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Improving functional outcomes in early stage bipolar disorder: The protocol for the REsearch into COgnitive and behavioural VERsatility (RECOVER) trial

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Abstract

Aim: Young people with bipolar disorder (BD) commonly experience reduced quality of life, persistent symptoms, and impaired functional recovery despite often superior school performance. Compromised long-term functioning can ensue. There is evidence that psychological therapies alongside pharmacology may be more efficacious earlier in the course of the disorder. Intervention in the early stages may thus reduce the burden and risk associated with BD, and mitigate the impact of the disorder on normal developmental trajectories. To date, however, the availability of evidence-based psychological therapies for young people with early BD is limited. Furthermore, there are no large scale randomised controlled trials of such interventions.

Methods: The study is a prospective, single-blind, randomised controlled trial (RCT) examining the effectiveness of an adjunctive individualised and manualised psychological intervention, compared with treatment as usual (TAU) within youth-specific early intervention services. The REsearch into COgnitive and behavioural VERsatility (RECOVER) intervention is delivered over a 6-month period. 122 young people in the early stages of BD-I (at least one manic episode in the previous 2 years, with no more than five lifetime treated/untreated manic or hypomanic episodes) will be recruited. The assessments will occur at baseline, 3-, 6- (primary endpoint, end of treatment), 9-, 12-, 15-, and 18-months.

Results: Recruitment will commence in January 2019 and is anticipated to occur over a 3.5-year period.

Conclusions: To date, there are no evidence-based psychological therapies tailored to young people with early BD. We will test whether early psychological intervention in the course of BD can reduce the symptomatic, psychological, vocational, and social impacts that are seen in entrenched disorder.

1. Introduction

Bipolar disorder (BD) is the fourth leading cause of disability worldwide for 10- to 24-year-olds due to marked economic, social, familial, and individual burden (Gore et al., 2011). First-line treatment for BD is pharmacotherapy with mood stabilisers such as lithium (Bauer & Mitchner, 2004), and other medications including antipsychotics, antidepressants, and anti-epileptics (Miziou et al., 2015). As an index of the lack of optimal utility of these agents, extensive polypharmacy is normative (Sachs, Peters, Sylvia, & Grunze, 2014). Outcomes remain less than ideal (Sachs et al., 2014), with medications not fully addressing patients' needs, particularly regarding functional recovery (Miziou et al., 2015). Medications are also less useful for depression than mania, with depression associated with the greatest burden (Judd et al., 2002). Furthermore, issues of tolerability and medication non-adherence increase risk of relapse and recurrence (Thase, 2012).

There is growing support for adjunctive psychological interventions for BD including cognitive behavioural therapy (CBT) (Murray, 2018; Reinares, Sánchez-Moreno, & Fountoulakis, 2014), psychoeducation (Reinares et al., 2014; Stafford & Colom, 2013), family focussed therapy (Miklowitz, 2016), interpersonal and social rhythm therapy (IPSRT) (Frank, Swartz, & Boland, 2007; Reinares et al., 2014), and intensive psychosocial interventions. Treatment guidelines in Australia and worldwide recommend the use of adjunctive psychological interventions in the management of people experiencing BD (Malhi et al., 2015; National Institute for Health and Care Excellence, 2014).

Much remains unknown about the optimal targeting and delivery of these interventions. Trials have differed in targeted populations, comparison groups, and duration and intensity of interventions (Reinares et al., 2014). Interventions, however, are mainly designed for chronic BD patients of middle-age (45+ years) (Vallarino et al., 2015). Consequently, it is difficult to ascertain the optimal timing for the delivery of psychological interventions, and which therapy works best (Reinares et al., 2014).

There is little work on psychological interventions for young people (15-24 years) in the early stages of BD (Macneil et al., 2012a; Vallarino et al., 2015). This is surprising given that psychological interventions – like pharmacotherapies - are potentially more effective early in the disorder (Berk et al., 2007; McMurrich et al., 2012; Miziou et al., 2015).

In a recent review (Vallarino et al., 2015), only five studies were identified with individuals with first episode mania; four were case series (Alvarez-Jimenez et al., 2013; Conus et al., 2010; Jones & Burrell-Hodgson, 2008; Searson, Mansell, Lowens, & Tai, 2012) and the other was our open-label matched controlled pilot study (Macneil et al., 2012a).

Two of the studies focused on the delivery of CBT in adult mental health services (Jones & Burrell-Hodgson, 2008; Searson et al., 2012). Jones and Burrell-Hodgson (2008) delivered 6 months of CBT to seven individuals (24-54 years, all BDI, length of time since diagnosis 3 months to 30 months) with the first episode BD-I. An inclusion criterion into the study was euthymia. The CBT was based on the work by Lam, Jones, Hayward, and Bright (1999). The therapy included psychoeducation surrounding the diathesis stress model, development of skills on how to monitor

moods and behaviours, how to recognise early warning signs of relapse, application of coping skills, and stabilisation of sleep and behaviour. Improvements were seen in moods and there was less sense of hopelessness. Self-control behaviours improved along with stabilisation of daily activities. Searson et al. (2012) also had seven patients (23-44 years, 2 BDI, 5 BDII, length of time since diagnosis 6 weeks to 8 years) who received 12 sessions of a CBT intervention called Think Effectively About Mood Swings (TEAM). At the end of therapy and at one month follow-up, there were significant improvements noticed across multiple domains including symptoms, functioning, cognitions and self-critical processes, with the largest effects seen for depressive symptoms (Searson et al., 2012). However, noticeably these two studies had small numbers of patients, some patients had only experienced hypomania (Searson et al., 2012), and others were required to be euthymic at commencement of the intervention (Jones & Burrell-Hodgson, 2008)). There were no control groups, and no random allocation, thus limiting the generalisability of their findings. Furthermore, because of the diverse age ranges of the study, there was a lack of consideration of developmental impacts of the disorder.

The remaining three studies described by Vallarino et al. (2015) were conducted in our specialist early intervention (SEI) services for psychotic disorders. Conus et al. (2010) examined the baseline and 12 months after symptom and functioning stabilisation of 87 individuals with first episode of psychotic mania. Patients had received 18 months of integrated, individualised case management in addition to a range of psychosocial and pharmacological interventions. This group were compared to young people experiencing first episode schizoaffective disorder (*n*=21), with those with BD having better outcomes at follow-up in terms of both negative symptoms and functioning. Alvarez-Jimenez et al. (2013) study was a pilot of a novel moderated online social therapy for individuals with first episode psychosis. Only two of 20 participants had an affective psychosis, so it is unclear why Vallarino et al. (2015) included the study in their review. The third study, was a case controlled study of psychotherapy delivered to individuals with first episode psychotic mania (15-25 years) and was embedded in a larger pharmacological trial (Macneil et al., 2012b). Twenty patients received 18 months of a manualised psychological intervention in addition to standard care in a SEI service and 20 patients received standard care. Those receiving the additional support had better outcomes at 18 months in terms of depressive symptoms and functioning.

There are other studies that have examined interventions in early onset BD, but are not necessary the incipient episode of mania. For example, Jones et al. (2015) conducted a pilot study of 18 hours of recovery-focused CBT delivered over a 6 month period for 67 patients aged 18-65 years with BD. The intervention was found to be feasible, promoted personal recovery, and delayed time to relapse. Inder et al. (2015) ran a RCT of 18-months of IPST compared to specialist support care for recent-onset BD (*n*=100, 15-36 years, 78.0% BDI, no information of duration since diagnosis). Both groups demonstrated significant improvements in depressive and manic symptoms, as well as social functioning; however, there were no significant differences found between groups on these outcomes.

Another group, have examined IPSRT specially designed for 12 adolescents (12-18 years) with BDI, BDII, or BD-NoS and who had an average of 5.2 episode lifetime (Hlastala, Kotler, McClellan, & McCauley, 2010). Eleven of the 12 patients participated in 16-18 sessions over 20 weeks. Significant improvements were seen across manic, depressive and general symptoms as well as global functioning over the 20 weeks. However, there were a number of limitations to the study including the small sample size, it was an open trial with even those conducting assessments not blind, and there was no control group. It is therefore difficult to ascertain whether the changes could be due to the intervention.

The studies that have been conducted to date for those with first episode mania, recent onset BD, or adolescents with BD, have had variable results. This is largely attributable to small and heterogeneous cohorts in terms of diagnoses and age-ranges, and the absence of appropriate controls. Not all interventions have been specifically designed for young people taking into consideration development considerations. This highlights the urgent need for work in this area.

Here we summarise the research protocol of the first randomised controlled trial (RCT) examining the effectiveness of a novel psychological intervention for young people 15-25 years in the early stages of BD-I, known as REsearch into COgnitive and behavioural VERsatility (RECOVER). RECOVER is adjunctive to treatment as usual (TAU) within specialised early intervention (SEI) services.

The primary hypothesis is that the RECOVER+TAU group will have significantly better outcomes on a global measure of functioning (the Global Assessment of Functioning, GAF) as compared to a TAU alone group at the 6-month (end of treatment) primary endpoint.

Three secondary hypotheses will be tested: (i) at 9-, 12-, 15-, and 18-months, the RECOVER+TAU group will maintain significantly better global functioning than the TAU group; (ii) at 3, 6-, 12-, and 18-months, the RECOVER+TAU group will have significantly better outcomes than the TAU group in terms of manic and depressive symptomatology; and (iii) at 3, 6-, 12-, and 18-months, the RECOVER+TAU group will have significantly better outcomes than the TAU group in terms of QoL.

2. Methods

2.1 Study Design

This is a prospective, single-blind, RCT examining the effectiveness of an individualised and manualised psychological intervention (RECOVER) compared to TAU within youth-specific SEI services. Participants will be diagnosed as having BD-I using the Diagnostic and Statistical Manual for Mental Disorders, (5th edition, DSM-5) criteria. The primary endpoint is at the end of treatment at 6-months; follow-up will occur at 3-, 6-, 9-, 12-, 15- and 18-months (see Figure 1). The study has been approved by the Melbourne Health Human Research and Ethics Committee (MH HREC 2017.146; HREC/17/MH/204_SSA/18/MH/57). The study sponsor is Orygen, The National Centre of Excellence

in Youth Mental Health. The study is registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12618001193268).

(Insert Figure 1 about here)

2.2 Settings

The study will be conducted across SEI sites in Victoria, Australia. The lead site is Orygen Youth Health (OYH), a youth mental health service. OYH is part of North West Mental Health and currently provides SEI services across multiple sites.

The second site is the Recovery and Prevention of Psychosis team (RAPPt). RAPPt sits within the Early in Life Mental Health Service at Monash Health, in Dandenong and provides SEI services across the south-eastern suburbs of Greater Melbourne. TAU at RAPPt is similar to that of OYH (Berk et al., 2017). This will allow meaningful inferences to be drawn about the effectiveness of RECOVER whilst having significant local differences to support generalisability should RECOVER prove effective as expected. Any minor differences noted in TAU across sites will be recorded. Site will be added as a variable within the statistical analysis models. Additional SEI sites within Victoria may be recruited, after determining whether their TAU is sufficiently similar to OYH and RAPPt.

2.3 Inclusion and exclusion criteria

The protocol is designed to be as broad and representative of usual care as possible. Male and female participants aged 15 to 25 years (inclusive) who meet the following inclusion criteria will be eligible to participate. *Diagnosis:* A Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM-5; 31) diagnosis of BD-I based on ratings on the Structured Clinical Interview for DSM-5 (SCID-5-RV; First, Williams, Karg, & Spitzer, 2015). *Early stage disorder*: Early stage BD-I is defined to include Stage 2 and the early phases of Stage 3 disorder (McGorry, Hickie, Yung, Pantelis, & Jackson, 2006). As outlined in previous treatment trials, operational criteria for early stage BD-I includes the first treatment seeking episode of mania with no more than five cumulative episodes in a person's lifetime. This may also include the first involuntary hospitalisation for the treatment of mania. This is necessary as clients in a SEI service frequently report prior undiagnosed manic and depressive episodes. This will be the first help-seeking presentation for mania; there are no criteria for prior depressive episodes. *Treatment duration:* recruitment will occur during the first 6 months of treatment at a SEI service. *Capacity:* Capacity to consent and comply with study procedures will be assessed by trained research assistants and by checking with potential participants' treating team prior to approaching them.

Exclusion criteria include: (i) inability to speak English without an interpreter; (ii) involvement in another psychological/pharmacotherapy study; (iii) presence of a developmental disability that would compromise understanding of cognitive and behavioural aspects of the intervention; (iv) a diagnosis of schizophrenia; and/or (v) manic symptoms related only to periods of peak drug intoxication.

Comorbidity (e.g., substance use disorders, anxiety disorders, personality disorder) is the norm is this cohort; and should not be excluded. This a pragmatic real world trial, which will ensure external validity and generalisability of the study.

2.4 Discontinuation and withdrawal

Discontinuation is when the study treatment is ceased but the participant continues to complete all other aspects as per the study schedule. Discontinuation can be guided by requests from the participant, investigator, or treating clinical team. Participants who discontinue will be asked about the reason(s) for discontinuation and the presence of any adverse events (AEs).

Withdrawal is when the participant ceases involvement in all aspects of the study. Consent can be withdrawn by the participant or carer if participant is aged under 18 years. A participant can also be withdrawn if a revised diagnosis during the first 6 months of participation indicates that the initial diagnosis was incorrect.

2.5 Intervention

RECOVER was developed by our multidisciplinary team in close collaboration with end-users. It targets symptoms and has a particular focus on obtaining improved functional outcomes and on identifying and modifying maladaptive schemas that can contribute to the disorder. It is developmentally appropriate and phase-specific (Macneil, Hasty, Conus, Berk, & Scott, 2009) and differs from existing psychological interventions for BD in key ways. Specifically, it has a strong focus on developmental and clinical staging issues that are critical when working with this population. Onset of BD typically occurs during the crucial developmental phase where young people are usually attempting to consolidate their identity, develop increased autonomy and separation from their parents, developing intimate and close peer relationships, setting and achieving educational and vocational goals, moving out of home, and gaining increased financial independence. RECOVER intervention takes this context and attainment of these milestones into account to minimise the potential negative effects of BD on a young person's developmental trajectory. The intervention includes phase-specific cognitive behavioural strategies should a young person experience a mood episode during the course of therapy. Engagement is also targeted, an issue that is not commonly addressed in existing treatments, where there can be an assumption of active help-seeking and insight, which often only occurs after multiple episodes (Macneil et al., 2009). Engagement strategies include paying particular attention to working collaboratively, respecting the young person's need for independence and control, conveying a sense of hope and optimism, taking time to understand them as a person, accurately reflecting their experiences and language, acknowledging strengths, and individual tailoring information and interventions to the young person's explanatory model, stage of recovery, and insight.

RECOVER is delivered over a 6-month period by psychologists who will have received formal training regarding the intervention. Treatment integrity (adherence, competency, and separation)

will be managed via regular supervision. A treatment fidelity checklist (MacCabe et al., 2010) will also be used by clinicians and case-managers to identify components of therapy delivered within each session.

The heterogeneity of young people with bipolar disorder demands an intervention that is adapted uniquely for each person. RECOVER comprises six core modules and four optional targeted modules that can be applied according to clinical need, and the young person's goals and formulation (see Figure 2).

(Insert Figure 2 about here)

The therapy is divided in four phases. The first phase (two sessions) covers the core modules of (i) assessment and engagement and (ii) cognitive behavioural formulation. These modules provide the basis for collaborative goal setting and development of a treatment plan. The second phase (eight sessions) focuses on delivery of the remaining core modules: (i) making sense of what has happened (psychoeducation); (ii) specific CBT interventions; (iii) social rhythm regulation; and (iv) wellness planning. Ideally, four of these sessions focus on CBT interventions including attending to underlying maladaptive schemas, and two sessions focus on social rhythm regulation. Selection of modules for the third phase (up to eight sessions) is guided by the young person's formulation and treatment goals and can include further focus on core modules and/or focus on any of the targeted modules which include: (i) relationship issues and family work; (ii) alcohol, substance use, and other co-morbid disorders; (iii) exploring medication; and (iv) functional recovery. The modules reflect available evidence supporting the use of CBT, social rhythm therapy, psychoeducation, and family work in BD. Therapy concludes with a termination session including discussion of a "goodbye letter".

Treatment sessions are typically of 50 minutes duration and include a typical CBT structure of: (i) brief initial discussion about how the person has been since the previous session, including review of mood, sleep, recent events, and any difficulties or stressors; (ii) young person's recall of the previous session; (iii) reviewing homework if any was assigned; (iv) collaborative agenda setting; (v) addressing agenda items and applying relevant module content; and (vi) brief review of the session and setting of homework tasks.

Those in the RECOVER+TAU group will receive between 10 and 18 sessions of RECOVER therapy over 6-months (weekly sessions until the minimum 10 sessions are reached, fortnightly sessions for the remaining). A review of the psychotherapy literature indicates that greater than 10 sessions but less than 18 are needed for alleviation of psychiatric symptoms (Hansen, Lambert, & Forman, 2002). It is less clear as to the optimal number of treatment sessions for functional recovery in BD. However, in a previous trial of IPSRT for adolescents with BD, 16-18 sessions was not only sufficient to produce changes in manic, depressive, and general psychiatric symptoms, but lead to improvements in functional outcome (Hlastala et al., 2010).

Participants in both groups will receive TAU including case management prior to, during, and following the allotted 6-month treatment period. This will comprise weekly to fortnightly sessions in the initial phase focusing on presenting difficulties, with sessions tapered during the recovery phase.

All participants will have regular medical reviews by a psychiatric registrar or consultant psychiatrist. Both treatment groups will be prescribed standardised antipsychotic and mood stabilising medication as per international treatment guidelines.

2.6 Outcome measures

The outcome measures that have been selected have been widely used, including in our own trials with young people with first episode mania (Berk et al., 2017; Conus et al., 2015b) and first episode psychosis (Killackey et al., 2018).

The primary outcome is the interviewer-rated **Global Assessment of Functioning (GAF)**. The GAF provides a single score is provided on a scale from 0-100, which takes into account the patient's psychological, social, and occupational functioning. It also covers symptomatology, ranging from positive mental health to severe psychopathology. A higher score indicates better global functioning. The GAF will be rated according to information relating to the two weeks prior to the assessment. The GAF was chosen as the primary outcome because it represent an aggregate of both symptoms and functional markers. Given that illness severity and poor functioning are highly correlated in bipolar disorder (Levy & Manove, 2012), it may be artificial to separate symptoms from functioning, when a composite measure may be more meaningful for young people. The GAF has been considered a valid measure of psychiatric disturbance in those with mental illness (Jones, Thornicroft, Coffey, & Dunn, 1995) and we have previously used the GAF in young people with psychotic mania (Berk et al., 2017; Conus et al., 2015a). Furthermore, in our pilot study of RECOVER, the strongest treatment effects were observed for the GAF (Macneil et al., 2012b). The GAF will be complemented by secondary outcome measures of specific symptoms and more detailed measures of functioning.

There are a number of secondary outcome measures. Severity of manic and depressive symptoms will be ascertained using the **Young Mania Rating Scale** (YMRS; Young, Biggs, Ziegler, & Meyer, 1978) and **Montgomery Åsberg Depression Rating Scale** (MADRS; Montgomery & Asberg, 1979), respectively**.**

The **Clinical Global Impression Scale for use in bipolar disorder** (CGI-BP; Spearing, Post, Leverich, Brandt, & Nolen, 1997) will assess global disorder severity and allows for the assessment of change from preceding assessment.

Other measures of functioning include the **Social and Occupational Functioning Assessment Scale** (SOFAS), **Functioning Assessment Short Test** (FAST; Rosa et al., 2007), and the **Sheehan Disability Scale** (SDS; Sheehan, Harnett-Sheehan, & Raj, 1996). Social inclusion will be measured using the **Filia Social Inclusion Measure** (F-SIM; Filia, 2015). The **Quality of Life in Bipolar Disorder-Brief** (QoL.BD-Brief; Michalak, Murray, & CREST-BD., 2010) and the **Assessment of Quality of Life** (AQoL-8D; Richardson, Iezzi, Khan, & Maxwell, 2014) will be used to measure disorder specific and health health-related QoL, respectively.

2.7 Treatment-related measures

The **Working Alliance Inventory** (WAI; Horvath & Greenberg, 1989) is a self-report scale measuring the quality of therapeutic alliance between client and therapist. Therapist (WAI-T) and client (WAI-C) versions will be used. The **Patient Attitudes and Expectations Form** (PAEF; Elkin, Parloff, Hadley, & Autry, 1985) measures participants' expectations related to treatment. The **Patient Global Impressions – Improvement** (Mohebbi, Dodd, Dean, & Berk, 2018) is a single-item self-report scale of perceived change in patient's lives since the beginning of treatment. The PGI is concordant with the recovery model and a patient centric philosophy of treatment and research. Information on psychosocial and pharmaceutical treatments received during the course of the study will be recorded.

2.8 Variables associated with treatment response

Additional variables may be associated with treatment response and will be measured using the following scales: **Medication Adherence Rating Scale** (MARS; Thompson, Kulkarni, & Sergejew, 2000); **Young Schema Questionnaire – third version – long form** (YSQ-L3; Dobson, 2009); **Perfectionism Inventory** (PI; Hill et al., 2004); **Self-Compassion Scale** (SCS; Neff, 2003); **Social Rhythm Metric-5** (SRM-5; Frank, 2005); **actigraphy-derived measures of stability of 24-hour daily activity rhythm** (Van Someren et al., 1999); **Structured Clinical Interview for DSM-5 Axis II Disorders Personality Questionnaire Screener** (SCID-5-PD; First, Williams, Benjamin, & Spitzer, 2016); **Personality Inventory for DSM-5 brief form** (PID-5-BF; Kruegar, 2013); The **Cannon-Spoor Premorbid Adjustment Scale** (PAS; Cannon-Spoor, Potkin, & Wyatt, 1982)**; General Anxiety Disorder – 7 item** (GAD-7; Spitzer, Kroenke, Williams, & Lowe, 2006); and **Overall Anxiety Severity and Impairment Scale** (OASIS; Norman, Cissell, Means-Christensen, & Stein, 2006).

2.9 Safety and adverse events

The trial will be monitored by a Data Safety and Monitoring Board (DSMB). Information pertaining to AEs will be collected from the time informed consent is obtained. Suicidal ideation will be rated using the **Columbia Suicide Severity Rating Scale** (C-SSRS; Posner et al., 2011).

2.10 Procedure

Informed, signed consent will be obtained from all participants aged 15-25 years inclusive (on the 'participant providing own consent' PICFs). Youth under the age of 18 years will also require informed, signed consent of their parent or guardian to participate (on the 'parent/guardian consenting on behalf of participant' PICFs). The initial, screening assessment will commence once written informed consent has been obtained. This assessment will confirm inclusion and exclusion criteria. The schedule of baseline and follow-up assessments is detailed in Table 1.

(Insert Table 1 about here)

2.11 Randomisation

Individuals will be randomised to receive either RECOVER+TAU or TAU based on a 1:1 ratio. The randomisation schedule will be computer-generated by a statistician independent of the study. It will be based on a permutated block randomisation scheme with stratification for site. The allocation sequence will be concealed within a web-based Research Project Management System (RPMS) developed at Orygen. The statistician conducting analyses and the research assistants will be blinded to treatment allocation. Participants and clinicians will be aware of group allocations; however, will be reminded on a regular basis to avoid disclosure to other young people in the services and research assistants.

2.12 Statistical analyses

Statistical analyses will follow the International Conference on Harmonization E9 statistical principles. Results will be reported in accordance with CONSORT guidelines (Moher, Schulz, & Altman, 2001). The primary analysis of effectiveness will assess average treatment group differences in change from baseline to 6 months (end of treatment, primary endpoint) for the primary outcome measure (GAF, a continuous outcome measure), and will use a restricted maximum likelihood (REML) based mixed-effects model, and a repeated measures approach (MMRM). The MMRM model includes the fixed, categorical effects of treatment, visit, and treatment-by-visit interaction. An MMRM includes all available data and is the preferred method of analysing clinical trial data in psychiatry as compared to more traditional repeated measures analysis of variance and analysis of covariance models (Gueorgieva & Krystal, 2004). Planned comparisons will be done within the MMRM to determine between group differences in change of global functioning from baseline to 6 months (primary effectiveness analysis). Estimated means and standard errors will be presented for each group at each visit. The same approach to analysis will be adopted for secondary outcome measures.

2.13 Determination of sample size

In our pilot study (Macneil et al., 2012b), there was a 14-point difference between RECOVER+TAU versus TAU on the GAF at 6 months, equating to a moderate-large effect size of 0.60 (Cohen's *d* based on dependence between means). The pilot data were based on a matched pairs design; therefore, we have set the effect size for the study at a more conservative level of 0.50. Based on this effect size, with an alpha (α) of .05, and power (1-*β*) set at 0.80, we would require 51 cases per group or a total of 102 participants. To allow for attrition rate of 20% (based on our previous studies), we would then recruit 61 per group, or a total of 122 participants. This sample size will be more than adequate for testing differences on secondary outcomes such as those where moderate-large effects were noted in our pilot study (Macneil et al., 2012b).

2.14 Data management

Data collection and collation will be conducted according to Good Clinical Practice guidelines (Therapeutic Good Administration, 2018). Monitoring of the trial will be managed by the DSMB, the Project Manager, and the Sponsor-appointed Clinical Research Associate.

3. Results

This study commenced recruitment in January 2019. Recruitment is anticipated to occur over 3.5 years.

4. Discussion

Current treatments for BD are not tailored to the needs of young people early in the course. Although pharmacological interventions can address symptomatology, functional impairments often remain (Conus et al., 2006). The disorder disrupts young people's normal developmental trajectory (Wolf & Wagner, 2003) and tends to become more refractory to both pharmacotherapy and psychotherapy. This is linked to progressive brain structural and cognitive changes, suggesting that remedial interventions need to be implemented as early as possible in the disorder course (Berk et al., 2014). Targeted psychological interventions may be useful adjunctive treatments to aid psychosocial recovery (Murray et al., 2017), but there is very limited evidence for these with young people (15-24 years) with early stage BDI (Vallarino et al., 2015).The RECOVER psychological intervention addresses this unmet need. If, as expected, RECOVER demonstrates effectiveness in improving symptomatic and functional outcomes at the early stage of BD, it can be readily translated broadly in Australia and internationally. The project has the potential to not only improve the lives of young people with BD, but to incrementally change the worldwide distribution of mental health burden associated with the disorder.

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Conflicts of interest.

No conflicts to report.

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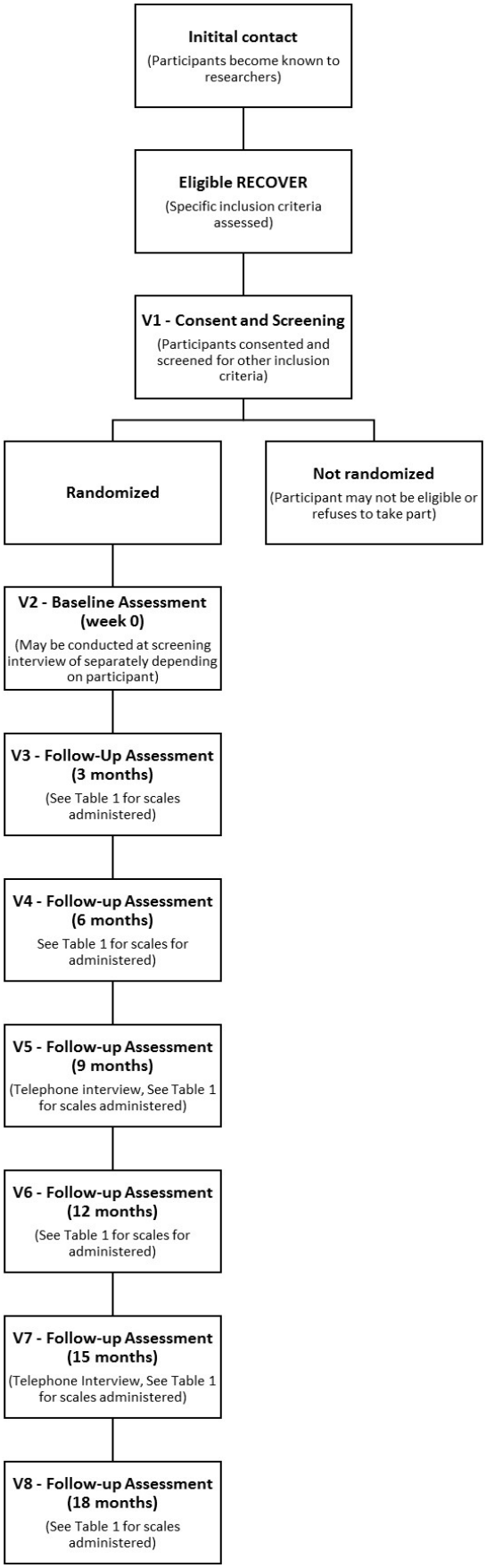

Figure 1. Flow chart of study design.

Note: Core modules are highlighted in blue

Figure 2. The modules from the RECOVER intervention

Table 1. *Assessments that are implemented at each study visit*.

VISIT NUMBER	1	2	3	4	5	6	7	8
Assessment	Screening Day -28 to 0	Baseline Day -7 to 1	3 Months -7 to +21 days	6 Months ± 21 days	9 Months ± 21 days (Telephone)	12 Months ± 21 days	15 Months ± 21 days (Telephone)	18 Months ± 42 days End of Study
Informed Consent	x							
Cohort Characteristics and Eligibility	x	-	-	-	-	-	-	-
Demographics	x	-	-	-	-	-	-	-
Demographics - employment/education	x	-	-	x	-	x	-	x
SCID-5 Modules A-D	x	-	-	-	-	-	-	-
SCID-5 Modules E-G, I	-	-	x	-	-	-	-	-
SCID 5 PD	-	-	x	-	-	-	-	-
PID-5	-	-	x	-	-	-	-	-
WASI	x	-	-	-	-	-	-	-
PAS	x	-	-	-	-	-	-	-
Randomisation	x	-	-	-	-	-	-	-
Safety								
Adverse events recording sheet								
C-SSRS	x	-	-	x	-	x	-	x
ASSIST	x	-	-	x	-	x	-	x
Primary Outcome								
GAF	-	x	x	x	x[†]	x	x	x
Secondary Outcomes								
Functioning								
FAST	-	x	x	x	-	x	-	x
SOFAS	-	x	x	x	x[†]	x	x	x
SDS	-	x	x	x	-	x	-	x
SIMI-LE	-	x	-	x	-	-	-	x
QoL.BD-Brief	-	x	-	x	-	x	-	x
AQoL-8D	-	x	-	x	-	x	-	x
Symptoms								
YMRS	-	x	x	x	-	x	-	x
MADRS	-	x	x	x	-	x	-	x
CGI-BP	-	x	x	x	-	x	-	x
GAD-7	-	x	-	x	-	x	-	x
OASIS	-	x	-	x	-	x	-	x
Schemas								
YSQ-L3 (complete)	-	x	-	-	-	-	-	-
YSQ-L3 (subscales) [‡]	-	-	x	x	-	x	-	x
Perfectionism Inventory		x	x	x	-	x	-	x
SCS	-	x	x	x	-	x	-	x
Service Utilisation and Treatment Adherence								
MARS	-	x	x	x	-	x	-	x
Psychosocial Treatment Form	-	x	x	x	-	x	-	x
Pharmaceutical Treatment Form	-	x	x	x	-	x	-	x
Treatment Related Variables								
PAEF	x	-	-	-	-	-	-	-
PGI-I	-	-	x	x	-	x	-	x
WAI-T & WAI-C	-	-	x	x	-	-	-	-

[†] The GAF and SOFAS will be completed by following the telephone assessment and complemented by information obtained in the participant's medical record

[‡] All participants will complete the Perfectionism and Unrelenting Standards subscales at the nominated time-points. Participants in the RECOVER+TAU group will be asked to complete additional subscales, specific to each individual, as identified during the initial administration of the complete YSQ-L3 and during the course of treatment. The Project Manager will coordinate the administration of these subscales, to maintain blinding for the RAs.

Note: AQOL-8D, Assessment of Quality of Life - 8 Dimensions; ASSIST, Alcohol, Smoking, and Substance Use Involvement Screening Test; CGI-BP, Clinical Global Impressions - Bipolar Disorder; C-SSRS, Columbia Suicide Severity Rating Scale; GAD-7, Generalised Anxiety Disorder 7-item scale; GAF, Global Assessment of Functioning; FAST; Functional Assessment Short Test; MADRS, Montgomery Asberg Depression Rating Scale; MARS, Medication Adherence Rating Scale; OASIS, Overall Anxiety Severity and Impairment Scale; PAEF, Patients Attitudes and Expectations Form; PAS, Premorbid Adjustment Scale; PID-5, Personality Inventory for DSM-5; QoL.BD-Brief, Quality of Life in Bipolar Disorder - Brief; SCID-5, Structured Clinical Interview for DSM-5; SCID-5 PD BPD, Structured Clinicial Interview for DSM-5 Personality Disorders; SCS, Self-Compassion Scale; SDS, Sheehan's Disability Scale; SIMI-LE, Social Inclusion for People with Mental Illness - Long Edition; SOFAS, Social and Occupational Functioning Scale; Wechsler Abbreviated Scale of Intelligence; YMRS, Young Mania Rating Scale

VISIT NUMBER	1	2	3	4	5	6	7	8
Assessment	Screening Day -28 to 0	Baseline Day -7 to 1	3 Months -7 to +21 days	6 Months ± 21 days	9 Months ± 21 days (Telephone)	12 Months ± 21 days	15 Months ± 21 days (Telephone)	18 Months ± 42 days End of Study
Cohort Characteristics and Eligibility								
PID-5			X					
Primary Outcome, Functioning and Quality of Life								
SDS		X	X	X		X		X
SIMI-LE		X		X				X
QOL.BD-Brief		X		X		X		X
AQoL-8D		X		X		X		X
Schemas								
Perfectionism Inventory		X	X	X		X		X
Self-Compassion Scale		X	X	X		X		X
Symptoms								
GAD-7		X		X		X		X
OASIS		X		X		X		X
Service Utilisation and Treatment Adherence								
MARS		X	X	X		X		X
Treatment Related Variables								
PAEF	X							
PGI-I			X	X		X		X
WAI-T[1] & WAI-C[1]			X	X				
Social Rhythm								
SRM-5		X	X	X		X		X
Actigraphy		X	X	X				
PSQI		X	X	X				
MCTQ		X		X				

1. *Participants in the TAU arm will not be administered this measure*

VISIT NUMBER	1	2	3	4	5	6	7	8
Assessment	Screening Day -28 to 0	Baseline Day -7 to 1	3 Months -7 to +21 days	6 Months ± 21 days	9 Months ± 21 days (Telephone)	12 Months ± 21 days	15 Months ± 21 days (Telephone)	18 Months ± 42 days End of Study
Informed Consent	x							
Cohort Characteristics and Eligibility	x	-	-	-	-	-	-	-
Demographics	x	-	-	-	-	-	-	-
Demographics - employment/education	x	-	-	x	-	x	-	x
SCID-5 Modules A-D	x	-	-	-	-	-	-	-
SCID-5 Modules E-G, I	-	-	x	-	-	-	-	-
SCID 5 PD	-	-	x	-	-	-	-	-
PID-5	-	-	x	-	-	-	-	-
WASI	x	-	-	-	-	-	-	-
PAS	x	-	-	-	-	-	-	-
Randomisation	x	-	-	-	-	-	-	-
Safety								
Adverse events recording sheet								
C-SSRS	x	-	-	x	-	x	-	x
ASSIST	x	-	-	x	-	x	-	x
Primary Outcome								
GAF	-	x	x	x	x†	x	x	x
Secondary Outcomes								
Functioning								
FAST	-	x	x	x	-	x	-	x
SOFAS	-	x	x	x	x†	x	x	x
SDS	-	x	x	x	-	x	-	x
SIMI-LE	-	x	-	x	-	-	-	x
QoL.BD-Brief	-	x	-	x	-	x	-	x
AQoL-8D	-	x	-	x	-	x	-	x
Symptoms								
YMRS	-	x	x	x	-	x	-	x
MADRS	-	x	x	x	-	x	-	x
CGI-BP	-	x	x	x	-	x	-	x
GAD-7	-	x	-	x	-	x	-	x
OASIS	-	x	-	x	-	x	-	x
Schemas								
YSQ-L3 (complete)	-	x	-	-	-	-	-	-
YSQ-L3 (subscales) ‡	-	-	x	x	-	x	-	x
Perfectionism Inventory		x	x	x	-	x	-	x
SCS	-	x	x	x	-	x	-	x
Service Utilisation and Treatment Adherence								
MARS	-	x	x	x	-	x	-	x
Psychosocial Treatment Form	-	x	x	x	-	x	-	x
Pharmaceutical Treatment Form	-	x	x	x	-	x	-	x
Treatment Related Variables								
PAEF	x	-	-	-	-	-	-	-
PGI-I	-	-	x	x	-	x	-	x
WAI-T & WAI-C	-	-	x	x	-	-	-	-

† The GAF and SOFAS will be completed by following the telephone assessment and complemented by information obtained in the participant's medical record

‡ All participants will complete the Perfectionism and Unrelenting Standards subscales at the nominated time-points. Participants in the RECOVER+TAU group will be asked to complete additional subscales, specific to each individual, as identified during the initial administration of the complete YSQ-L3 and during the course of treatment. The Project Manager will coordinate the administration of these subscales, to maintain blinding for the RAs.

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