation positive affect, but rather to help participants find a sustainable pattern and balance of activity that enables them to live well within their situation, to support them to change their situation where possible and needed, and to make changes to patterns of behaviour that lead to problems or distress. This typically entails reducing mood-driven

behaviour and increasing behaviours guided by the person's values, plans or goals. These principles apply equally to depressed versus hypomanic states.

- People with IEBS have often experienced many years of extreme mood states which have led to problems and distress. Clinically, these patients often express fear of particular emotions or mood states, and may feel it is difficult to distinguish between "normal" emotional responses and those that are part of an "illness". Concepts from emotion regulation approaches are used to help patients to recognise and discriminate between different mood and emotional states and to reduce anxiety and fear about these states, Whilst also helping them to use this information about discriminating emotional states to then optimise implementation of behavioural principles.

As the planned case series is part of a development process, the therapy protocol is expected to evolve across the life of the case series, in part based upon learning from the case series. This may involve changes to the detailed content of the therapy (although not the underpinning principles) as well as the number, duration and spacing of sessions. Our starting point, to be used in the case series, is that the intervention will consist of up to 20 individual therapy sessions (plus up to two initial assessment sessions) of behavioural therapy, delivered over up seven months. Therapy will end after 20 sessions or 7 months, whichever is sooner, and participants will be able to choose to space sessions out over more than a week if they wish or to take a short break from therapy. Sessions will be an hour long as default but with the option for participants to agree shorter or longer (up to 75 minute) session duration if needed (approach devised in consultation with PPI panel and therapists experienced in working with this patient group). This will be followed by a period of consolidation whereby patients can opt to see the therapist up to three times over 6 months.

All sessions will be audio-recorded (where participants consent to this) to allow for supervision and the piloting, evaluation and refinement of a therapy adherence and competence measure.

Therapy will be delivered by up to 4 therapists with an existing training in cognitive behavioural, behavioural or dialectical behavioural therapy and experience of working with people with bipolar disorder. They will receive additional training in the approach as necessary (three of the intended therapists are involved in the current therapy development process and thus formal training needed will be minimal).

Therapy will be delivered face-to-face, online or by phone according to patient preference and what is practically possible. Face-to-face therapy will by default be delivered in the treatment centre however in keeping with the ethos of the approach (patient-centred, flexible, contextual and experiential) therapy sessions may take place outside of the centre if the patient wishes and it is appropriate and safe to do so. This may include practising activities together (e.g. visiting a shop) or sessions within the person's home.

4. RESEARCH AIMS

4.1 Objectives

i) To allow initial evaluation of intervention safety, feasibility and acceptability.

ii) To investigate whether the pattern of change in symptoms is consistent with the potential of the intervention to deliver benefit, namely a decrease symptoms (depressive symptoms, mood instability) and / or an increase in sense of living well with the symptoms (quality of life, sense of personal recovery).

iii) To refine the therapy protocol and procedures for training and supervising therapists.

iv) To develop an initial therapy competence and adherence measure.

Minimum thresholds to progress from this case series to feasibility trial (which will be the subject of a later, separate HRA application):

1. No serious concerns about therapy safety (no serious adverse events that are attributable to the therapy, or if there are therapy-attributable adverse events, the TSC are satisfied that suitable modifications have been made to the therapeutic protocol to mitigate sufficiently against future risk).

2. On the outcome measures overall, number of instances of reliable improvement exceed instances of reliable deterioration.

4.2 Outcome

Primary outcomes

As this is a feasibility trial, the primary outcomes relate to the key feasibility objectives. Objective 1 is to evaluate if the treatment is safe and acceptable to service users and therapists. This will be measured by rates of therapy-related adverse events, therapy uptake and completion rates, rates of reliable deterioration, and quantitative and qualitative feedback from participants and therapists.

Objective 2 is to evaluate whether the pattern of change in symptoms is consistent with the potential of the intervention to deliver benefit. This will be measured by rates of reliable, and reliable and clinically significant, change in the Patient Health Questionnaire (9 item version, PHQ-9: Kroenke et al., 2001) and the bipolar-depression scale of the Affective Lability Scale (ALS: Oliver et al., 2004), from the baseline period (mean score) to the post therapy period (mean score). These self-report measures offer reduced participant burden compared to alternative observer-rated instruments which typically involve lengthy interviews. The PHQ-9 is used extensively in the evaluation of therapies for unipolar depression (for example, it was the primary outcome measure in the COBRA trial, Richards et al., 2016). The ALS is used to measure ongoing mood instability, a construct for which we do not have a gold-standard measure; an aim of the wider programme of work is to explore and compare potential measures. The ALS has been used in previous research examining affective instability in individuals with bipolar and in a previous feasibility trial (Wright et al., 2021).

Objectives 3 and 4 are to refine the therapy protocol and procedures for training and supervising therapists, and to develop an initial therapy competence and adherence measure. Therapists will complete an interview about their experiences of using the therapy and views on training and supervision needed. We will obtain initial internal consistency estimates for the therapy competence and adherence measure. This work is expected to result in outputs including a revised draft therapy manual, a written set of procedures for training and supervising therapists and a draft therapy competence and adherence measure.

Secondary outcomes

The secondary outcomes are the rates of reliable and reliable and clinically significant change on the following measures: Bipolar Disorder Recovery Questionnaire (BDRQ: Jones et al., 2013 – measure of sense of personal recovery), Quality of Life in Bipolar Disorder Scale (QoL.BD: Michalak et al., 2010 – measure of quality of life) and Generalised Anxiety Disorder assessment scale (GAD-7: Spitzer et al., 2006 – measure of anxiety symptoms) from pre therapy to 7 month follow up. This will also include reliable and reliable and clinically significant change on the Altman Scale for Rating Mania (ASRM: Altman et al., 1997 – measure of hypomanic / manic symptoms) from the baseline period to the post-therapy period (mean scores). Furthermore we will report group-level change in all outcome measures from baseline to 6 month follow up and pre-therapy to 7 month follow up.

We will also measure mood and activity at five time points per day for 14 days on two occasions (pre and post therapy) for each participant. This allows for calculation of mood instability before and after therapy and provides an additional means of examining this to the ALS, which is limited by its reliance on retrospective ratings made by the participant.

5. STUDY DESIGN, METHODS OF DATA COLLECTION AND DATA ANALYSIS

5.1 Study Design

This project will follow a two cohort randomised multiple baseline ABA case-series design.

In an ABA design, for an individual receiving a treatment there is a measurement period (baseline) before the treatment phase, and then again after the treatment phase. This allows you to compare change in the baseline phase to change in the treatment phase and the post treatment phase. It is also possible can look for change in both slope and level of scores on weekly measures. Evidence of efficacy is indicated by reliable improvements in participants' scores from pre to post therapy as well as improvement in level and increase in slope from the baseline to treatment phases.

In a multiple baseline case series, individuals in the study are randomly allocated to baseline periods of different lengths (in other words the timing of the start of treatment is staggered across participants). This design increases the likelihood that symptom change which onsets following the start of treatment is due to the effects of treatment rather than to non-treatment related factors such as measurement repetition effects, or spontaneous recovery over time.

In the current study, following guidelines on the design of multiple baseline ABA case series (Levin & Ferron, 2021, Tate & Perdices, 2018), we will randomise participants to between three and five weeks of baseline measurement (allowing a minimum of three weekly measurements during the baseline phase, and three baseline lengths that participants can be randomised to). Symptoms of depression, hypomania and mood instability will be measured weekly across the baseline period, treatment phase and for three weeks immediately post-treatment. Participants will also complete additional self-report measures and give qualitative feedback at pre-treatment and 7 month follow-up.

5.2 Methods of Data Collection

5.2.1 Measures

Weekly assessment

- Patient Health Questionnaire – 9 (PHQ-9) – a 9 item self-report measure of depression symptom severity over the past week
- Depression-Elation subscale of the Affective Lability Scales - short version (ALS) – 8 self report items that ask about the extent to which mood has fluctuated between high and low.
- Altman Self-Rating Mania Scale (ASRM) – a 5 item self-report measure of hypomania symptoms over the past week (although a secondary outcome this is measured weekly as it provides important information to the therapist and patient).

Demographic Assessment at baseline only

- Demographic screening questionnaire (age, gender, ethnicity, use of medication, employment, relationship status, highest level of education, smoking and alcohol intake, previous treatment)

Measures at baseline, pre-treatment and 7 month follow-up

To establish if the intervention changes mental health symptoms, quality of life and functioning the following measures will be completed at intake, pre and post-treatment.

- Structured clinical interview for depression (SCID-5; First, Williams, Karg, & Spitzer, 2015) – at baseline only, a standardised interview to establish whether the participant meets research diagnostic criteria for lifetime bipolar I or II disorder, cyclothymic disorder, other specified bipolar disorder, current depressive episode and current manic episode in order to assess whether they meet inclusion / exclusion criteria. The Hamilton Depression Rating Scale (HAM-D: Hamilton, 1960) will be used with participants who meet criteria for a current depressive episode to establish severity (those scoring in the severe range of >=24 will not be eligible). The International Classification of Diseases, 11th revision (ICD-11) will be used to determine presence or absence of current substance dependence. This is because DSM-V does not distinguish between substance abuse versus dependence (discriminating on the

basis of severity instead), yet the former distinction is the most relevant to the patient group targeted by this intervention.

- Brief Quality of Life in Bipolar Disorder (QoLBD) – a 12 item self-report measure of disorder-specific quality of life
- General Anxiety Disorder Assessment – 7 (GAD-7) – a 7 item self-report measure of anxiety symptoms
- Bipolar Recovery Questionnaire (BRQ) – a 36 item self report measure of sense of personal recovery

Additional Measures

Post therapy, participants will complete a feedback questionnaire post-therapy within which they will be asked to rate their satisfaction with the therapy, how acceptable it was and the likelihood they would recommend it to a friend, and their overall satisfaction with the research element of the therapy, and also to give written comment on their answers to each questions and any general comments on the therapy or research. After the booster session phase they will be invited to complete a brief feedback form about their views on these.

In addition participants will be invited to report on their current mood and activity 5 times per day for 14 days via a purpose-built web application (momentary assessment block). These momentary assessment blocks will take place on two occasions: during the first 14 days of the baseline phase, and during the first 14 days of the post-therapy phase. This allows calculation of mood instability based on real-time mood ratings rather than self-report

To evaluate if the treatment results in no significant adverse reaction for participants an ‘Asking about adverse events’ form will be completed at baseline (because participants will have had contact with the study team prior to this point), pre-therapy and at the qualitative interview by the researcher, and at each therapy session by therapists. This includes questions about medical treatment and deliberate self-harm since the last research assessment or therapy session. This information will be recorded to quantify harms in the study and will also be shared with the CI in order to detect and respond to serious adverse events as per standard operating procedures.

Qualitative interview

Post treatment therapists and clients will undergo an audio-recorded qualitative interview of approximately 60 minutes with one of our research team exploring their experiences of the therapy. This will allow participants to describe their views in detail. The exact wording and focus of the interview will be determined with input from our PPI consultants, however it is likely to ask about how participants found the therapy, any perceived effects of the therapy, aspects that were helpful / unhelpful, and views on the length and delivery format of the treatment and the feasibility/acceptability of both the intervention and the outcome measurement. It will also ask about experienced process of change, including questions on hypothesised mechanisms but also leaving space for these to arise inductively from participant reports. The interviews will follow a topic guide, but with flexibility to adapt

this based on the answers given. This enables us to explore the meaning of participants' responses and to elicit more detail on themes which arise during the interview.

5.2.2 Procedure

Following initial contact with the research team, and having been sent the Participant Information Sheet (e-mail or post), participants will attend an intake assessment interview lasting approximately 90 minutes. In this interview the study will be discussed and any questions the participant has will be addressed. Those giving written informed consent to take part will then be asked to complete the demographic information form, will complete the mood disorders, psychosis screening and substance dependence sections of the SCID-5, the PHQ-9 and the depression-elation scale of the ALS, and will be asked additional questions to establish whether the inclusion and exclusion criteria are met. Participants eligible and willing to continue will complete the GAD7, ASRM, QoLBD, remaining ALS items and BRQ.

Where possible the intake assessment will be conducted face to face (either at the research site or at the participant's home, or another mutually agreed confidential space) however if participants have a strong preference for the assessment to be conducted remotely this will be accommodated. Written consent will be obtained prior to the meeting via post following a brief telephone or online conversation with the researcher to allow the participant to ask questions about the study and have it explained to them. The intake assessment will not be conducted unless written informed consent has been given. Self-report measures at intake will be completed on online (using a bespoke data collection platform), or using pen and paper if participants would prefer not to complete them online.

Participants will then be randomised by a researcher independent of the study to one of three wait periods (3, 4, or 5 weeks) and will complete the first momentary assessment block. Starting one week after the baseline assessment participants will complete weekly symptom measures (PHQ-9, ASRM and ALS depression-elation questions) over the baseline period, therapy period and for 3 weeks post therapy. These will be completed online where possible or posted in a batch at the start of the wait period if participants decline online measures. Reminders to complete the measures are built in to the data collection system and participants will be made aware of this. They will also agree with the researchers how the team should attempt to reach out to them if they do not complete measures, including the option to nominate a friend or family member as a point of contact.

Within one week of the initial assessment participants will be contacted by the researcher to check on their wellbeing, and also to check if they have any questions about measure completion and to inform them of the wait length until therapy starts.

After reaching the end of their allocated wait period, participants will complete the GAD7, ASRM, BQoLBD, additional ALS items and BRQ. At this point they will speak with the researcher to check that they are satisfied with the arrangements for commencing therapy. Therapy will then commence on an approximately weekly basis. At the end of therapy participants will complete three weeks of post-therapy monitoring during which time they will continue to complete the weekly measures and

will be invited to take part in a semi-structured, audio-recorded interview about their experiences of the study and the therapy. They will also complete the second momentary assessment block. At seven months after their pre-therapy assessment they will be invited to complete the battery of measures used at baseline and pre-treatment for a final time.

After attending any “booster” sessions (if they choose to do so) participants will be asked to complete a brief feedback questionnaire about this aspect of the therapy.

Individuals who choose not to continue with the therapy will be assumed to be continuing with the research aspect of the study. If participants opt to discontinue the research element of the study they will not be contacted further by the research team, other than to be sent a brief survey to ascertain their reasons for not taking part if they initially gave their consent for this. If the participant has commenced therapy, for ethical reasons they will be able to continue with the treatment if they opt to.

The end of the study will be defined as the final piece of available data being collected from the final participant.

See Appendix 11.3 for a diagram of the procedure from the point of view of the participant.

5.2.3 Randomisation and blinding

Participants will be randomised to different baseline assessment lengths (between 3 and 5 weeks). The randomisation sequence will be generated and administered by an individual independent of the study on a 1:1:1 allocation sequence (block randomisation) stratified by cohort.

It is not possible to blind the assessor to phase or baseline duration of participants in the case-series, as the length of time between assessments will reveal this. Nevertheless, the assessor and clients will be asked not to disclose which therapist is treating them. Use of self-report measures as the primary outcome measure is intended to minimise potential biases on the side of the researcher.

5.3 Data Analysis

Because of the intention to rapidly proceed to a feasibility trial if the therapy protocol appears promising, we will assess the data against the minimum thresholds for progression after those in cohort one have each attended at least eight therapy sessions (or have discontinued therapy, if before session 8). If the progression thresholds are met we will apply for approval for a feasibility trial at this point. The trial preparation and approval process will take around six months; over this period learning from the remainder of the case series will continue to inform the therapy protocol. The progression rules are in place simply to ensure we do not progress with a therapy that is likely to be unsafe or unacceptable and this cannot be rectified in time prior to the trial commencing. If the progression thresholds are not met at the end of cohort one we will alter the research and therapy protocols as required (with support from the PPI panel and TSC) and progress with cohort 2. The rules will be re-examined in relation to cohort 2 (in relation to whether to proceed to a feasibility trial) once all six participants have attended at least 8 sessions or discontinued therapy.

In relation to aim (i) which concerns safety, feasibility and acceptability, we will report descriptively the number of adverse events, serious adverse events and the number of each judged to be related to the therapy, and rates of reliable deterioration. We will also report the number of participants expressing an interest in the study, giving consent, found to be eligible, commencing treatment and completing treatment (defined as attending at least 8 sessions including therapy assessment sessions), as well and the median, mode and range of sessions attended during treatment. We will report descriptively the average and distribution of scores on the therapy feedback items.

Aim (ii) investigates the potential for clinical efficacy. Analytical approaches to examining clinical outcome data in a case series can include visual and statistical methods, and focus on change at the level of the individual participants, or aggregated across the sample. In this population the extent to which a stable baseline can be expected is not clear, therefore we will use visual methods combined with descriptive statistics (Lane & Gast, 2013) to allow examination of overall patterns of change. Assessment of patterns will be made by two independent raters and will include calculation of overlap between weekly scores in the baseline, therapy and post-therapy periods (Tarlow, 2017).

In terms of statistical analyses, reliable change index scores (RC) will be calculated to assess for the statistical reliability of the changes on the clinical outcome variables between each phase of the case-series for each participant. A participant is said to show reliable change when their change score from pre to post therapy is more than 1.96x the standard error of the difference, the latter being calculated with respect to the sample as a whole (Ferguson, Robinson, & Splaine, 2002). RC scores greater than the z-score level of 1.96 are statistically significant at p>.05. We will report the proportion of participants showing: i) reliable improvement /no change / reliable deterioration in the clinical outcome measures; ii) improvement that is both reliable and clinically significant, using Jacobson and colleagues (1984) criteria a, b or c to define clinically significant change depending upon the information available in the literature for each measure.

Using continuous scores on the outcome measures, effect sizes and 95% confidence intervals will be computed to obtain a preliminary estimate of the potential magnitude of change on each measure from baseline to post therapy and pre to post therapy: these statistics can be used by other researchers in future meta-analyses seeking to synthesise the outcomes of a number of studies (Manolov et al., 2022).

Relevant to aim (iv) which is to develop an initial therapy competence and adherence measure, using the version of the measure developed during the case series two therapists will independently assess the same 12 recordings of therapy sessions to estimate inter-rater agreement on the measure.

Additional Analyses

Relevant to aim (i), qualitative interviews will be audio-recorded and then transcribed. Participants' responses will be read closely and coded using a framework approach. Data relevant to each category will be compared and summarised and non-conforming cases examined closely in order to understand similarities and differences in perspective. Interview recordings will be transcribed by a

member of the study team, or a suitable individual working with the team who has signed a confidentiality agreement.

Relevant to aim (ii), data from the momentary assessment blocks will be used to examine change in mood variability from the baseline to post therapy phases, by calculating mean variability across each of the two blocks.

We will also look at change over time taking into account week-by-week scores. In statistical analyses of case-series data it is important to control for auto-correlation (sequential observations on the same participant over time are not independent from one another). Therefore, multilevel modelling approaches will be used that are able to take this into account. Efforts will be made to minimise missing data; where this occurs maximum likelihood estimation methods will be used to replace the data.

It is noted that the optimal method for examining time series data will depend in part upon the features of the data including the number of observations actually obtained per participant and whether or not the statistical model applied converges (Manalov & Moeyart, 2017). Alternative methods may need to be used, dependent on data structure.

6. STUDY SETTING

This study will take place at the AccEPT Clinic, an NHS service that runs through the Mood Disorders Centre at the University of Exeter, Devon U.K. Devon Partnership NHS Trust will act as a second study site, as the study is being run in partnership with the Trust. The setting is appropriate as it is a research clinic that spans primary and secondary care psychological therapies, and the therapy in question is aimed at patients who may be in primary or secondary care, or between the two.

7. SAMPLE AND RECRUITMENT

7.1 Eligibility Criteria

Participants aged 18 or over and currently experiencing interepisode symptoms (within the context of Bipolar I or II Disorder, other specified bipolar disorder or cyclothymic disorder) as the primary presenting problem will be recruited into the study.

7.1.1 Inclusion criteria

Participants will be adults in the catchment area of the study site(s) who i) meet research diagnostic criteria for Bipolar I or II Disorder, Other Specified Bipolar Disorder or Cyclothymic Disorder; ii) do not meet criteria for a manic or severe depressive episode; iii) have IEBS, defined as at least mild depressive symptoms (Patient Health Questionnaire [PHQ9] >=5) or above-average bipolar mood instability defined as >=1.3 on the brief Affective Lability Scale (ALS) depression-elation scale (Aas et al., 2015); iv) are willing to engage in psychological work addressing IEBS or its impact on

functioning; v) have sufficient English to complete research questionnaires without translation; vi) have completed the intake measures.

7.1.2 Exclusion criteria

Exclusion criteria include: i) substance dependence according to ICD-11 diagnostic criteria; ii) frequent and serious self-harm that cannot be safely managed in a community outpatient setting; iii) currently engaged in psychological therapy for bipolar disorder.

7.2 Sampling

7.2.1 Size of sample

It is good practice to have at least 3 replications of the pattern of change across different cases (inter-case replication) as well as more than one therapist treating patients. Patients are treated in two cohorts within the current study: a total of 12 participants, 6 in each cohort, would allow these criteria to be met within each cohort.

Participants who do exit the study before completing the pre-therapy measures will be replaced to give N=12 commencing the therapy period.

7.2.2 Sampling technique

To reflect the likely composition of the client group who would receive this intervention in the future within health services, participants will be recruited from both primary and secondary health services. To increase the likelihood that the study recruits to target we will also recruit via advertisement / self-referral. In terms of ethnicity the population in the study sites (in the South West of England) is predominantly white (95%) and white British (91.8%). To enhance the diversity of our sample in terms of ethnicity as well as other characteristics we will pro-actively target recruitment via self-referral towards groups that are typically under-represented in research of this nature. This will be done with the support of our PPI panel and will involve working with local organisations who can promote the study to underserved populations.

7.3.1. Recruitment and sampling identification

Participants for the case series will be identified from local NHS services including primary care psychological therapies services, GP practices, secondary care mental health teams, early intervention services and secondary care psychological therapies services. They will also be recruited from the AccEPT service, the NHS service hosting the study. GP practices will contact potentially eligible patients by letter inviting them to contact the study team if interested. Mental health NHS Trust and AccEPT Service staff will contact potentially eligible patients by phone, email or letter (as appropriate for that particular patient) letting them know about the study; potentially eligible patients will also be informed of the study during routine appointments with clinicians. The University of Exeter Wellbeing Service will also be invited to publicise the study to potentially eligible service users.

Potential participants who are interested in the study will be given the choice of contacting the researchers directly by telephone, email or post, or giving consent for their name and contact details to be passed to the researchers so that s/he can be contacted by us directly.

Advertisements for the study will be placed in healthcare settings, public places and distributed through traditional and social media, and third sector organisations.

Individuals who have been in contact with our research centre expressing an interest in taking part in research of this nature will be informed of the study where appropriate.

Initial contact: A member of the research team will first discuss the study with interested participants by telephone or online video call, and – if not completed already – send them a form gaining their consent for contact and an initial telephone screening call, as well as the Participant Information Sheet and Consent Form. After consent to the screening call is received the researcher will arrange a time to complete this with the participant. In the screening call the researcher will go through the inclusion and exclusion criteria with the participant, to give an indication of the likelihood that the participant will be eligible. Very sensitive lines of enquiry, and points where subtle distinctions must be made, will be left until the face to face baseline interview (this can be conducted via online video call if the participant would prefer). Those likely to be eligible and willing to continue will be invited to the baseline appointment. Those not interested or not likely to be eligible will have the reason for this explained and will be signposted to relevant support, or permission sought to re-contact them if their eligibility is likely to change within the recruitment period of the study.

Intake assessment appointment/interview: At the appointment the researchers will go through the Participant Information Sheet, give the participant an opportunity to raise questions, and then take written consent if the participant wishes to proceed (online consent will be taken via the Qualtrics platform if the patient has opted for an online meeting). If the potential participant is eligible to partake in the study, is fully informed and has consented to participate, then they will be entered into the study.

Participants will receive the Participant Information Sheet at least several days (>48 hours) before the appointment in which consent is taken, and usually considerably earlier than this.

Participants receive an honorarium payment of £20 for each of the baseline assessment, the pre-therapy assessment and the post-therapy assessment. This includes completion of the momentary assessment blocks.

7.3.2 Consent

At the initial contact with the research team, a member of the research team will first discuss the study with interested participants by telephone, and – if not completed already – send them a form gaining their consent for contact and an initial telephone screening call, as well as the Participant Information Sheet and Consent Form. After consent to the screening call is received the researcher will arrange a time to complete this with the participant. In the screening call the researcher will go through the

inclusion and exclusion criteria with the participant, to give an indication of the likelihood that the participant will be eligible. Those likely to be eligible and willing to continue will be invited to a face to face appointment. Those not interested or not likely to be eligible will have the reason for this explained and will be signposted to relevant support, or permission sought to re-contact them if their eligibility is likely to change within the recruitment period of the study.

At the intake assessment appointment the researcher will discuss the study information sheet and full consent form with the patient, and give them the opportunity to ask any questions. Because participants will have been given the information sheet after initial contact with the research team (or earlier, by their clinician), they will have had a number of days to consider their participation.

If at this appointment the patient wishes to consent to participation, at that point the researcher will take consent and then proceed to the research assessment; if the patient does not wish to participate their involvement will finish at this point. If the patient wishes to take more time to consider the study, the research assessment appointment will be rescheduled to allow sufficient time for them to consider their participation. Participants judged not to have capacity due to severe symptom levels will be reassessed at a later point convenient to them and directed to sources of support in the meantime.

Therapists will be invited to take part in an interview following the end of their involvement in the intervention phase. They will be given a therapist information sheet and consent form. They will have the opportunity to ask questions at that point and at any point afterwards, and will have until the end of the study period to decide whether or not to take part.

The content of the participant information sheet and consent form will also be available to potential participants as a video or audio recording.

8. ETHICAL REGULATORY CONSIDERATIONS

The study will be carried out in accordance with the Declaration of Helsinki (Fortaleza, Brazil, October 2013), the UK Policy Framework for Health and Social Care Research (2020) and the general principles of Good Clinical Practice E6 (R2).

Before the start of the study, approval will be sought from a UK Health Department NHS REC for the study protocol, participant facing documents, consent forms and other relevant documents and an assessment of governance and legal compliance via the Health Research Authority's online IRAS portal. When HRA Approval is in place local site level approval will be sought via Capacity and Capability processes, before the study commences.

Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the study. All correspondence with the REC will be retained in the Trial Master File/Investigator Site File. The Investigator will produce an annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended. The Investigator will notify the REC of the end

of the study. Within one year of study completion, the Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

All of the above will also be notified promptly to the Sponsor.

Discontinuation

Discontinuation criteria for individual participants:

1. Participant does not wish to continue with the intervention and study.

2. The participant experiences a serious adverse reaction (mental or physical health event that results in significant impairment, hospitalisation or death) that is judged to be the direct result of the intervention or trial participation.

3. Participant and / or therapy / research team believe that the intervention or trial participation will result in, or is likely to result in, a serious adverse reaction if continued.

4. The participant does not attend more than three consecutive therapy sessions without explanation (sometimes referred to as “DNA”): this will be judged to indicate discontinuation of therapy.

Discontinuation of the trial:

1. Should an unexpected serious adverse reaction occur to either the therapy or the trial procedures, and this is judged to be directly related to trial participation or to the therapy, the trial will be temporarily halted pending investigation and analysis of the extent to which future risk can be mitigated against. If it is judged that this is not possible, the trial will be discontinued. This process will be led by the sponsor in collaboration with the TSC chair and CI.

2. Should information come to light that indicates that the therapy intervention or trial procedures are unsafe, the process outlined in (1) above will be followed.

Ethical issues arising from the intervention

The administration of a novel therapeutic intervention raises the potential of risk to those in the trial. Nevertheless we believe that these risks are minimal: the approach is an adaptation of two widely used existing therapies (Behavioural Activation and Dialectical Behavioural Therapy), both of which have been delivered previously in our service to people with bipolar disorder in case series / trial contexts with no significant concerns about therapy safety resulting (Wright et al., 2021; Wright et al., submitted).

Potential ethical issues arising from delivery of the treatment will be approached as is standard within the clinical service hosting the research. Risk to / from self or others, if detected, will be responded to

in accordance with established protocols. The therapy protocol will directly address strategies for monitoring and responding to escalations in manic symptoms.

All information provided by participants as part of their treatment will be treated in confidence and will be available only to members of the research team, other than where it is necessary to share information with other professionals as per standard practice. Participants will be informed of the circumstances under which confidentiality may be broken and will be consulted with as far as possible if this should become necessary. Treatment sessions will be audio recorded (where participants consent to this). Recordings will not be played to anyone outside of the research team unless the participant agrees they can be used for training purposes. If they wish (as is standard in our service) participants can opt to be contacted about future research conducted through the research centre.

Use of randomisation

In this study, participants are randomised to various durations of wait prior to commencing therapy. These range from 3-5 weeks. This is necessary in order to permit a multiple baseline design where, in accordance with case study methodology recommendations, outcomes are measured at least three times during the baseline phase, and participants can be randomised to one of at least six start points. An enforced delay before the onset of treatment is an ethical issue, however there is a clear scientific rationale for this and patients will be informed of this feature of the trial. In fact, a wait of up to 5 weeks is typical of wait times in primary care psychological therapies services; in our experience, for individuals with Bipolar Disorder in our area (who are rarely eligible for these services) the wait for psychological therapy in secondary care is typically a minimum of several months. Therefore what is being offered reflects what is currently available in routine care, in terms of time from assessment to intervention.

Participants will be informed of the nature and purpose of the randomisation element (to minimise bias in the allocation of participants to the different wait times).

During the baseline phase the research team will follow established protocols in our centre should any patients report significant risk to self in their completion of weekly measures.

Whilst participants currently receiving psychological therapy for depression or bipolar disorder will not be eligible to join the study, no restrictions are placed on the treatments that participants can choose to access outside of the study whilst they are a part of it.

Informed consent

At the initial contact with the research team, the study will be discussed and patients asked whether they wish to move to the next stage (receiving the full information sheet and arranging the intake assessment meeting). If the patient indicates at this point – or later - that they do not wish to take part they will not be contacted further by the research team.

At the intake assessment appointment the researcher will discuss the study information sheet and full consent form with the patient, and give them the opportunity to ask any questions. Because

participants will have been given the information sheet after initial contact with the research team (or earlier, by their clinician), they will have had a number of days to consider their participation.

If at the baseline assessment the patient wishes to consent to participation, at that point the researcher will take consent and then proceed to the research assessment; if the patient does not wish to participate their involvement will finish at this point. If the patient wishes to take more time to consider the study, the research assessment appointment will be rescheduled to allow sufficient time for them to consider their participation. Participants judged not to have capacity due to severe symptom levels will be reassessed at a later point convenient to them and directed to sources of support in the meantime, or if necessary, safeguarding procedures followed.

Therapists will be invited to take part in an interview following the end of their involvement in the intervention phase. They will be given a therapist information sheet and consent form. They will have the opportunity to ask questions at that point and at any point afterwards, and will have until the end of the study period to decide whether or not to take part.

Participant and researcher risk

Inherent in the nature of the population under scrutiny is the risk of suicide and/or self-harm. We will follow good clinical practice in monitoring for suicide risk during all research assessments with participants. Risk to/from self or others, if detected, will be responded to in accordance with the established research protocols in place at the Mood Disorders Centre, University of Exeter. Participants will be informed of any circumstances under which confidentiality may be broken.

Research assessments and therapy sessions may take place outside of University / NHS premises. Where this is the case, lone working protocols will be followed. If workers see participants outside of usual working hours the lone working protocol will be followed.

Completing Measures

There is a chance that completion of study measures may induce low mood. Our experience of using similar methods in routine clinical practice in the AccEPT service and in previous research projects is that a significant adverse reaction is rare and if it occurs it is transient. The information sheet will make clear to participants that filling in the measures may temporarily lower mood. The therapist/researcher will ask participants if they suffer any adverse reaction completing measures and will follow service or research distress management protocols if a significant level of distress is observed. Participants will be contacted within a week of completing the initial assessment to check on their welfare.

The burden on participants of completing multiple measures is also a potential ethical issue. This has been taken into account in the design of this study, with the number of questionnaires kept to a level that balances participant burden against the need to collect information on key variables.

Weekly measures will be available to be completed online or on paper (according to participant preference), as will the intake, pre-treatment and post-treatment measure sets, so as to minimise inconvenience caused.

Subject withdrawal (including data collection / retention for withdrawn participants)
Participants will be informed in the study information sheet that they may opt to withdraw from the study at any point, without giving a reason and without affecting their standard clinical care or access to future research. If participants withdraw from both the therapy and the research element of the study, no further data will be collected from them (other than inviting them to give their views on the therapy via the feedback form or semi-structured interview). All data collected up until that point will be retained. If participants withdraw from the therapy, they will remain in the study unless they indicate that they also wish to withdraw from the study, and vice versa. Participants taking part in the semi-structured interviews about their experiences of the study will be given a 14 day period after the interview during which they can opt to withdraw their data if they wish.

The study will be conducted in compliance with the principles of the Declaration of Helsinki, the principles of Good Clinical Practice (GCP) and in accordance with all applicable regulatory requirements.

Adverse Events

All serious adverse events that are study or treatment related will be recorded and immediately reported to the Chief Investigator and trial sponsor. If these are also classed as unexpected they will be reported to the ethics committee. We will also, in line with other complex intervention studies, monitor non-serious adverse events, serious adverse events that are not study or treatment related, clinically significant deterioration and active withdrawals from treatment. Definitions of these will be given in the standard operating procedures for the study. Symptoms of Bipolar Disorder themselves are not defined as adverse events. The reporting period for all events and reactions will be from baseline assessment to the end of the post treatment assessment phase, or qualitative interview of this occurs later. Data on any adverse events will be collected by a member of the research team at baseline and pre-treatment assessment points and at the qualitative interview, and also by therapists at each therapy session, or at any other point that the participant reports potential adverse events.

8.1 Assessment and management of risk

The researchers will follow established protocols used within the Mood Disorders Centre, University of Exeter when responding to indications of risk to self or others, or other safeguarding concerns that arise in the conduct of the study. Researchers will be trained in these protocols prior to having contact with participants.

Therapists will follow the established protocols used within the AccEPT service for the assessment and management of risk and safeguarding concerns. All therapists will have received appropriate training in risk management and safeguarding prior to commencing contact with patients.

8.2 HRA and other regulatory review & reports

Before the start of the study, HRA approval including ethical approval will be sought for the study protocol, informed consent forms and other relevant documents e.g. advertisements.

All correspondence with the REC will be retained.

It is the Chief Investigator's responsibility to produce the annual reports as required.

The Chief Investigator will notify the REC of the end of the study.

If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination.

Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

Regulatory Review & Compliance

Before any site can enrol patients into the study, the Chief Investigator or designee will ensure that appropriate approvals from participating organisations are in place.

For any amendment to the study, the Chief Investigator or designee, in agreement with the sponsor will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or designee will work with sites (R&D departments at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as amended.

Amendments

If the sponsor wishes to make a substantial amendment to the REC application or the supporting documents, they will submit a valid notice of amendment to HRA for consideration.

Amendments will also be communicated to the participating organisations (R&D office and local research team) departments of participating sites to assess whether the amendment affects the NHS permission for that site.

The CI in conjunction with the sponsor will be responsible for the decision to amend the protocol and for deciding whether an amendment is substantial or non-substantial. Substantive changes will be communicated to relevant stakeholders according to their protocols.

Amendment history will be tracked by the version numbers used, with previous versions being archived, in order to identify the most recent protocol.

8.3 Peer review

The protocol has been reviewed by a research clinician with expertise in the development of psychological interventions, and independent of the project team, as well as by five academic collaborators. In addition the plan for this study formed part of a successful NIHR Fellowship application that was peer-reviewed by the funding panel and three external expert reviewers.

8.4 Patient & Public Involvement

Throughout this study we are working with a patient and public involvement panel (PPI panel) of 8 individuals with personal experience of bipolar disorder, or who have a relative with bipolar disorder. The panel are contributing towards the design of the therapy protocol and the materials for patients such as the information sheet, consent form and interview topic guide; a subgroup contributed to the initial design of the study itself. The panel will advise on the running of this study throughout.

8.5 Protocol compliance

Accidental protocol deviations can happen at any time. They must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately.

Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

8.6 Data protection and patient confidentiality

Data Security

Information will be stored according to standard practice within the NHS service hosting the intervention, the AccEPT service. Hard copies of information / measures gathered as part of this research study will be anonymised and stored in a locked filing cabinet in a locked office in the Department of Psychology, University of Exeter or in a locked cabinet in a locked office on Devon Partnership Trust premises (Research and Development Team base). Participants will be identified by a code, with the document linking participant name with ID code being stored separately to the rest of the data, and accessible only to measures of the research team. Consent forms will be stored in a locked cabinet separately to data. Audio recordings will be recorded directly to, or immediately transferred in digital form to, a secure data storage area hosted by the University of Exeter. Personal data will be transferred and stored only where necessary.

Study data will be stored in linked-anonymous form. General Data Protection Regulation (2018) will be followed, and the NHS services providing therapy will abide by the Information Governance requirements of their service. Within NHS services providing the therapy, participant information will not be stored anonymously as it will form part of the patient record.

At the end of the study any anonymised paper data will be scanned into electronic form or entered into electronic databases (if not already done) and stored securely in the secure data storage area of the University of Exeter and the original paper copies and audio-recordings destroyed confidentially. The project CI will act as custodian for the data. If the CI leaves employment of the University of Exeter, a data custodian will be appointed by the University of Exeter (a member of the research group or of Exeter IT Services) who will manage continued archiving of the data. Anonymised data will be retained for 20 years. Personally identifiable information will be stored for 12 months after the end of the study.

Clinical data gathered as part of the individual's treatment within the AccEPT service will be stored according to local protocols on the retention of NHS clinical records.

Because of the potentially sensitive nature of the data and the potential for participants to be identifiable by their data by some members of the public, the public will not be given unrestricted access to the data.

In accordance with good practice and institutional policy the research database will be registered with the University of Exeter public access database. The dataset will be anonymous and will be registered with a metadata only record, allowing the research team to control access to the dataset, restricting it to appropriately qualified third parties with appropriate ethical approvals and data sharing agreements in place.

Some of the data collected as part of the research will be shared with therapists providing therapy, in order to eliminate repetitious assessment for the participants allocated to the treatment arm. This includes baseline assessment information about current and past mood, and any risk information. Likewise, adverse events / risk events, therapy recordings, session attendance and weekly measure scores collected during the treatment will be shared with the research team and will constitute research data. Participants will be informed that this will be the case in the Participant Information Sheet.

As part of the informed consent process, participants will be informed that anonymised data from the study may be shared with suitably qualified individuals for the conduct of further analyses.

8.7 Indemnity

The sponsor, University of Exeter, will provide indemnity to meet the potential legal liability for harm to participants arising from the management, design or conduct of the research.

The sponsor has not made arrangements for payment of compensation in the event of harm to the research participants where no legal liability arises.

8.8 Access to the final study dataset

The study team members will have access to the final dataset, with the agreement of the CI.

Consent will be sought from participants to share anonymised data with other researchers for secondary analyses. Because of the potentially sensitive nature of the data and the potential for participants to be identifiable by their data by some members of the public, the public will not be given unrestricted access to the data. In accordance with good practice and institutional policy the research database will be registered with the University of Exeter public access database. The dataset will be anonymous and will be registered with a metadata only record, allowing the research team to control access to the dataset, restricting it to appropriately qualified third parties.

9. DISSEMINATION POLICY

9.1 Dissemination policy

The data arising from the study will be the property of the University of Exeter and the Chief Investigator. On completion of the study, the data will be analysed and tabulated and a Final Study Report prepared. The full study report will be made available in open access form via the University of Exeter and publication via a peer reviewed journal will be sought, acknowledging contributions to the study in line with journal policy. Participants will be asked to state whether they wish to receive a copy of the findings which they will be sent once these have been finalised. In order to protect participant anonymity in this small number study, the raw data will not be made publicly accessible.

9.2 Authorship eligibility guidelines and any intended use of professional writers

Proposal for publications

To ensure all activity is captured and there is no overlap we need to monitor it, all proposals for papers based on data need to be submitted for agreement by co-applicants and CI. Proposals will comprise a brief rationale indicating both hypotheses and data required. The final decision will rest with the CI.

Authorship

In general, the following guidelines will be used to guide decisions about authorship:

http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html.

However, this may need to vary depending on specific criteria for authorship of individual journals.

Co-applicants will all be invited to be authors on all publications based on their various roles in trial development, delivery and supervision. Additional authorship invitations will be based on the particular output and based on the ICMJE principles above.

Each invited individual decides for themselves if they meet authorship criteria as set out in ICMJE criteria above. If they feel they do, then they should summarise in an email to the lead author what they believe their contribution has been and ensure they approve the final draft before submission.

To ensure timely publication of outputs, papers should be drafted within six months of the data becoming available to the proposed lead author. If this is not possible, then alternative lead authors should be considered. Authorship order will be proposed by the lead author but final decisions will require the agreement of co-applicants and CI.

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11. APPENDICES

11.1 Appendix 1 – Schedule of Procedures

Table 1: Summary of when each measure or survey will be administered

Measure	Approximate time to complete	Weekly*	Intake, pre-treatment, immediately post treatment, 7 month follow up, after end of "booster" phase
PHQ-9	2 minutes	X	Intake, pre-treatment, 7 month follow up
ASRM	2 minutes	X	Intake, pre-treatment, 7 month follow up
Depression-elation subscale of ALS short form	1 minute	X	
Asking about adverse events	2 minutes	X during therapy period	Intake, pre-treatment, immediately post treatment
Demographic information	2 minutes		Intake
ALS short form	2 minutes		Intake, pre-treatment, 7 month follow up
SCID-V sections on bipolar, substance use disorder and psychosis screener	40 minutes		Intake
HAM-D depression interview	10 minutes		At intake if required (to establish depression severity in participants meeting criteria for current depressive episode on SCID-V)
Brief QoL.BD	2 minutes		Intake, pre-treatment, 7 month follow up
BRQ	4 minutes		Intake, pre-treatment, 7 month follow up
GAD-7	2 minutes		Intake, pre-treatment, 7 month follow up
Momentary assessment block	2 minutes per assessment; 3 assessments per day for 14 days		Intake, immediately post treatment
Post therapy feedback questionnaire	5 minutes		Immediately post treatment, after end of booster phase
Post therapy interview	30 minutes		Immediately post treatment

*Weekly measures continue until the end of the post-treatment monitoring block

11.2 Appendix 2 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1	1.2	27.4.23	Kim Wright	Change to progression rules to proceed to feasibility trial.

11.3 Appendix 3 – Flow chart of study procedure from the point of view of the participant