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## Effects of adjunctive brexpiprazole on sleep-wake and circadian parameters in youth with depressive syndromes: Study protocol for a clinical trial

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**Effects of adjunctive brexpiprazole on sleep-wake and circadian parameters in youth with depressive syndromes: Study protocol for a clinical trial**

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## ABSTRACT

### Introduction

Sleep-wake and circadian disturbance is a key feature of mood disorders with a potential causal role and particular relevance to young people. Brexpiprazole is an atypical antipsychotic medication with demonstrated efficacy as an adjunct to antidepressant treatment for Major Depressive Disorder (MDD) in adults, with preliminary evidence suggesting greater effectiveness in subgroups of depressed patients with sleep disturbances. This clinical trial aims to evaluate the relationships between changes in sleep-wake and circadian parameters and changes in depressive symptoms following adjunctive brexpiprazole treatment in young adults with MDD and sleep-wake disturbance.

### Methods and analysis

This study is designed as a 16 week (8 weeks active treatment, 8 weeks follow up) mechanistic, open-label, single-arm phase IV clinical trial and aims to recruit 50 young people aged 18 to 30 with MDD and sleep-wake cycle disturbance through an early intervention youth mental health clinic in Sydney, Australia. At baseline, participants will undergo multidimensional outcome assessment and subsequently receive 8 weeks of open-label treatment with brexpiprazole as adjunctive to their stable psychotropic medication. Following 4 weeks of treatment, clinical and self-report measures will be repeated. Ambulatory sleep-wake monitoring will be conducted continuously for the duration of treatment. After 8 weeks of treatment, all multidimensional outcome assessments will be repeated. Follow-up visits will be conducted 4 and 8 weeks after trial completion (including sleep-wake, clinical, and self-report assessments).

### Ethics and dissemination

This trial protocol has been approved by the Human Research Ethics Committee of the Sydney Local Health District (X19-0417 and 2019/ETH12986, Protocol Version v 1-3, dated 25.02.2021).

The results of this study, in de-identified form, will be disseminated through publication in peer-reviewed journals, scholarly book chapters, presentation at conferences and publication in conference proceedings.

## Trial Registration

Australian New Zealand Clinical Trials Registry (ANZCTR) Number: ACTRN12619001456145p, Date 22 October, 2019.

## KEYWORDS:

Mental health, adjunctive brexpiprazole, sleep-wake cycle, youth depression.

## ARTICLE SUMMARY

### Strengths and limitations of this study

- The use of comprehensive assessment battery, including actigraphy and circadian assessment, and collection of metabolic and inflammatory markers to help acquire a greater understanding of the mechanisms of antidepressant action of adjunctive brexpiprazole
- This trial will help to inform personalised treatment plans for specific clinical phenotypes, placing the participant at the centre of care
- As part of the study, all participants will receive a psychoeducational session about sleep and circadian rhythms with information on how to improve their sleep based on their actigraphy data

## INTRODUCTION

In young adults, Major Depressive Disorder (MDD) is highly prevalent, recurrent, and comorbid with other mental and physical conditions, generating a substantial burden of disease and disability [1, 2]. While multiple psychological and pharmacological treatments are commonly provided, a large proportion of patients with MDD fail to respond to first-line psychotherapy or antidepressant treatments [3-5], and augmentation with atypical antipsychotics is often recommended in these treatment-resistant cases [6]. Common features of depressive disorders are sleep-wake cycle disturbances, including not only insomnia [7-9], hypersomnia [10, 11], and abnormal sleep duration [7, 8], but also abnormal timing of 24-hour patterns of rest and activity [12, 13]. In addition, abnormalities

1  
2 in biological circadian rhythms have been reported in depressive disorders [14, 15], suggesting that in  
3  
4 some cases sleep disturbances are accompanied or underpinned by disturbances of the underlying  
5  
6 circadian timing system [16].  
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8  
9

10  
11 Adolescents and young adults are particularly vulnerable to circadian perturbations due to significant  
12  
13 developmental changes in circadian rhythms across this age period [17], and sleep-wake phase delays  
14  
15 are common in young people with depressive disorders [18]. Recently, we reported delayed and  
16  
17 disrupted circadian rhythms in a subgroup of young people with depressive disorders, and this group  
18  
19 also presented with greater symptom severity [19]. Furthermore, there is some evidence that correction  
20  
21 of circadian abnormalities is associated with antidepressant effects in response to treatments targeting  
22  
23 the circadian system such as Agomelatine [20] and bright light therapy [21].  
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28  
29 Brexpiprazole is an atypical antipsychotic with demonstrated efficacy as an adjunct to antidepressant  
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31 treatment in major depressive disorder in adults, as evidenced by multiple randomised controlled trials  
32  
33 [22-25], however the exact mechanism of antidepressant action is unknown [26]. The pharmacodynamic  
34  
35 properties of brexpiprazole, together with evidence from preclinical studies, suggest that there may be  
36  
37 specific effects on anxiety, cognitive function, and sleep [26, 27]. Further, there is preliminary evidence  
38  
39 to suggest that brexpiprazole may have greater effectiveness in subgroups of depressed patients with  
40  
41 sleep disturbances, anxiety, or irritability [16, 28].  
42  
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46  
47 One previous study has investigated sleep disturbances in individuals with MDD treated with adjunctive  
48  
49 brexpiprazole and reported both reduced insomnia symptoms and improved daytime alertness [29].  
50  
51 This is consistent with effects on circadian rhythms, with potential influences on the entire 24-hour  
52  
53 pattern of rest and activity rather than simply on the sleep period in isolation. In order to improve the  
54  
55 personalisation of treatment selection for mood disorders, it is necessary to acquire a greater  
56  
57 understanding of the mechanisms of antidepressant action of specific compounds. As such, we aim to  
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investigate whether the impact of brexpiprazole on depressive symptoms is linked to changes in sleep-wake cycle or circadian parameters in young people with MDD.

## **METHODS AND ANALYSIS**

### **Study Objectives**

The primary objective of this study is to determine if changes in depressive symptoms following adjunctive brexpiprazole treatment are correlated with changes in sleep-wake cycle or circadian parameters in young people with depressive syndromes.

The secondary objective is to determine if changes in social and occupational functioning following adjunctive brexpiprazole are correlated with changes in sleep-wake cycle or circadian parameters in young people with depressive syndromes.

The tertiary objectives of this study are to determine if changes in depressive symptoms or changes in sleep-wake cycle or circadian parameters following adjunctive brexpiprazole treatment are associated with a range of multidimensional outcome measures in young people with depressive syndromes[30]. These include other mental illness symptoms, self-harm and suicidal thoughts and behaviours, physical health parameters, alcohol and substance use, and genomic markers.

### **Trial design**

This investigator-initiated, mechanistic study involving 50 young people with depressive syndromes and sleep-wake cycle disturbances is designed as a 16-week (8 weeks active treatment, 8 weeks follow-up) open-label, single-arm, phase IV clinical trial.

### **Participants**

Participants aged 18 to 30 with a diagnosis of MDD according to DSM-5 criteria on a current antidepressant treatment of either selective serotonin reuptake inhibitor (SSRI) or serotonin-

1  
2 norepinephrine reuptake inhibitor (SNRI) with a disrupted sleep-wake cycle will be recruited through the  
3  
4 youth mental health clinics associated with the Brain and Mind Centre (BMC), University of Sydney. All  
5  
6 participants will provide written informed consent. The research team will make explicit to any potential  
7  
8 participants both verbally and in writing (in the Participant Information Statement) that participation is  
9  
10 voluntary and will not affect the patient's care received by the mental health service.  
11  
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14

15 The inclusion criteria for this trial are: (i) aged 18 to 30, (ii) diagnosis of MDD as per DSM-5 (Structured  
16  
17 Clinical Interview for DSM; SCID[31]) criteria, (iii) current major depressive episode of moderate severity  
18  
19 as defined by a Quick Inventory of Depressive Symptomatology (QIDS)[32] rating  $\geq 11$  at two  
20  
21 assessments two weeks apart, (iv) failure to respond to at least one adequate (minimum four weeks)  
22  
23 trial of pharmacological treatment, (v) current antidepressant treatment with SSRI or SNRI for at least 6  
24  
25 weeks, at a stable dose for two weeks prior to study commencement, and (vi) a perturbed sleep-wake  
26  
27 cycle as evidenced by: delayed sleep onset; delayed sleep offset; disrupted sleep; high day-to-day  
28  
29 variability of sleep-wake cycle; non-restorative sleep; or daytime fatigue.  
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35 Exclusion criteria are: (i) any adjunctive antipsychotic treatment for current episode in the past month,  
36  
37 (ii) use of medications which affect sleep, (iii) primary psychotic disorder diagnosis, (iv) acute suicidal  
38  
39 behaviour (score of 6 on Comprehensive Assessment of At-Risk Mental States (CAARMS) item 7.3[33]),  
40  
41 (v) medical condition contributing to sleep-wake dysfunction, (vi) significant alcohol or substance misuse  
42  
43 or dependence (assessed via DSM-5 SCID[31] and World Health Organisation Alcohol, Smoking and  
44  
45 Substance Involvement Screening Test (WHO-ASSIST[34, 35]), (vii) shift work or (viii) recent  
46  
47 transmeridian travel, (ix) previous hypersensitivity to brexpiprazole, (x) taking CYP2D6 or CYP3A4  
48  
49 inhibitors, and (xi) pregnancy or lactation.  
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54

### 55 **Study course and procedure**

56  
57 Patients presenting for mental health care who may be eligible for the study will be screened by phone  
58  
59 before being invited to participate and attending an enrolment visit. The enrolment visit will formally assess  
60



1  
2 eligibility criteria and confirm the presence of MDD as per DSM-5 (SCID)[31]. Participants will be provided  
3  
4 with an actigraphy device (non-invasive, wrist-worn device used to objectively measure activity and sleep  
5  
6 patterns) and will be given instructions to wear the device for the following two week period.  
7  
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9

10  
11 *Visit 1 (Baseline):* Within two weeks of completing the diagnostic and screening assessments, data from  
12  
13 the actigraphy device will be downloaded and reviewed. A further assessment of depressive symptom  
14  
15 severity (QIDS Clinician-Rated; QIDS-CR)[32] will be conducted to ensure that participants meet all  
16  
17 inclusion criteria. Bloods will be collected for the assessment of metabolic and inflammatory measures,  
18  
19 and genomic analysis. Clinical and self-report assessments will be conducted, as well as circadian  
20  
21 assessments in which the participant will remain in the sleep lab overnight. The following morning,  
22  
23 participants will attend a 1-hour psychoeducation session about sleep and circadian rhythms covering  
24  
25 the following topics: i) sleep and circadian education with tailored discussion based on their personal  
26  
27 actigraphy data; ii) individualized plan for progressive sleep rescheduling; and iii) lifestyle factors and  
28  
29 behaviours impacting on sleep (e.g. exercise, light, sleep environment, sleep regulation, foods, stress,  
30  
31 anxiety, mood).  
32  
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38 Once all baseline clinical and self-report assessments have been conducted, and the medical assessment  
39  
40 completed by the study doctor to confirm the inclusion and exclusion criteria, participants will be issued  
41  
42 with the study medication to receive 8 weeks of open-label pharmacotherapy with brexpiprazole  
43  
44 (REXULTI®-Lundbeck) as adjunctive to their stable psychotropic medication (treatment as usual).  
45  
46 Brexpiprazole will be provided to participants at Visit 1 (Baseline) and Visit 2 (Week 4) for the following  
47  
48 four weeks and will be titrated from 1 mg once daily in week 1, to 2 mg once daily in weeks 2-8.  
49  
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52

53 *Monitoring visits:* Participants will be contacted by telephone on a weekly basis for the duration of the 8  
54  
55 week treatment period to monitor adverse events and adherence. Any changes in concomitant  
56  
57 medications will also be investigated and recorded. In addition, participants will be provided with a  
58  
59 medication diary and asked to complete during the study to monitor adherence.  
60

1  
2 More detailed information about potential side-effects will be further assessed by the study doctor at visits  
3  
4 2, 3, 4 and 5 using the UKU Side Effect Rating Scale [36], Abnormal Involuntary Movement Scale (AIMS) [37]  
5  
6 and the Simpson-Angus Scale (SAS) [38] for evaluation of extrapyramidal symptoms (EPS).  
7  
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10  
11 *Visit 2 (Week 4):* Following four weeks of the treatment phase, participants will return to BMC, where  
12  
13 clinical and self-report assessments will be completed to assess changes in clinical and functional  
14  
15 measures.  
16

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19  
20 *Visit 3 (Week 8):* Following eight weeks of the treatment phase, participants will return again to  
21  
22 complete clinical and self-report assessments, and will also complete a second circadian (overnight) in-  
23  
24 lab assessments. Bloods will be collected at this visit for follow-up metabolic and inflammatory markers.  
25  
26

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29 *Visit 4 and 5 (Follow-up visits 1 and 2, 12 and 16 weeks respectively):* Twelve and sixteen weeks after  
30  
31 commencing treatment (i.e. four and eight weeks after completing the eight-week treatment period  
32  
33 respectively), participants will return to BMC and complete clinical and self-report assessments.  
34  
35 Participants will be provided with an actigraphy device to wear for two weeks prior to these  
36  
37 assessments.  
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41  
42 Participants will be reimbursed for their time and the cost of transportation to and from the BMC and/or  
43  
44 sleep labs.  
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## 47 48 49 **Outcomes**

### 50 51 52 53 **Primary Outcome Measures**

54  
55 The primary endpoint will be the correlation between change in sleep-wake and circadian parameters and  
56  
57 change in depressive symptoms from baseline to week eight.  
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1  
2 Notably, the primary depressive symptom measures (QIDS-CR total score, QIDS-Self Report (QIDS-SR) total  
3 score, The Montgomery-Åsberg Depression Rating Scale (MADRS) total score) contain sleep items. These  
4 will be removed from these scales for analyses to provide a measure of depressive symptoms that is not  
5  
6 biased by changes in sleep-wake parameters.  
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12  
13 Primary sleep-wake and circadian variables of interest include actigraphy parameters, as well as in-lab  
14  
15 circadian and self-report measures.  
16

### 17 18 19 20 **Secondary Outcome Measures**

21  
22 The secondary endpoint will be correlation between change in sleep-wake and circadian parameters and  
23  
24 change in functioning from baseline to week eight.  
25

### 26 27 28 29 **Tertiary Outcome Measures**

30  
31 Tertiary endpoints will be correlation between change in sleep-wake and circadian parameters and other  
32  
33 multidimensional outcome measures based on assessments of symptoms, self-harm and suicidal thoughts  
34  
35 and behaviours, physical health, and alcohol and substance use.  
36

37  
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40 Further tertiary endpoints will be comparison of primary endpoints between Clinical Stages [39-42], illness  
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42 trajectories [43], and genomic variants with potential relevance to mood disorders and/or circadian  
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44 rhythms (e.g. CLOCK, BMAL1).  
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49 Detailed outcome measures are summarized in Table 1.  
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**Table 1 – Primary, Secondary and Tertiary Outcome Measures**

<b>Primary Outcome Measures</b> (Correlation between change in sleep-wake and circadian parameters and change in depressive symptoms from baseline to week eight)	<b>Secondary Outcome Measures</b> (Correlation between change in sleep-wake and circadian parameters and change in functioning from baseline to week eight)	<b>Tertiary Outcome measures</b> (Correlation between change in sleep-wake and circadian parameters and other multidimensional outcome measures)
<p><b>Primary depressive symptom measures:</b></p> <ul style="list-style-type: none"> <li>• QIDS-CR total score (minus sleep items)</li> <li>• QIDS-Self Report (QIDS-SR) total score (minus sleep items)</li> <li>• The Montgomery-Åsberg Depression Rating Scale (MADRS) total score (minus sleep items)</li> </ul> <p><b>Primary sleep-wake and circadian variables of interest:</b></p> <p>Actigraphy parameters (in the two-week period prior to baseline and prior to week eight):</p> <ul style="list-style-type: none"> <li>• Sleep onset time</li> <li>• Sleep offset (wake) time</li> <li>• Total sleep time (duration)</li> <li>• Wake after sleep onset (estimation of number of minutes awake during the sleep period)</li> <li>• Sleep efficiency (% of sleep period estimated as sleep)</li> <li>• Inter-daily stability</li> <li>• Intra-daily variability</li> </ul> <p><b>In-lab circadian measures:</b></p> <ul style="list-style-type: none"> <li>• Dim Light Melatonin Onset (DLMO) timing</li> <li>• Phase angle (time lapse) between DLMO and habitual sleep</li> <li>• Core body temperature nadir</li> </ul>	<p><b>Functioning measures:</b></p> <ul style="list-style-type: none"> <li>• Social and Occupational Functioning Assessment Scale (SOFAS) rating</li> <li>• The Work and Social Adjustment Scale (WSAS) total score</li> <li>• Adapted Schuster Social Support Scale (SSSS) total score</li> <li>• Not in Education, Employment, or Training (NEET) status</li> <li>• Number of days 'out of role' (unable to perform usual activities) in the past 30 days</li> </ul>	<p><b>Symptom Measures:</b></p> <ul style="list-style-type: none"> <li>• Young Mania Rating Scale (YMRS) total score</li> <li>• Brief Psychiatric Rating Scale (BPRS) total score and subscale scores</li> <li>• Overall Anxiety Severity Impairment Scale (OASIS) total score</li> <li>• Altman Self-Rating Mania scale (ASRM) total score</li> <li>• Prodromal Questionnaire (brief version) (PQ-16) total score</li> <li>• DSM-5 Primary Care Post-Traumatic Stress Disorder screen (PC-PTSD-5) total score</li> <li>• Adapted Eating Disorder Examination (EDE) total score</li> <li>• Clinical Global Impressions scale (CGI) severity and improvement scores</li> </ul> <p><b>Self-harm and suicidal thoughts and behaviours:</b></p> <ul style="list-style-type: none"> <li>• Suicidal risk (score from Suicidal Ideation Attributes Scale (SIDAS) and Columbia-Suicide Severity Rating Scale (C-SSRS) items)</li> <li>• Adapted Brief Non-Suicidal Self-Injury Assessment Tool (B-NSSI-AT) total score</li> </ul> <p><b>Physical Health:</b></p> <ul style="list-style-type: none"> <li>• Body Mass Index (BMI) calculated from height and weight</li> <li>• Waist circumference</li> </ul>

<p>• Evening cortisol area under the curve</p> <p><b>Self-report measures:</b></p> <ul style="list-style-type: none"> <li>• Non-restorative sleep score (based on the Pittsburgh Sleep Quality Index (PSQI), and Munich Chronotype Questionnaire (MCTQ))</li> <li>• <i>Pittsburgh Sleep Quality Index</i> (PSQI) total score</li> <li>• Epworth Sleepiness Score (ESS) total score</li> <li>• Insomnia Severity Index (ISI) total score</li> <li>• Morningness -Eveningness Questionnaire (MEQ) total score*</li> <li>• Seasonal Pattern Assessment Questionnaire (SPAQ) total score*</li> </ul> <p>*baseline scores will be used rather than change scores as these are trait measures</p>		<ul style="list-style-type: none"> <li>• International Physical Activity Questionnaire (IPAQ) total score</li> <li>• Metabolic blood markers including triglycerides, cholesterol (total, Low Density Lipoprotein (LDL), High Density Lipoprotein (HDL)), and Homeostasis Model of Insulin Resistance (HOMA2-IR) calculated from fasting glucose and insulin measures</li> <li>• Inflammatory blood markers including Interleukin-1<math>\beta</math> (IL-1<math>\beta</math>), Interleukin-6 (IL-6), Tissue Necrosis Factor (TNF-<math>\alpha</math>), C-Reactive Protein (CRP)</li> </ul> <p><b>Alcohol and Substance Use:</b></p> <ul style="list-style-type: none"> <li>• World Health Organisation Alcohol, Smoking, and Substance Involvement Screening Test (WHO ASSIST) score for tobacco, and cannabis</li> <li>• Alcohol Use Disorders Identification Test-Consumption (AUDIT C) total score</li> <li>• WHO ASSIST alcohol-related impairment</li> <li>• Age of onset of alcohol use</li> </ul> <p><b>Comparison of primary endpoints between:</b></p> <ul style="list-style-type: none"> <li>• Clinical Stages</li> <li>• Illness Trajectories</li> <li>• Genomic variants with potential relevance to mood disorders and/or circadian rhythms (e.g. CLOCK, BMAL1).</li> </ul>
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## Assessments

Assessments used in this trial are based on the multidimensional assessment and outcomes framework [30] and include clinical ratings of mental health symptoms, social and occupational functioning, self-

1  
2 harm, suicidal thoughts and behaviours, self-report questionnaires, physical health parameters, alcohol  
3  
4 and substance use, illness type, stage and trajectory, as well as circadian parameters and metabolic,  
5  
6 inflammatory and genomic markers.  
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10  
11 Our recent research[30, 44-46] indicates the capacity of the multidimensional outcomes framework to  
12  
13 further deepen our understanding of the pathophysiological mechanisms and illness progression in this  
14  
15 cohort, as well as to inform more personalized and measurement-based models of care.  
16  
17

### 18 19 20 Diagnostic assessments

21  
22 The presence of MDD and any comorbidity will be evaluated using the Structured Clinical Interview for  
23  
24 DSM-5 Axis I Disorders (SCID) [31]. The diagnostic assessment is expected to take 30-75 minutes to  
25  
26 complete.  
27  
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29

### 30 31 Mental Risk Assessment

32  
33 Acute suicidal behaviour will be assessed by relevant subscale of the Comprehensive Assessment of At-  
34  
35 Risk Mental States (CAARMS) [33]. The mental risk assessment is expected to take 5 minutes to  
36  
37 complete.  
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39  
40

### 41 42 Clinical Assessments

- 43  
44 1. *Clinical-rated Quick Inventory of Depressive Symptomatology (QIDS-CR)* [32], a rating scale that  
45  
46 assesses the nine criterion symptom domains designated by the DSM to diagnose a major depressive  
47  
48 episode.  
49
- 50  
51 2. *Montgomery-Åsberg Depression Rating Scale (MADRS)* [47] will also be used to assess depressive  
52  
53 symptoms, to allow for direct comparisons with previous studies of brexpiprazole in MDD.  
54
- 55  
56 3. *Young Mania Rating Scale (YMRS)* [48], an eleven-item, multiple-choice diagnostic questionnaire  
57  
58 which psychiatrists use to measure the severity of manic episodes in patients.  
59  
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1  
2 4. *Brief Psychiatric Rating Scale (BPRS)* [49], a rating scale used to measure psychiatric symptoms  
3  
4 such as depression, anxiety, hallucinations and unusual behaviour.

5  
6 5. *Social and Occupational Functioning Assessment Scale (SOFAS)* [50] a clinician-rated measure will  
7  
8 assess functioning on a 0 to 100 scale, with lower scores suggesting more severe impairment.

9  
10 6. *Clinical Global Impressions scale (CGI)* [51] will be used as a measure of clinical improvement.

11  
12 7. Participants will also be rated on previously established *clinical stage* [39-42] and *illness trajectory*  
13  
14 [43] models on the basis of information collected throughout the clinical interview.

15  
16 8. *World Health Organisation (WHO) Alcohol, Smoking and Substance Involvement Screening Test*  
17  
18 (*WHO-ASSIST*) [34, 35]: a reliable, culturally adaptable, valid screening test for problematic or risky  
19  
20 substance use.

21  
22 The clinical interview is expected to take around 35 minutes to complete.  
23  
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28

### 29 Self-report Assessments

30  
31 1. *Demographics and Mental Health History*: including details of work and education, physical  
32  
33 health (height, weight, and waist circumferences), history of mental health as well as family  
34  
35 history

36  
37 2. *International Physical Activity Questionnaire (IPAQ) - short version* [52, 53] a 7-item  
38  
39 questionnaire providing internationally comparable data on health-related physical activity.

40  
41 3. *Alcohol Use Disorders Identification Test – Consumption (AUDIT-C)* [54]: the questionnaire has  
42  
43 three short questions that estimate alcohol consumption in a standard, meaningful and non-  
44  
45 judgmental manner. Additional questions assessing age of onset of alcohol consumption will also  
46  
47 be used.

48  
49 4. *Suicidal Ideation Attributes Scale (SIDAS)* [55]: a five-item self-report questionnaire assessing the  
50  
51 frequency, controllability, closeness to attempt, distress, and interference with daily activities on  
52  
53 a 10-point Likert scale over the past month.  
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5. *Columbia-Suicide Severity Rating Scale (C-SSRS) [56]*: The scale comprises 3 sections: suicidal ideation, intensity of ideation, and suicidal behaviour. In this study, a self-rating adaptation of this questionnaire will be used in combination with the SIDAS.
6. *Brief Non-Suicidal Self-Injury Assessment Tool (B-NSSI-AT) [57]*: a measure of NSSI designed to assess primary (such as form, frequency, and function) and secondary (including but not limited to NSSI habituation; contexts in which NSSI is practiced; and NSSI perceived life interference, treatment, and impacts) NSSI characteristics.
7. *Quick Inventory of Depressive Symptomatology – self-report (QIDS-SR) [58]*: a self-rating (SR) version includes 16 questions with equivalent weightings (0-3) for each symptom item that assesses the nine criterion symptom domains designated by the DSM-IV to diagnose a major depressive episode.
8. *Overall Anxiety Severity Impairment Scale (OASIS) [59]*: a 5-item self-report measure that can be used to assess severity and impairment associated with any anxiety disorder or multiple anxiety disorders.
9. *Altman Self-Rating Mania Scale (ASRM) [60]*: a five-item self-rating scale, designed to assess the presence and/or severity of manic symptoms.
10. *Primary Care Post-Traumatic Stress Disorder Screen for DSM-5 (PC-PTSD-5) [61]*: a 5-item screen that was designed for use in primary care settings, designed to identify respondents with probable PTSD.
11. *Prodromal Questionnaire (PQ-16) [62]*: a self-report screen for use in secondary mental health care services to select subjects for psychosis risk.
12. *Eating Disorder Examination (EDE) [63, 64]*: comprises a range of health-related and demographic questions, including present height and weight, and a detailed and comprehensive assessment of symptoms, particularly binge eating. In this study, three eating disorder behaviours are assessed, namely binge eating, purging and strict dieting or fasting.
13. *Sleep questions*: 7 questions regarding time falling asleep, waking up during weekdays and weekends, hours of sleep, feelings when waking up. Sleep timing items are based on the



1  
2 Pittsburgh Sleep Quality Index (PSQI), and Munich Chrono Type Questionnaire (MCTQ), while  
3  
4 sleep quality items are based on expert consensus in the literature.

5  
6 14. *Work and Social Adjustment Scale (WSAS) [65]*: a five-item scale of functional impairment  
7  
8 attributable to an identified problem.

9  
10 15. *Schuster Social Support Scale (SSSS) [66]*: a 15-item measure of social support used to examine  
11  
12 an individual's social relationships with others (relatives, friends, spouse) and the associated  
13  
14 impact on their emotional functioning

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16 16. *Additional sleep questionnaires*: participants will complete the BMC sleep-wake self-report  
17  
18 questionnaire battery including questions regarding ethnicity, caffeine consumption, menstrual  
19  
20 cycle, visual impairments, and non-restorative sleep, as well as the *Pittsburgh Sleep Quality*  
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22 *Inventory (PSQI) [67]*, *Epworth Sleepiness Scale (ESS) [68]*, *Insomnia Severity Index (ISI) [69]*,  
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24 *Horne-Ostberg Morningness-Eveningness Questionnaire (MEQ) [70]*, and the *Seasonal Patterns*  
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26 *Assessment Questionnaire (SPAQ) [71]*.

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31 The questionnaires are tailored (using skip logic) to the individual so the amount of time taken to  
32  
33 complete the questionnaire varies, but we estimate that on average the self-report assessment will take  
34  
35 around 45 minutes to complete.

### 36 37 38 39 40 **Sleep wake assessments**

41  
42 24-hour sleep-wake and circadian rest-activity parameters will be measured by actigraphy recordings  
43  
44 (ambulatory measurement of motor activity using a wrist-worn device). Actigraphy is a non-invasive tool  
45  
46 to objectively measure activity profiles used to estimate sleep and circadian patterns based on validated  
47  
48 algorithms. Participants will be asked to complete a sleep diary and to wear an actigraph (GENEActiv  
49  
50 device; Activinsights, Kimbolton, UK) on the non-dominant wrist for at least 10 days prior to  
51  
52 commencing the study, and continuously for the 8-week treatment phase. Two-week actigraphy  
53  
54 recordings will also be completed at the 12- and 16-week follow up assessments. The GENEActiv devices  
55  
56 have been validated against several types of accelerometry-based activity monitors [72-75] as well as for  
57  
58 sleep-wake scoring [76, 77]. For over three decades, actigraphy monitors like the GENEActiv devices  
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60

1  
2 have been considered as non-invasive instruments to measure sleep and activity patterns and have been  
3  
4 used extensively for research purposes in diverse clinical settings including sleep disorders, various  
5  
6 medical illnesses (e.g. cancer, HIV, traumatic brain injuries, neurodegenerative diseases) and mental  
7  
8 disorders (e.g. anxiety, depression, bipolar and psychotic disorders)[13, 78, 79].  
9

10 For details on the parameters measured, please refer to the actigraphy parameters under the 'Primary  
11  
12 sleep-wake and circadian variables of interest' in Table 1.  
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14  
15

### 16 17 **In-Lab Circadian Assessment**

18  
19 Biological circadian rhythms will be measured in an evening/overnight recording period, including  
20  
21 collection of salivary melatonin, salivary cortisol, and core body temperature to characterise 24-hour  
22  
23 rhythms. All circadian assessments will be performed in accordance with established Dim Light  
24  
25 Melatonin Onset (DLMO) protocols [80-83].  
26  
27

28 For details on the parameters measured, please refer to the in-lab circadian measures in the 'Primary  
29  
30 Outcome Measures column' in Table 1.  
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### 35 36 **Metabolic and inflammatory markers**

37  
38 The following markers will be collected at Baseline and 8-weeks follow up visits: (i) Triglycerides, (ii)  
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40 Cholesterol (including total, High Density Lipoprotein (HDL), and Low Density Lipoprotein (LDL)), (iii)  
41  
42 Fasting glucose, (iv) Fasting insulin, (v) Interleukin (IL)-1 $\beta$ , (vi) IL-6, (vii) Tissue Necrosis Factor (TNF)- $\alpha$ ,  
43  
44 (viii) C-Reactive Protein (CRP). Height, weight, and waist circumference will also be recorded.  
45  
46 Furthermore, insulin resistance will be estimated based on paired fasting plasma glucose and insulin  
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48 levels [84] by the updated homeostatic model assessment (HOMA2-IR) using iHOMA2 software V.8.8  
49  
50 [85].  
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### 55 56 **Genomics**

57  
58 Additional blood will be collected at baseline for the assessment of genomic risk markers as per  
59  
60 established procedures from the University of Queensland Human Studies Unit.

The schedule of trial assessments is summarized in Table 2.

**Table 2. Schedule of assessments**

<i>Study week</i>	Enrolment Visit	Visit 1 (Baseline)	Visit 2 (Week 4)	Visit 3 (Week 8)	Visit 4 (Follow-up 1)	Visit 5 (Follow-up 2)
		<i>0</i>	<i>4</i>	<i>8</i>	<i>12</i>	<i>16</i>
Informed Consent	✓					
Inclusion/Exclusion Criteria	✓	✓				
Diagnostic Assessment (SCID)	✓					
Mental Risk Assessment (CAARMS)	✓	✓	✓	✓	✓	✓
Demographics and Mental Illness History		✓				
Clinical Assessment (QIDS- CR, MADRS, YMRS, BPRS, SOFAS)		✓	✓	✓	✓	✓
Self-report Assessment		✓	✓	✓	✓	✓
Sleep-wake Assessment (actigraphy monitoring)		✓	✓	✓	✓	✓
In-lab Circadian Assessment		✓		✓		
Blood Sample Collection (Metabolic and Inflammatory Markers)		✓		✓		
Safety, side-effects, and adherence assessment			✓	✓	✓	✓
IP dispensing		✓	✓	✓*	✓*	✓*
IP return			✓	✓		

\*if clinically indicated, at the discretion of the treating clinician

In addition to the visits listed above, safety, side-effects, and adherence assessment will be conducted weekly between weeks 0 and 8 via phone calls.

The Participant timeline is presented in Figure 1 – Study flow chart.

## Sample Size

Sample size was determined based on a previous study of circadian changes in response to Agomelatine [20] where a correlation coefficient of 0.54 was found for the key outcome of interest, namely correlation between change in DLMO and change in depressive symptoms. We conservatively estimated that the correlation coefficient for Brexpiprazole would be smaller, around 0.35 (i.e. a medium effect size), as the effects on the circadian system may be less direct. Assuming an alpha of 0.05 and 80% power for a one-tailed correlation analysis, a sample size of 49 would be required to detect this effect.

## Data Analysis/Statistical methods

Correlations will be performed between change scores (i.e., Visit 2 score minus Visit 1 score) for sleep and circadian measures, and change scores for depressive symptoms. The intention-to-treat principle will be used for missing data, with last observations carried forward. Prior to analysis, scatter plots and box plots with outlier and normality statistics will be generated for all variables to identify outliers and issues with variable distribution. Extreme outliers (beyond three z scores in either direction) will be checked against source data and testing notes to verify whether they are the result of an error in data entry or a specific issue during testing (e.g., equipment failure), and any errors rectified. If they are not the result of an error in data entry, outliers will be curtailed. Pearson's or Spearman's correlations will be selected to perform analyses based on normative or non-normative data distribution; a significance level will be set at  $\alpha=0.05$ . Correlations will be performed between other change scores to assess secondary and tertiary endpoints using the same methodology. Further tertiary endpoints will be assessed by partial correlations comparing categorical variables.

## Patient and public involvement

Clinical professionals working with young people with mental health issues were invited to comment on the study design and procedures. Research findings will be disseminated into the scientific, clinical and wider community.

## **Ethics and dissemination**

This trial has been approved by the Human Research Ethics Committee of the Sydney Local Health District (X19-0417 and 2019/ETH12986, Protocol Version v 1-3, dated 25.02.2021). The study will be conducted in compliance with all stipulations of the protocol, the conditions of ethics committee approval, the NHMRC National Statement on Ethical Conduct in Human Research and the Good Clinical Practice guidelines.

The results of this study will be disseminated as widely as possible into the scientific and broader community. This will include publication in peer-reviewed journals, scholarly book chapters, presentation at conferences and publication in conference proceedings. Publications arising from this project will be deposited into an open access institutional repository, where possible. Results will also be disseminated into the wider community in a format appropriate for a lay audience, through links including the BMC website and social media, as well as newsletters.

## **CONCLUSION**

This clinical trial investigates the effects of the adjunctive brexpiprazole treatment and the associated changes in sleep-wake cycle or circadian parameters in young people with depressive syndromes.

This protocol is one of a series of clinical trials that have been established to support a broader Youth Mental Health Clinical Trial Program at the BMC[86]. A series of clinical trials underpin the broader need to improve diagnosis and treatment outcomes for the youth mental health population. These trials aim to inform personalised treatment plans for specific clinical phenotypes, assisting to provide more effective and targeted interventions, thus necessitating the breadth of assessments used in this clinical trial, to reflect a wider range of questions than just the research questions asked in the current study.

Specifically, this trial will help to understand brexpiprazole's antidepressant mechanism of action in depressed youth with disturbed sleep patterns, and to determine the effectiveness of this treatment in this vulnerable population.

## Figure 1. Study flow chart

Legend: This figure illustrates the study design and participant timeline from referral to the last follow up visit, including withdrawal and safety procedures.

### TRIAL STATUS

Protocol ID: BMC-YMH-005-2018, Version: v 1-3, dated 25/02/2021.

The trial has not commenced recruitment.

### LIST OF ABBREVIATIONS

ABBREVIATION	TERM
AE	Adverse Event
AIMS	Abnormal Involuntary Movement Scale
ANZCTR	Australian New Zealand Clinical Trials Registry
ASRM	Altman Self-Rating Mania scale
AUDIT-C	Alcohol Use Disorders Identification Test- Consumption
BMC	Brain and Mind Centre
BMI	Body Mass Index
B-NSSI-AT	Brief Non-Suicidal Self-Injury Assessment Tool
BPRS	Brief Psychiatric Rating Scale
CAARMS	Comprehensive Assessment of At-Risk Mental States
CGI	Clinical Global Impressions scale
CRP	C-Reactive Protein
C-SSRS	Columbia- Suicide Severity Rating Scale
DLMO	Dim Light Melatonin Onset
DSM-5	Diagnostic and Statistical Manual for Mental Disorders, 5th Edition
EDE	Eating Disorder Examination
EPS	Extrapyramidal Symptoms
ESS	Epworth Sleepiness Scale
HDL	High Density Lipoprotein
HOMA2-IR	Homeostasis Model of Insulin Resistance
HREC	Human Research Ethics Committee
IL	Interleukin
IP	Investigational Product
IPAQ	International Physical Activity Questionnaire
ISI	Insomnia Severity Index
LDL	Low Density Lipoprotein
MADRS	Montgomery-Åsberg Depression Rating Scale
MCTQ	Munich Chronotype Questionnaire
MDD	Major Depressive Disorder
MEQ	Morningness-Eveningness Questionnaire
NEET	Not in Education, Employment or Training
OASIS	Overall Anxiety Severity Impairment Scale

PC-PTSD-5	Primary Care Post-Traumatic Stress Disorder screen
PIS	Participant Information Statement
PQ-16	Prodromal Questionnaire (brief version)
PSQI	Pittsburgh Sleep Quality Index
QIDS-CR	Quick Inventory of Depressive Symptomatology (clinician-rated)
QIDS-SR	Quick Inventory of Depressive Symptomatology (self-report)
SAS	Simpson-Angus Scale
SCID	Structured Clinical Interview for DSM 5
SIDAS	Suicidal Ideation Attributes Scale
SNRI	Selective Serotonin and Norepinephrine Reuptake Inhibitor
SOFAS	Social and Occupational Functioning Assessment Scale
SPAQ	Seasonal Patterns Assessment Questionnaire
SSRI	Selective Serotonin Reuptake Inhibitor
SSSS	Schuster Social Support Scale
TAU	Treatment As Usual
TNF	Tissue Necrosis Factor
WHO-ASSIST	World Health Organisation Alcohol, Smoking, and Substance Involvement Screening Test
WSAS	Work and Social Adjustment Scale
YMRS	Young Mania Rating Scale

## AUTHOR CONTRIBUTIONS

JSC and IBH conceived the study, led the proposal and protocol development. JSC wrote the trial protocol.

AG drafted the first version of the manuscript. NZ drafted the final version of the manuscript with input from other authors. JSC, AG, AN, NZ, YJSS, CW, CR, JJC, CMM, FML, DK and EMS were all involved with modifications to the design of the study and with drafting of this paper. All authors have read and approved the final manuscript.

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## COMPETING INTERESTS

Professor Ian Hickie is the Co-Director, Health and Policy at the Brain and Mind Centre (BMC) University of Sydney, Australia. The BMC operates an early-intervention youth services at Camperdown under contract to headspace. Professor Hickie has previously led community-based and pharmaceutical industry-

1 supported (Wyeth, Eli Lilly, Servier, Pfizer, AstraZeneca) projects focused on the identification and better  
2 management of anxiety and depression. He is the Chief Scientific Advisor to, and a 5% equity shareholder  
3  
4 in, InnoWell Pty Ltd. InnoWell was formed by the University of Sydney (45% equity) and PwC (Australia;  
5  
6 45% equity) to deliver the \$30 M Australian Government-funded Project Synergy (2017-20) and to lead  
7  
8 transformation of mental health services internationally through the use of innovative technologies.  
9  
10

11 Associate Professor Elizabeth M Scott is the Medical Director, Young Adult Mental Health Unit, St  
12  
13 Vincent's Hospital Darlinghurst, Discipline Leader of Adult Mental Health, School of Medicine, University  
14  
15 of Notre Dame, Research Affiliate, The University of Sydney and Consultant Psychiatrist. She has  
16  
17 received honoraria for educational seminars related to the clinical management of depressive disorders  
18  
19 supported by Servier and Eli-Lilly pharmaceuticals. She has participated in a national advisory board for  
20  
21 the antidepressant compound Pristiq, manufactured by Pfizer. She was the National Coordinator of an  
22  
23 antidepressant trial sponsored by Servier.  
24  
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30 Other authors declare no competing interests.  
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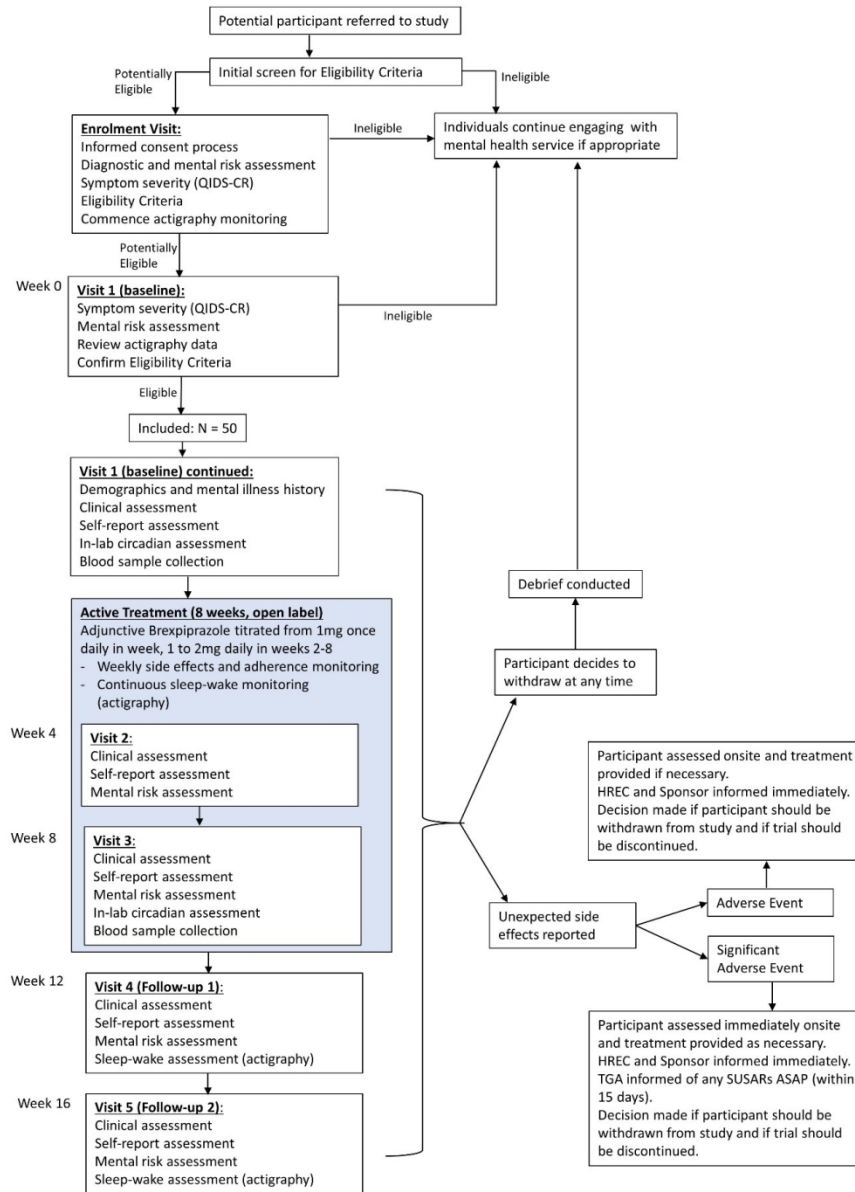
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This figure illustrates the study design and participant timeline from referral to the last follow up visit, including withdrawal and safety procedures.

155x209mm (220 x 220 DPI)

# BMJ Open

## Effects of adjunctive brexpiprazole on sleep-wake and circadian parameters in youth with depressive syndromes: Study protocol for a clinical trial

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Secondary Subject Heading:	Research methods, Mental health, Medical publishing and peer review
Keywords:	MENTAL HEALTH, PSYCHIATRY, Depression & mood disorders < PSYCHIATRY

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Manuscripts

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2 1 **Effects of adjunctive brexpiprazole on sleep-wake and circadian parameters in youth with depressive**  
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4 2 **syndromes: Study protocol for a clinical trial**

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## ABSTRACT

### Introduction

Sleep-wake and circadian disturbance is a key feature of mood disorders with a potential causal role and particular relevance to young people. Brexpiprazole is a second generation antipsychotic medication with demonstrated efficacy as an adjunct to antidepressant treatment for Major Depressive Disorder (MDD) in adults, with preliminary evidence suggesting greater effectiveness in subgroups of depressed patients with sleep disturbances. This clinical trial aims to evaluate the relationships between changes in sleep-wake and circadian parameters and changes in depressive symptoms following adjunctive brexpiprazole treatment in young adults with MDD and sleep-wake disturbance.

### Methods and analysis

This study is designed as a 16 week (8 weeks active treatment, 8 weeks follow up) mechanistic, open-label, single-arm phase IV clinical trial and aims to recruit 50 young people aged 18 to 30 with MDD and sleep-wake cycle disturbance through an early intervention youth mental health clinic in Sydney, Australia. At baseline, participants will undergo multidimensional outcome assessment and subsequently receive 8 weeks of open-label treatment with brexpiprazole as adjunctive to their stable psychotropic medication. Following 4 weeks of treatment, clinical and self-report measures will be repeated. Ambulatory sleep-wake monitoring will be conducted continuously for the duration of treatment. After 8 weeks of treatment, all multidimensional outcome assessments will be repeated. Follow-up visits will be conducted 4 and 8 weeks after trial completion (including sleep-wake, clinical, and self-report assessments). Circadian rhythm biomarkers including salivary melatonin, cortisol, and core body temperature will be collected during an in-lab assessment. Additionally, metabolic, inflammatory, and genetic risk markers will be collected at baseline and after 8 weeks of treatment.

### Ethics and dissemination

This trial protocol has been approved by the Human Research Ethics Committee of the Sydney Local Health District (X19-0417 and 2019/ETH12986, Protocol Version v 1-3, dated 25.02.2021). The results of this study,



1  
2 62 in de-identified form, will be disseminated through publication in peer-reviewed journals, scholarly book  
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4 63 chapters, presentation at conferences and publication in conference proceedings.  
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## 8 65 **Trial Registration**

10 66 Australian New Zealand Clinical Trials Registry (ANZCTR) Number: ACTRN12619001456145p, Date 22  
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13 67 October, 2019.  
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## 17 69 **KEYWORDS:**

20 70 Mental health, adjunctive brexpiprazole, sleep-wake cycle, youth depression.  
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## 24 72 **ARTICLE SUMMARY**

### 26 73 **Strengths and limitations of this study**

- 29 74 • The use of comprehensive assessment battery, including actigraphy and circadian assessment, and  
30  
31 75 collection of metabolic and inflammatory markers to help acquire a greater understanding of the  
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33 76 mechanisms of antidepressant action of adjunctive brexpiprazole.
- 35 77 • This trial will help to inform personalised treatment plans for specific clinical phenotypes, placing the  
37  
38 78 participant at the centre of care.
- 40 79 • As part of the study, all participants will receive a psychoeducational session about sleep and  
41  
42 80 circadian rhythms with information on how to improve their sleep based on their actigraphy data  
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44
- 45 81 • This trial focuses on the measurement of the 24-hour sleep-wake cycle and will not examine the  
46  
47 82 sleep quality or the parameters of any sleep disorder.
- 49 83 • Circadian assessment used in the study will provide important information about the participants  
51  
52 84 current sleep wake cycle patterns but will not include the assessment of the possible factors that  
53  
54 85 may be contributing to circadian rhythms disruption in the long term.  
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## INTRODUCTION

In young adults, Major Depressive Disorder (MDD) is highly prevalent, recurrent, and comorbid with other mental and physical conditions, generating a substantial burden of disease and disability [1, 2]. While multiple psychological and pharmacological treatments are commonly provided, a large proportion of patients fail to respond to first-line psychotherapy or antidepressant treatments [3-10], and augmentation with a second generation antipsychotic is often recommended in these treatment-resistant cases [11, 12]. Sleep-wake cycle disturbances are common features of depressive disorders, including insomnia [13-15], hypersomnia [16, 17], abnormal sleep duration [13, 14], and abnormal timing of 24-hour patterns of rest/activity [18, 19]. Moreover, abnormalities in biological circadian rhythms (e.g., melatonin) have been reported [20, 21], suggesting that in some cases sleep disturbances are accompanied or underpinned by disturbances of the underlying circadian system [22].

The human circadian system is controlled by a master oscillator in the brain's hypothalamus (suprachiasmatic nucleus) which projects to circuits that govern bio-behavioural processes altered in depression (e.g., mood, vigilance, 24-hour sleep-wake cycle). The circadian system is primarily entrained by bright light, and its functioning can be disrupted by factors including aberrant light exposure and irregular sleep-wake behaviours [23, 24]. Adolescents and young adults are particularly vulnerable to circadian perturbations due to significant developmental changes in circadian rhythms across this age period [25], and sleep-wake phase delays are common in young people with depressive disorders [26]. Recently, we reported delayed and disrupted circadian rhythms in a subgroup of young people with depressive disorders (who also presented with greater symptom severity) [27]. During adolescence there is a phase shift in the circadian rhythm of the sleep-wake cycle, such that adolescents typically develop a bio-behavioural preference for going to sleep later and waking later (a manifestation of changes in the biology of the circadian system) [28, 29]. Furthermore, there is some evidence that correction of circadian abnormalities is associated with antidepressant effects of treatments targeting the circadian system such as Agomelatine [30] and light therapy [31].

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4 113 Brexpiprazole is a second generation antipsychotic with demonstrated efficacy by multiple randomised  
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6 114 controlled trials as an adjunct to antidepressant treatment in MDD in adults [32-35]; however the  
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8 115 mechanism of antidepressant action is unknown [36]. The pharmacodynamic properties of brexpiprazole,  
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11 116 together with evidence from preclinical studies, suggest that there may be specific effects on anxiety,  
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13 117 cognitive function, and sleep [36, 37]. Further, there is preliminary evidence to suggest that brexpiprazole  
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15 118 may have greater effectiveness in subgroups of depressed patients with sleep disturbances, anxiety, or  
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17 119 irritability [22, 38]. As an adjunctive treatment in MDD patients with inadequate response to  
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20 120 antidepressant treatment, brexpiprazole has been reported to lead to clinical improvement of sleep  
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22 121 disturbances (e.g., insomnia) and depressive symptoms, as well as improvement of daytime alertness and  
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24 122 functioning [39]. This pattern of changes is consistent with effects on circadian rhythms, with potential  
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26 123 influences on the entire 24-hour pattern of rest/activity, rather than simply on sleep period in isolation.  
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29 124 To improve the personalisation of treatment selection for mood disorders, a greater understanding of the  
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31 125 mechanisms of antidepressant action of specific compounds is needed.  
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35 127 Accordingly, in this clinical trial we aim to investigate whether the effect of brexpiprazole on depressive  
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37 128 symptoms is associated with changes in 24-hour sleep-wake cycle or circadian parameters in young people  
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40 129 with MDD. While disturbances in electrophysiological measures of sleep (e.g., REM sleep) have been  
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42 130 considered by some to represent biomarkers for depression [40-43], this trial focuses instead on the  
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44 131 investigation and measurement of bio-behavioural changes associated with the circadian system (e.g.,  
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46 132 rest/activity, melatonin, cortisol, and core body temperature rhythms), rather than changes in  
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49 133 electrophysiological sleep architecture (which is beyond the scope of this study).  
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## 53 135 **METHODS AND ANALYSIS**

### 55 136 **Study Objectives**

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2 137 The primary objective of this study is to determine if changes in depressive symptoms following adjunctive  
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4 138 brexpiprazole treatment are correlated with changes in sleep-wake cycle or circadian parameters in young  
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6 139 people with depressive syndromes.

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11 141 The secondary objective is to determine if changes in social and occupational functioning following  
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13 142 adjunctive brexpiprazole are correlated with changes in sleep-wake cycle or circadian parameters in young  
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15 143 people with depressive syndromes.

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20 145 The tertiary objectives of this study are to determine if changes in depressive symptoms or changes in  
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22 146 sleep-wake cycle or circadian parameters following adjunctive brexpiprazole treatment are associated  
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24 147 with a range of multidimensional outcome measures in young people with depressive syndromes[44].  
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26 148 These include other mental illness symptoms, self-harm and suicidal thoughts and behaviours, physical  
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28 149 health parameters, alcohol and substance use, and genomic markers.

### 31 150 32 33 151 **Trial design**

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35 152 This investigator-initiated, mechanistic study involving 50 young people with depressive syndromes and  
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37 153 sleep-wake cycle disturbances is designed as a 16-week (8 weeks active treatment, 8 weeks follow-up)  
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39 154 open-label, single-arm, phase IV clinical trial.

### 41 42 155 43 44 156 **Participants**

45  
46 157 Participants aged 18-30 years with a diagnosis of MDD according to DSM-5 criteria on a current  
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48 158 antidepressant treatment of either selective serotonin reuptake inhibitor (SSRI) or serotonin-  
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50 159 norepinephrine reuptake inhibitor (SNRI) with a disrupted sleep-wake cycle will be recruited through the  
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52 160 youth mental health clinics associated with the Brain and Mind Centre (BMC), University of Sydney. All  
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54 161 participants will provide written informed consent. The research team will make explicit to any potential  
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56 162 participants both verbally and in writing (in the Participant Information Statement) that participation is  
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58 163 voluntary and will not affect the patient's care received by the mental health service.

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4 165 The inclusion criteria for this trial are: (i) aged 18-30, (ii) diagnosis of MDD as per DSM-5 (Structured  
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6 166 Clinical Interview for DSM; SCID[45]) criteria, (iii) current major depressive episode (MDE) of moderate  
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9 167 severity as defined by a Quick Inventory of Depressive Symptomatology (QIDS)[46] rating  $\geq 11$  at two  
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11 168 assessments two weeks apart, (iv) failure to respond to at least one adequate (minimum four weeks) trial  
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13 169 of pharmacological treatment, (v) current antidepressant treatment with SSRI or SNRI for at least 6 weeks,  
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15 170 at a stable dose for two weeks prior to study commencement, and (vi) a perturbed sleep-wake cycle as  
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17 171 evidenced by: delayed sleep onset; delayed sleep offset; disrupted sleep; high day-to-day variability of  
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20 172 sleep-wake cycle; non-restorative sleep; or daytime fatigue.

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24 174 Exclusion criteria are: (i) any adjunctive antipsychotic treatment for current episode in the past month, (ii)  
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26 175 use of medications which affect sleep, (iii) primary psychotic disorder diagnosis, (iv) acute suicidal  
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29 176 behaviour (score of 6 on Comprehensive Assessment of At-Risk Mental States (CAARMS) item 7.3[47]), (v)  
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31 177 medical condition contributing to sleep-wake dysfunction, (vi) significant alcohol or substance misuse or  
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33 178 dependence (assessed via DSM-5 SCID[45] and World Health Organisation Alcohol, Smoking and  
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35 179 Substance Involvement Screening Test (WHO-ASSIST[48, 49]), (vii) shift work or (viii) recent transmeridian  
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37 180 travel (i.e., participants will be required to wait three days for each jet lag hour before entering the study),  
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40 181 (ix) previous hypersensitivity to brexpiprazole, (x) taking CYP2D6 or CYP3A4 inhibitors (or other  
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42 182 contraindicated medications listed in the Rexulti product information), and (xi) pregnancy or lactation.

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#### 45 46 47 184 **Study course and procedure**

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49 185 Patients presenting for mental health care who may be eligible for the study will be screened by phone before  
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51 186 being invited to participate and attending an enrolment visit. The enrolment visit will formally assess  
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53 187 eligibility criteria and confirm the presence of MDD as per DSM-5 (SCID)[45]. Participants will be provided  
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55 188 with an actigraphy device (non-invasive wrist-worn device used to objectively measure rest/activity patterns)  
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58 189 and will be given instructions to wear the device for the following two-week period.

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2 191 *Visit 1 (Baseline):* Within two weeks of completing the diagnostic and screening assessments, data from  
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4 192 the actigraphy device will be downloaded and reviewed. A further assessment of depressive symptom  
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6 193 severity (QIDS Clinician-Rated; QIDS-CR)[46] will be conducted to ensure participants meet all inclusion  
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8  
9 194 criteria. Bloods will be collected for assessment of metabolic and inflammatory measures and genomic  
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11 195 analysis. Clinical and self-report assessments will be conducted, as well as circadian assessments in which  
12  
13 196 participants will remain in the sleep lab overnight. The following morning, participants will attend a 1-  
14  
15 197 hour psychoeducation session about sleep and circadian rhythms covering the following topics: i) sleep  
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17 198 and circadian education with tailored discussion based on their personal actigraphy data; ii) individualized  
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19 199 plan for progressive sleep rescheduling; and iii) lifestyle factors and behaviours impacting on sleep (e.g.,  
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21 200 exercise, light, sleep environment, sleep regulation, foods, stress, anxiety, mood).  
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25  
26 202 Once all baseline clinical and self-report assessments have been conducted, and the medical assessment  
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28 203 completed by the study doctor to confirm inclusion and exclusion criteria, participants will be issued with  
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30 204 the study medication to receive 8 weeks of open-label pharmacotherapy with brexpiprazole (REXULTI®-  
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32 205 Lundbeck) as adjunctive to their stable psychotropic medication (treatment as usual). Brexpiprazole will  
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34 206 be provided to participants at Visit 1 (Baseline) and Visit 2 (Week 4) for the following four weeks and will  
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36 207 be titrated from 1 mg once daily in week 1, to 2 mg once daily in weeks 2-8.  
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42 209 Patients will receive 2mg/day, once daily as tablets, for oral use. The brexpiprazole dosage will be steadily  
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44 210 increased from 1mg/day during week 1, to 2mg/day during weeks 2-8 (up-titration). This is the dosage and  
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46 211 titration regime recommended for adjunctive use in major depression by the Federal Drug Administration  
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48 212 (USA). Several previous clinical trials have used this titration regime from 1mg to 2mg [33, 39, 50], and a  
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50 213 dose of 2mg has been shown to be effective in reducing depressive symptoms [32]. As doses higher than  
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52 214 2mg have been shown to increase incidence of akathisia [36], a maximum dose of 2mg will be used in the  
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54 215 present study to minimise side effects.  
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2 217 *Monitoring visits:* Participants will be contacted by telephone on a weekly basis for the duration of the 8-  
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4 218 week treatment period to monitor adverse events and adherence. Any changes in concomitant  
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6 219 medications will also be investigated and recorded. In addition, participants will be provided with a  
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9 220 medication diary and asked to complete during the study to monitor adherence. More detailed  
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11 221 information about potential side-effects will be further assessed by the study doctor at visits 2, 3, 4 and 5  
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13 222 using the UKU Side Effect Rating Scale [51], Abnormal Involuntary Movement Scale (AIMS) [52] and the  
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15 223 Simpson-Angus Scale (SAS) [53] for evaluation of extrapyramidal symptoms (EPS).

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20 225 *Visit 2 (Week 4):* Following four weeks of the treatment phase, participants will return for clinical and self-  
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22 226 report assessments to assess changes in clinical and functional measures.

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26  
27 228 *Visit 3 (Week 8):* Following eight weeks of the treatment phase, participants will return to complete clinical  
28  
29 229 and self-report assessments and will also complete a second circadian (overnight) in-lab assessment.  
30  
31 230 Bloods will be collected at this visit for follow-up metabolic and inflammatory markers.

32  
33 231  
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35  
36 232 *Visit 4 and 5 (Follow-up visits 1 and 2, 12 and 16 weeks respectively):* Twelve and sixteen weeks after  
37  
38 233 commencing treatment (i.e., four and eight weeks after completing the eight-week treatment period  
39  
40 234 respectively), participants will return to complete clinical and self-report assessments. Participants will be  
41  
42 235 provided with an actigraphy device to wear for two weeks prior to these assessments.

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45 236  
46  
47 237 Participants will be reimbursed for their time and the cost of transportation to and from the research sites.

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## 50 51 239 **Outcomes**

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53 240

### 54 55 241 **Primary Outcome Measures**

56  
57  
58 242 The primary endpoint will be the correlation between change in sleep-wake and circadian parameters and  
59  
60 243 change in depressive symptoms from baseline to week eight. Notably, the primary depressive symptom

measures (QIDS-CR total score, QIDS-Self Report (QIDS-SR) total score, The Montgomery–Åsberg Depression Rating Scale (MADRS) total score) contain sleep items. These will be removed from these scales for analyses to provide a measure of depressive symptoms not biased by changes in sleep-wake parameters.

Primary sleep-wake and circadian variables of interest include actigraphy parameters, as well as in-lab circadian and self-report measures.

### Secondary Outcome Measures

The secondary endpoint will be correlation between change in sleep-wake and circadian parameters and change in functioning from baseline to week eight.

### Tertiary Outcome Measures

Tertiary endpoints will be correlation between change in sleep-wake and circadian parameters and other multidimensional outcome measures based on assessments of symptoms, self-harm and suicidal thoughts and behaviours, physical health, and alcohol and substance use.

Further tertiary endpoints will be comparison of primary endpoints between Clinical Stages [54-57], illness trajectories [58], and genomic variants with potential relevance to mood disorders and/or circadian rhythms (e.g. CLOCK, BMAL1).

Detailed outcome measures are summarized in Table 1. **Table 1 – Primary, Secondary and Tertiary**

### Outcome Measures

Primary Outcome Measures (Correlation between change in sleep-wake and circadian parameters and change in depressive symptoms from baseline to week eight)	Secondary Outcome Measures (Correlation between change in sleep-wake and circadian parameters and change in functioning from baseline to week eight)	Tertiary Outcome measures (Correlation between change in sleep-wake and circadian parameters and other multidimensional outcome measures)
Primary depressive symptom measures:	Functioning measures:	Symptom Measures:



<p>1</p> <p>2</p> <p>3</p> <p>4</p> <p>5</p> <p>6</p> <p>7</p> <p>8</p> <p>9</p> <p>10</p> <p>11</p> <p>12</p> <p>13</p> <p>14</p> <p>15</p> <p>16</p> <p>17</p> <p>18</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p> <p>25</p> <p>26</p> <p>27</p> <p>28</p> <p>29</p> <p>30</p> <p>31</p> <p>32</p> <p>33</p> <p>34</p> <p>35</p> <p>36</p> <p>37</p> <p>38</p> <p>39</p> <p>40</p> <p>41</p> <p>42</p> <p>43</p> <p>44</p> <p>45</p> <p>46</p> <p>47</p> <p>48</p> <p>49</p> <p>50</p> <p>51</p> <p>52</p> <p>53</p> <p>54</p> <p>55</p> <p>56</p> <p>57</p> <p>58</p> <p>59</p> <p>60</p> <ul style="list-style-type: none"> <li>• QIDS-CR total score (minus sleep items)</li> <li>• QIDS-Self Report (QIDS-SR) total score (minus sleep items)</li> <li>• The Montgomery-Åsberg Depression Rating Scale (MADRS) total score (minus sleep items)</li> </ul> <p><b>Primary sleep-wake and circadian variables of interest:</b></p> <p>Actigraphy parameters (in the two-week period prior to baseline and prior to week eight):</p> <ul style="list-style-type: none"> <li>• Sleep onset time</li> <li>• Sleep offset (wake) time</li> <li>• Total sleep time (duration)</li> <li>• Wake after sleep onset (estimation of number of minutes awake during the sleep period)</li> <li>• Sleep efficiency (% of sleep period estimated as sleep)</li> <li>• Inter-daily stability</li> <li>• Intra-daily variability</li> </ul> <p><b>In-lab circadian measures:</b></p> <ul style="list-style-type: none"> <li>• Dim Light Melatonin Onset (DLMO) timing</li> <li>• Phase angle (time lapse) between DLMO and habitual sleep</li> <li>• Core body temperature nadir</li> <li>• Evening cortisol area under the curve</li> </ul> <p><b>Self-report measures:</b></p> <ul style="list-style-type: none"> <li>• Non-restorative sleep score (based on the Pittsburgh Sleep Quality Index</li> </ul>	<ul style="list-style-type: none"> <li>• Social and Occupational Functioning Assessment Scale (SOFAS) rating</li> <li>• The Work and Social Adjustment Scale (WSAS) total score</li> <li>• Adapted Schuster Social Support Scale (SSSS) total score</li> <li>• Not in Education, Employment, or Training (NEET) status</li> <li>• Number of days 'out of role' (unable to perform usual activities) in the past 30 days</li> </ul>	<ul style="list-style-type: none"> <li>• Young Mania Rating Scale (YMRS) total score</li> <li>• Brief Psychiatric Rating Scale (BPRS) total score and subscale scores</li> <li>• Overall Anxiety Severity Impairment Scale (OASIS) total score</li> <li>• Altman Self-Rating Mania scale (ASRM) total score</li> <li>• Prodromal Questionnaire (brief version) (PQ-16) total score</li> <li>• DSM-5 Primary Care Post-Traumatic Stress Disorder screen (PC-PTSD-5) total score</li> <li>• Adapted Eating Disorder Examination (EDE) total score</li> <li>• Clinical Global Impressions scale (CGI) severity and improvement scores</li> </ul> <p><b>Self-harm and suicidal thoughts and behaviours:</b></p> <ul style="list-style-type: none"> <li>• Suicidal risk (score from Suicidal Ideation Attributes Scale (SIDAS) and Columbia-Suicide Severity Rating Scale (C-SSRS) items)</li> <li>• Adapted Brief Non-Suicidal Self-Injury Assessment Tool (B-NSSI-AT) total score</li> </ul> <p><b>Physical Health:</b></p> <ul style="list-style-type: none"> <li>• Body Mass Index (BMI) calculated from height and weight</li> <li>• Waist circumference</li> <li>• International Physical Activity Questionnaire (IPAQ) total score</li> <li>• Metabolic blood markers including triglycerides, cholesterol (total, Low Density Lipoprotein (LDL), High Density Lipoprotein (HDL)), and Homeostasis</li> </ul>
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<p>(PSQI), and Munich Chronotype Questionnaire (MCTQ)</p> <ul style="list-style-type: none"> <li>• <i>Pittsburgh Sleep Quality Index (PSQI)</i> total score</li> <li>• <i>Epworth Sleepiness Score (ESS)</i> total score</li> <li>• <i>Insomnia Severity Index (ISI)</i> total score</li> <li>• <i>Morningness -Eveningness Questionnaire (MEQ)</i> total score*</li> <li>• <i>Seasonal Pattern Assessment Questionnaire (SPAQ)</i> total score*</li> </ul> <p>*Baseline scores will be used rather than change scores as these are trait measures</p>		<p>Model of Insulin Resistance (HOMA2-IR) calculated from fasting glucose and insulin measures</p> <ul style="list-style-type: none"> <li>• Inflammatory blood markers including Interleukin-1<math>\beta</math> (IL-1<math>\beta</math>), Interleukin-6 (IL-6), Tissue Necrosis Factor (TNF-<math>\alpha</math>), C-Reactive Protein (CRP)</li> </ul> <p><b>Alcohol and Substance Use:</b></p> <ul style="list-style-type: none"> <li>• World Health Organisation Alcohol, Smoking, and Substance Involvement Screening Test (WHO ASSIST) score for tobacco, and cannabis</li> <li>• Alcohol Use Disorders Identification Test-Consumption (AUDIT C) total score</li> <li>• WHO ASSIST alcohol-related impairment</li> <li>• Age of onset of alcohol use</li> </ul> <p><b>Comparison of primary endpoints between:</b></p> <ul style="list-style-type: none"> <li>• Clinical Stages</li> <li>• Illness Trajectories</li> <li>• Genomic variants with potential relevance to mood disorders and/or circadian rhythms (e.g., CLOCK, BMAL1).</li> </ul>
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**Assessments**

Assessments used here are based on the multidimensional assessment and outcomes framework [44] and include clinical and self-report ratings of mental health symptoms, social and occupational functioning, self-harm, suicidal thoughts and behaviours, physical health, alcohol and substance use, illness type, stage and trajectory, as well as circadian parameters and metabolic, inflammatory and genomic markers.

1  
2 273 Our recent research [44, 59-61] indicates the capacity of the multidimensional outcomes framework to  
3  
4 274 further our understanding of the pathophysiological mechanisms and illness progression in this cohort, as  
5  
6 275 well as to inform more personalized and measurement-based models of care.  
7

8  
9 276

#### 10 11 277 Diagnostic assessments

12  
13 278 The presence of MDD and any comorbidity will be evaluated using the Structured Clinical Interview for  
14  
15 279 DSM-5 Axis I Disorders (SCID) [45]. This assessment is expected to take 30-75 minutes to complete.  
16

17  
18 280

#### 19 20 281 Mental Risk Assessment

21  
22 282 Acute suicidal behaviour will be assessed by relevant subscale of the Comprehensive Assessment of At-  
23  
24 283 Risk Mental States (CAARMS) [47]. This assessment is expected to take 5 minutes to complete.  
25

26  
27 284

#### 28 29 285 Clinical Assessments

30  
31 286 1. *Clinical-rated Quick Inventory of Depressive Symptomatology (QIDS-CR)* [46]: assesses the nine  
32  
33 287 criterion symptom domains designated by the DSM to diagnose a MDE.

34  
35 288 2. *Montgomery-Åsberg Depression Rating Scale (MADRS)* [62]: will also be used to assess depressive  
36  
37 289 symptoms, to allow for direct comparisons with previous studies of brexpiprazole in MDD.

38  
39  
40 290 3. *Young Mania Rating Scale (YMRS)* [63]: an 11-item, multiple-choice diagnostic questionnaire which  
41  
42 291 psychiatrists use to measure the severity of manic episodes.

43  
44 292 4. *Brief Psychiatric Rating Scale (BPRS)* [64]: used to measure psychiatric symptoms (e.g., depression,  
45  
46 293 anxiety, hallucinations, unusual behaviour).

47  
48  
49 294 5. *Social and Occupational Functioning Assessment Scale (SOFAS)* [65]: clinician-rated measure used  
50  
51 295 to assess functioning on a 0-100 scale (lower scores suggesting greater impairment).

52  
53 296 6. *Clinical Global Impressions scale (CGI)* [66]: will be used as a measure of clinical improvement.

54  
55  
56  
57 297 7. Participants will also be rated on previously established *clinical stage* [54-57] and *illness trajectory*  
58  
59 298 [58] models on the basis of information collected throughout the clinical interview. The clinical staging  
60

1  
2 299 framework differentiates those in the earliest phases of mental health problems with non-specific  
3  
4 300 clinical presentations (stage 1a; ‘help-seeking’) from those at greater-risk with more specific, sub-  
5  
6 301 threshold presentations (stage 1b; ‘attenuated syndromes’) and those who have already reached a  
7  
8  
9 302 threshold for a progressive or recurrent disorder meeting diagnostic criteria (stage 2, 3, or 4). The  
10  
11 303 illness trajectory model is a novel tripartite framework based on three proposed pathophysiological  
12  
13 304 pathways leading to youth-onset mental disorders: (i) “neurodevelopmental-psychosis”, (ii)  
14  
15 305 “circadian-bipolar spectrum”, and (iii) “hyperarousal-anxious depression”[67-69].

17  
18 306 8. *World Health Organisation (WHO) Alcohol, Smoking and Substance Involvement Screening Test*  
19  
20 307 (*WHO-ASSIST*) [48, 49]: a reliable, culturally adaptable, valid screening test for problematic or risky  
21  
22 308 substance use.

24 309 The clinical interview is expected to take around 35 minutes to complete.

#### 29 311 Self-report Assessments

- 31 312 1. *Demographics and Mental Health History*: including details of work and education, physical health  
32  
33 313 (height, weight, waist circumference), history of mental health, and family history
- 35 314 2. *International Physical Activity Questionnaire (IPAQ) - short version* [70, 71]: 7-item questionnaire  
36  
37 315 providing internationally comparable data on health-related physical activity.
- 40 316 3. *Alcohol Use Disorders Identification Test – Consumption (AUDIT-C)* [72]: includes three short  
41  
42 317 questions that estimate alcohol consumption in a standard, meaningful, non-judgmental manner.  
43  
44 318 Additional questions assessing age of onset of alcohol consumption will also be used.
- 46 319 4. *Suicidal Ideation Attributes Scale (SIDAS)* [73]: 5-item self-report questionnaire assessing the  
47  
48 320 frequency, controllability, closeness to attempt, distress, and interference with daily activities on  
49  
50 321 a 10-point Likert scale over the past month.
- 53 322 5. *Columbia-Suicide Severity Rating Scale (C-SSRS)* [74]: The scale comprises 3 sections: suicidal  
54  
55 323 ideation, intensity of ideation, and suicidal behaviour. A self-rating adaptation will be used in  
56  
57 324 combination with the SIDAS.

- 1  
2 325 6. *Brief Non-Suicidal Self-Injury Assessment Tool (B-NSSI-AT)* [75]: designed to assess primary (such  
3  
4 326 as form, frequency, and function) and secondary (including but not limited to NSSI habituation;  
5  
6 327 contexts in which NSSI is practiced; and NSSI perceived life interference, treatment, and impacts)  
7  
8  
9 328 NSSI characteristics.
- 10  
11 329 7. *Quick Inventory of Depressive Symptomatology – self-report (QIDS-SR)* [76]: a self-rating (SR)  
12  
13 330 version includes 16 questions with equivalent weightings (0-3) for each symptom item that  
14  
15 331 assesses the nine criterion symptom domains designated by the DSM-IV to diagnose a MDE.
- 16  
17 332 8. *Overall Anxiety Severity Impairment Scale (OASIS)* [77]: 5-item self-report measure used to assess  
18  
19  
20 333 severity and impairment associated with any anxiety disorder or multiple anxiety disorders.
- 21  
22 334 9. *Altman Self-Rating Mania Scale (ASRM)* [78]: 5-item self-rating scale designed to assess the  
23  
24 335 presence and/or severity of manic symptoms.
- 25  
26 336 10. *Primary Care Post-Traumatic Stress Disorder Screen for DSM-5 (PC-PTSD-5)* [79]: 5-item screen  
27  
28  
29 337 designed for use in primary care settings to identify respondents with probable PTSD.
- 30  
31 338 11. *Prodromal Questionnaire (PQ-16)* [80]: self-report screen for use in secondary mental health care  
32  
33 339 services to select subjects for psychosis risk.
- 34  
35 340 12. *Eating Disorder Examination (EDE)* [81, 82]: comprises a range of health-related and demographic  
36  
37  
38 341 questions, including present height and weight, and a detailed and comprehensive assessment of  
39  
40 342 symptoms, particularly binge eating. In this study, three eating disorder behaviours are assessed:  
41  
42 343 binge eating, purging, and strict dieting or fasting.  
43  
44 344 13. *Sleep questions*: 7 questions regarding time falling asleep, waking up during weekdays and  
45  
46  
47 345 weekends, hours of sleep, feelings when waking up. Sleep timing items are based on the  
48  
49 346 Pittsburgh Sleep Quality Index (PSQI) and Munich Chrono Type Questionnaire (MCTQ), while sleep  
50  
51 347 quality items are based on expert consensus in the literature.  
52  
53 348 14. *Work and Social Adjustment Scale (WSAS)* [83]: 5-item scale of functional impairment attributable  
54  
55  
56 349 to an identified problem.  
57  
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1  
2 350 15. *Schuster Social Support Scale (SSSS)* [84]: 15-item measure of social support used to examine an  
3  
4 351 individual's social relationships with others (relatives, friends, spouse) and the associated impact  
5  
6 352 on their emotional functioning  
7

8  
9 353 16. *Additional sleep questionnaires*: participants will complete the BMC sleep-wake self-report  
10  
11 354 questionnaire battery including questions regarding ethnicity, caffeine consumption, menstrual  
12  
13 355 cycle, visual impairments, and non-restorative sleep, as well as the *Pittsburgh Sleep Quality*  
14  
15 356 *Inventory (PSQI)* [85], *Epworth Sleepiness Scale (ESS)* [86], *Insomnia Severity Index (ISI)* [87], *Horne-*  
16  
17 357 *Ostberg Morningness-Eveningness Questionnaire (MEQ)* [88], and the *Seasonal Patterns*  
18  
19 358 *Assessment Questionnaire (SPAQ)* [89].  
20  
21

22 359 The questionnaires are tailored (using skip logic) to the individual so the amount of time taken to complete  
23  
24 360 the questionnaire varies, but we estimate that on average the self-report assessment will take 45 minutes  
25  
26 361 to complete.  
27  
28

### 29 362

#### 30 363 **Sleep wake assessments**

31 364 24-hour sleep-wake and circadian rest-activity parameters will be measured by actigraphy  
32  
33 365 recordings. Actigraphy is a non-invasive tool to objectively measure activity profiles used to estimate  
34  
35 366 sleep and circadian patterns based on validated algorithms. Participants will be asked to complete  
36  
37 367 a sleep diary and to wear an actigraph (GENEActiv device; Activinsights, Kimbolton, UK) on the non-  
38  
39 368 dominant wrist for at least 10 days prior to commencing the study, and continuously for the 8-week  
40  
41 369 treatment phase. The device is comfortable and easy to use, battery operated wrist-worn device,  
42  
43 370 similar in appearance to Fitbit, designed to record and provide data on movement, light,  
44  
45 371 temperature and sleep patterns. The device will provide objective monitoring of participants' 24-  
46  
47 372 hour circadian rhythm, including their sleep onset and duration, rise time, any night-time sleep  
48  
49 373 interruptions, and activity patterns (for details, see Table 1). The device allows for the outputting of  
50  
51 374 real time raw measurement data for up to a month without charging. Instructions will be provided  
52  
53 375 to participants on how to use the device upon their recruitment into the study. Two-week actigraphy  
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1  
2 376 recordings will also be completed at the 12- and 16-week follow up assessments. The GENEActiv  
3  
4 377 devices have been validated against several types of accelerometry-based activity monitors [90-93]  
5  
6  
7 378 as well as for sleep-wake scoring [94, 95]. For decades, actigraphy monitors like the GENEActiv  
8  
9 379 devices have been used extensively in research to measure sleep and activity patterns in diverse  
10  
11  
12 380 clinical settings including sleep disorders, medical illnesses (e.g. cancer, neurodegenerative  
13  
14 381 diseases) and mental disorders (e.g. anxiety, depression, bipolar, and psychotic disorders) [19, 96,  
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17 382 97].

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### **In-Lab Circadian Assessment**

Biological circadian rhythms will be measured in an evening/overnight recording period, including collection of salivary melatonin, salivary cortisol, and core body temperature to characterise 24-hour rhythms. All circadian assessments will be performed in accordance with established Dim Light Melatonin Onset (DLMO) protocols [98-101]. For details on the parameters measured, please refer to the in-lab circadian measures in Table 1.

### **Metabolic and inflammatory markers**

The following markers will be collected at Baseline and 8-weeks follow up visits: (i) Triglycerides, (ii) Cholesterol (including total, High Density Lipoprotein (HDL), and Low-Density Lipoprotein (LDL)), (iii) Fasting glucose, (iv) Fasting insulin, (v) Interleukin (IL)-1 $\beta$ , (vi) IL-6, (vii) Tissue Necrosis Factor (TNF)- $\alpha$ , (viii) C-Reactive Protein (CRP). Height, weight, and waist circumference will also be recorded. Furthermore, insulin resistance will be estimated based on paired fasting plasma glucose and insulin levels [102] by the updated homeostatic model assessment (HOMA2-IR) using iHOMA2 software V.8.8 [103].

### **Genomics**

Additional blood will be collected at baseline for the assessment of genomic risk markers as per established procedures from the University of Queensland Human Studies Unit.

1  
2 402 The schedule of trial assessments is summarized in Table 2.

3  
4 403 **Table 2. Schedule of assessments**

5  
6 404

	Enrolment Visit	Visit 1 (Baseline)	Visit 2 (Week 4)	Visit 3 (Week 8)	Visit 4 (Follow-up 1)	Visit 5 (Follow-up 2)
<i>Study week</i>		<i>0</i>	<i>4</i>	<i>8</i>	<i>12</i>	<i>16</i>
Informed Consent	✓					
Inclusion/Exclusion Criteria	✓	✓				
Diagnostic Assessment (SCID)	✓					
Mental Risk Assessment (CAARMS)	✓	✓	✓	✓	✓	✓
Demographics and Mental Illness History		✓				
Clinical Assessment (QIDS- CR, MADRS, YMRS, BPRS, SOFAS)		✓	✓	✓	✓	✓
Self-report Assessment		✓	✓	✓	✓	✓
Sleep-wake Assessment (actigraphy monitoring)		✓	✓	✓	✓	✓
In-lab Circadian Assessment		✓		✓		
Blood Sample Collection (Metabolic and Inflammatory Markers)		✓		✓		
Safety, side-effects, and adherence assessment			✓	✓	✓	✓
IP dispensing		✓	✓	✓*	✓*	✓*
IP return			✓	✓		

31 405 \*if clinically indicated, at the discretion of the treating clinician

32  
33 406 In addition to the visits listed above, safety, side-effects, and adherence assessment will be conducted  
34  
35  
36 407 weekly between weeks 0 and 8 via phone calls.

37  
38 408  
39  
40 409 The Participant timeline is presented in Figure 1 – Study flow chart.

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42 410

#### 43 411 **Safety and Side-Effects Monitoring**

44  
45 412 Previous studies have shown that brexpiprazole is generally well tolerated, with no unexpected or severe  
46  
47 413 side effects [32, 35, 104, 105].

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50  
51 415 Safety and tolerability of the investigational product will be closely monitored throughout the trial. For the  
52  
53 416 duration of the 8-week treatment period, weekly phone calls will be conducted to participants to monitor  
54  
55 417 safety and elicit information regarding side effects and potential adverse events. Any changes in concomitant  
56  
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1  
2 418 medications will also be investigated and recorded. In addition, participants will be provided with a  
3  
4 419 medication diary and asked to complete during the study to monitor tolerability and adherence.  
5

6 420  
7  
8  
9 421 Further formal assessment of side effects and potential adverse events following the end of the treatment  
10  
11 422 phase will be conducted at the two follow-up visits (visit 4 and 5). At the baseline visit, participants will be  
12  
13 423 informed that any serious negative side effects should be reported to the study doctor immediately and will  
14  
15 424 be provided with the relevant contact details to do so.  
16

17  
18 425  
19  
20 426 All Adverse Events will be assessed for causality and symptom severity according to the study protocol and  
21  
22 427 followed up by the study doctor if required. In the occurrence of a Serious Adverse Event, appropriate  
23  
24 428 diagnostic and therapeutic measures will be taken and the participant will be kept under observation for as  
25  
26 429 long as is medically indicated. The Principal Investigator will then determine if the seriousness of the event  
27  
28  
29 430 warrants the removal of the participant from the study or abandonment of the study. For serious side effects  
30  
31 431 or medical problems, the patient may be taken immediately to Royal Prince Alfred Hospital for further  
32  
33 432 treatment. The Principal Investigator will ensure that follow-up of the participant is appropriate to the nature  
34  
35 433 of any event, and that it continues until resolution.  
36

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38 434  
39  
40 435 Throughout the trial the study doctor will monitor participants for pregnancy. It is not currently included  
41  
42 436 in the protocol, but the trial Standard Operating Procedures manual explains that the study doctor will be  
43  
44 437 giving relevant contraception advice to the participants based on the current investigational product  
45  
46 438 information.  
47

48  
49 439  
50  
51 440 According to the investigational product information, participants will be advised to not drive a car,  
52  
53 441 operate machinery, or do other dangerous activities until they know how the investigational product  
54  
55 442 affects them, as it may induce drowsiness in some subjects.  
56

57  
58 443  
59  
60 444 **Sample Size**

1  
2 445 Sample size was determined based on a previous study of circadian changes in response to Agomelatine  
3  
4 446 [30] where a correlation coefficient of 0.54 was found for the key outcome of interest, namely correlation  
5  
6 447 between change in DLMO and change in depressive symptoms. We conservatively estimated that the  
7  
8 448 correlation coefficient for Brexpiprazole would be smaller, around 0.35 (i.e., a medium effect size), as the  
9  
10  
11 449 effects on the circadian system may be less direct. Assuming an alpha of 0.05 and 80% power for a one-  
12  
13 450 tailed correlation analysis, a sample size of 49 would be required to detect this effect.  
14

15 451

### 17 452 **Data Analysis/Statistical methods**

19  
20 453 Correlations will be performed between change scores (i.e., Visit 2 score minus Visit 1 score) for sleep and  
21  
22 454 circadian measures, and change scores for depressive symptoms. The intention-to-treat principle will be used  
23  
24 455 for missing data, with last observations carried forward. Prior to analysis, scatter plots and box plots with  
25  
26 456 outlier and normality statistics will be generated for all variables to identify outliers and issues with variable  
27  
28  
29 457 distribution. Extreme outliers (beyond three z scores in either direction) will be checked against source data  
30  
31 458 and testing notes to verify whether they are the result of an error in data entry or a specific issue during  
32  
33 459 testing (e.g., equipment failure), and any errors rectified. If they are not the result of an error in data entry,  
34  
35 460 outliers will be curtailed. Pearson's or Spearman's correlations will be selected to perform analyses based on  
36  
37  
38 461 normative or non-normative data distribution; a significance level will be set at  $\alpha=0.05$ . Correlations will be  
39  
40 462 performed between other change scores to assess secondary and tertiary endpoints using the same  
41  
42 463 methodology. Further tertiary endpoints will be assessed by partial correlations comparing categorical  
43  
44 464 variables.  
45

### 47 465 48 49 466 **Patient and public involvement**

50  
51 467 Clinical professionals working with young people with mental health issues were invited to comment on the  
52  
53 468 study design and procedures. Research findings will be disseminated into the scientific, clinical, and wider  
54  
55 469 community.  
56  
57  
58 470  
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1  
2 471 **Ethics and dissemination**  
3  
4 472 This trial has been approved by the Human Research Ethics Committee of the Sydney Local Health District  
5  
6 473 (X19-0417 and 2019/ETH12986, Protocol Version v 1-3, dated 25.02.2021). The study will be conducted in  
7  
8 474 compliance with all stipulations of the protocol, the conditions of ethics committee approval, the NHMRC  
9  
10 National Statement on Ethical Conduct in Human Research and the Good Clinical Practice guidelines.  
11 475  
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15 477 The results of this study will be disseminated as widely as possible into the scientific and broader community.  
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17 478 This will include publication in peer-reviewed journals, scholarly book chapters, presentation at conferences  
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19 and publication in conference proceedings. Publications arising from this project will be deposited into an  
20 479  
21 open access institutional repository, where possible. Results will also be disseminated into the wider  
22 480  
23 community in a format appropriate for a lay audience, through links including the BMC website and social  
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25 media, as well as newsletters.  
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31 484 **Figure 1. Study flow chart**

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33 Legend: This figure illustrates the study design and participant timeline from referral to the last follow up  
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35 visit, including withdrawal and safety procedures.  
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40 488 **TRIAL STATUS**

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42 Protocol ID: BMC-YMH-005-2018, Version: v 1-3, dated 25/02/2021.  
43 489  
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45 490 The trial has not commenced recruitment.  
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49 492 **LIST OF ABBREVIATIONS**  
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ABBREVIATION	TERM
AE	Adverse Event
AIMS	Abnormal Involuntary Movement Scale
ANZCTR	Australian New Zealand Clinical Trials Registry
ASRM	Altman Self-Rating Mania scale
AUDIT-C	Alcohol Use Disorders Identification Test- Consumption
BMC	Brain and Mind Centre

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BMI	Body Mass Index
B-NSSI-AT	Brief Non-Suicidal Self-Injury Assessment Tool
BPRS	Brief Psychiatric Rating Scale
CAARMS	Comprehensive Assessment of At-Risk Mental States
CGI	Clinical Global Impressions scale
CRP	C-Reactive Protein
C-SSRS	Columbia- Suicide Severity Rating Scale
DLMO	Dim Light Melatonin Onset
DSM-5	Diagnostic and Statistical Manual for Mental Disorders, 5th Edition
EDE	Eating Disorder Examination
EPS	Extrapyramidal Symptoms
ESS	Epworth Sleepiness Scale
HDL	High Density Lipoprotein
HOMA2-IR	Homeostasis Model of Insulin Resistance
HREC	Human Research Ethics Committee
IL	Interleukin
IP	Investigational Product
IPAQ	International Physical Activity Questionnaire
ISI	Insomnia Severity Index
LDL	Low Density Lipoprotein
MADRS	Montgomery-Åsberg Depression Rating Scale
MCTQ	Munich Chronotype Questionnaire
MDD	Major Depressive Disorder
MEQ	Morningness-Eveningness Questionnaire
NEET	Not in Education, Employment or Training
OASIS	Overall Anxiety Severity Impairment Scale
PC-PTSD-5	Primary Care Post-Traumatic Stress Disorder screen
PIS	Participant Information Statement
PQ-16	Prodromal Questionnaire (brief version)
PSQI	Pittsburgh Sleep Quality Index
QIDS-CR	Quick Inventory of Depressive Symptomatology (clinician-rated)
QIDS-SR	Quick Inventory of Depressive Symptomatology (self-report)
SAS	Simpson-Angus Scale
SCID	Structured Clinical Interview for DSM 5
SIDAS	Suicidal Ideation Attributes Scale
SNRI	Selective Serotonin and Norepinephrine Reuptake Inhibitor
SOFAS	Social and Occupational Functioning Assessment Scale
SPAQ	Seasonal Patterns Assessment Questionnaire
SSRI	Selective Serotonin Reuptake Inhibitor
SSSS	Schuster Social Support Scale
TAU	Treatment As Usual
TNF	Tissue Necrosis Factor
WHO-ASSIST	World Health Organisation Alcohol, Smoking, and Substance Involvement Screening Test
WSAS	Work and Social Adjustment Scale
YMRS	Young Mania Rating Scale

#### AUTHOR CONTRIBUTIONS

1  
2 495 JSC and IBH conceived the study, led the proposal and protocol development. JSC wrote the trial protocol.  
3  
4 496 AG drafted the first version of the manuscript. NZ drafted the final version of the manuscript with input from  
5  
6 497 other authors. JSC, AG, AN, NZ, YJSS, CW, CR, JJC, CMM, FML, DK and EMS were all involved with modifications  
7  
8  
9 498 to the design of the study and with drafting of this paper. All authors have read and approved the final  
10  
11 499 manuscript.

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18  
19 502 (award/grant number is not applicable).

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27  
28 506 Leadership Fellowship.

## 33 508 **COMPETING INTERESTS**

35 509 Professor Ian Hickie is the Co-Director, Health and Policy at the Brain and Mind Centre (BMC) University of  
36  
37 510 Sydney, Australia. The BMC operates an early-intervention youth services at Camperdown under contract to  
38  
39  
40 511 headspace. Professor Hickie has previously led community-based and pharmaceutical industry-supported  
41  
42 512 (Wyeth, Eli Lilly, Servier, Pfizer, AstraZeneca) projects focused on the identification and better management  
43  
44 513 of anxiety and depression. He is the Chief Scientific Advisor to, and a 5% equity shareholder in, InnoWell Pty  
45  
46 514 Ltd. InnoWell was formed by the University of Sydney (45% equity) and PwC (Australia; 45% equity) to deliver  
47  
48  
49 515 the \$30 M Australian Government-funded Project Synergy (2017-20) and to lead transformation of mental  
50  
51 516 health services internationally through the use of innovative technologies.

55 518 Associate Professor Elizabeth M Scott is the Medical Director, Young Adult Mental Health Unit, St Vincent's  
56  
57  
58 519 Hospital Darlinghurst, Discipline Leader of Adult Mental Health, School of Medicine, University of Notre  
59  
60 520 Dame, Research Affiliate, The University of Sydney and Consultant Psychiatrist. She has received honoraria

1  
2 521 for educational seminars related to the clinical management of depressive disorders supported by Servier  
3  
4 522 and Eli-Lilly pharmaceuticals. She has participated in a national advisory board for the antidepressant  
5  
6 523 compound Pristiq, manufactured by Pfizer. She was the National Coordinator of an antidepressant trial  
7  
8  
9 524 sponsored by Servier.

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11 525  
12 526 Other authors declare no competing interests.  
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16 528 **DATA AVAILABILITY STATEMENT**

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18  
19 529 As this trial has not commenced recruitment, no data is available at present. Once the dataset is generated,  
20  
21 530 de-identified data may be made available from the corresponding author upon reasonable request.  
22

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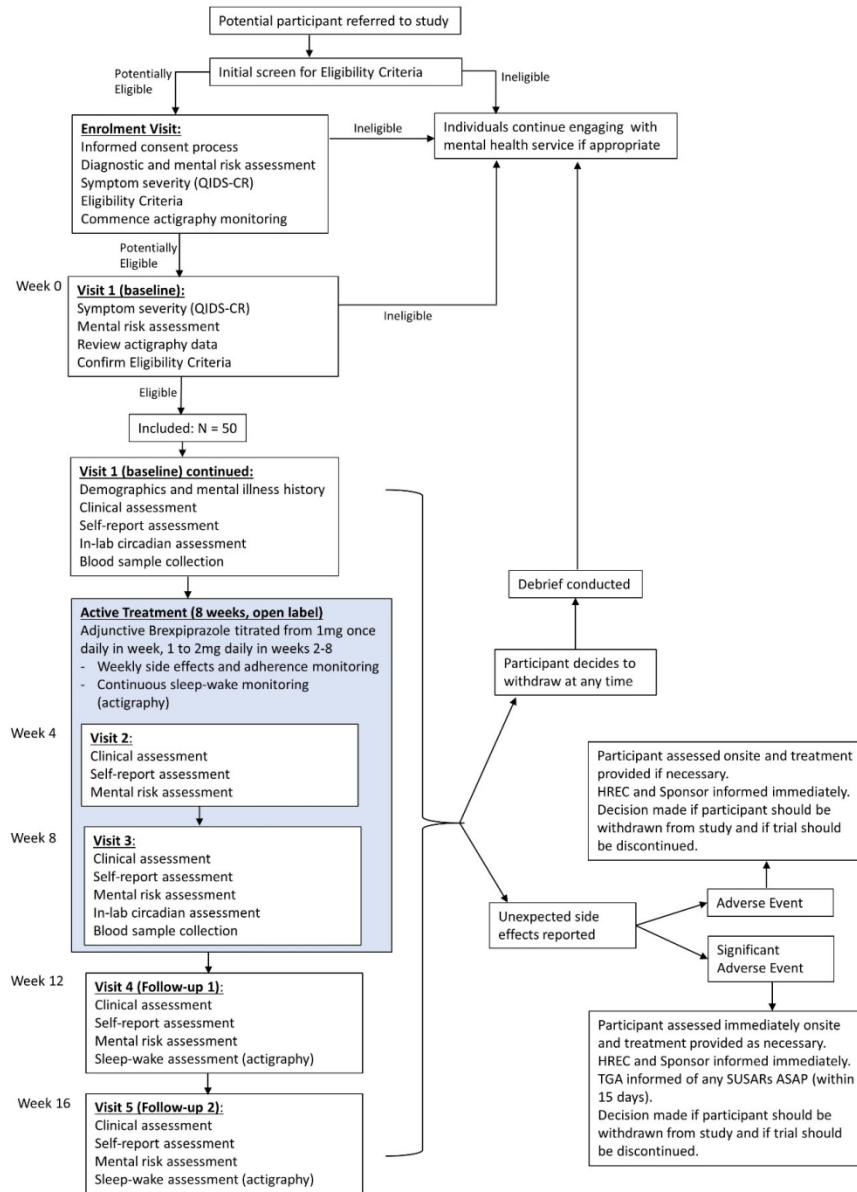


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This figure illustrates the study design and participant timeline from referral to the last follow up visit, including withdrawal and safety procedures.

155x209mm (220 x 220 DPI)



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description	Addressed on page number
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	___ 1 ___
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	___ 3 ___
	2b	All items from the World Health Organization Trial Registration Data Set	___ 3 ___
Protocol version	3	Date and version identifier	___ 2; 21 ___
Funding	4	Sources and types of financial, material, and other support	___ 23 ___
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	___ 1; 22-23 ___
	5b	Name and contact information for the trial sponsor	___ 1 ___
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Please refer to the Protocol (page 37)
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	___ N/A ___



1 **Introduction**

2

3 Background and 6a Description of research question and justification for undertaking the trial, including summary of relevant \_\_\_ 4-5 \_\_\_  
 4 rationale studies (published and unpublished) examining benefits and harms for each intervention  
 5

6 6b Explanation for choice of comparators N/A as one arm  
 7 study  
 8

9 Objectives 7 Specific objectives or hypotheses \_\_\_ 5-6 \_\_\_  
 10

11 Trial design 8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),  
 12 allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) \_\_\_ 6 \_\_\_  
 13  
 14

15 **Methods: Participants, interventions, and outcomes**

16

17 Study setting 9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will \_\_\_ 6 \_\_\_  
 18 be collected. Reference to where list of study sites can be obtained  
 19

20 Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and \_\_\_ 7 \_\_\_  
 21 individuals who will perform the interventions (eg, surgeons, psychotherapists)  
 22

23 Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be \_\_\_ 7-9 \_\_\_  
 24 administered  
 25

26 11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose \_\_\_ 19 \_\_\_  
 27 change in response to harms, participant request, or improving/worsening disease)  
 28

29 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence \_\_\_ 9; 18-19 \_\_\_  
 30 (eg, drug tablet return, laboratory tests)  
 31

32 11d Relevant concomitant care and interventions that are permitted or prohibited during the trial \_\_\_ 7 \_\_\_  
 33

34 Outcomes 12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood  
 35 pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, \_\_\_ 9-12 \_\_\_  
 36 median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen  
 37 efficacy and harm outcomes is strongly recommended  
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1	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	____ 18 ____ Please also refer to Figure 1
2				
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5	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	____ 19-20 ____
6				
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8	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	____ 6 ____
9				

11 **Methods: Assignment of interventions (for controlled trials)**

13 Allocation:

15	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	N/A as not a controlled trial
16				
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20	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A as not a controlled trial
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25	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A as not a controlled trial
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28	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A as not a controlled trial
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31		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A as not a controlled trial
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35 **Methods: Data collection, management, and analysis**

37	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	____ 12-17 ____
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1		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Please refer to Figure 1
2				
3				
4	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	____20____ Please also refer to the Protocol (page 35)
5				
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9	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	____20____
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13		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	____N/A____
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15		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	____20____
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19	<b>Methods: Monitoring</b>			
20				
21	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Please refer to the Protocol (page 11)
22				
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26		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Please refer to the Protocol (page 28)
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29	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	____19____
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33	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Please refer to the Protocol (page 34)
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37	<b>Ethics and dissemination</b>			
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39	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	____21____
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1	Protocol	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes,	_____21_____
2	amendments		analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals,	Please also refer
3			regulators)	to the Protocol
4				(page 36)
5				
6	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and	_____6_____
7			how (see Item 32)	
8				
9		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary	Please refer to the
10			studies, if applicable	Supplementary
11				materials (page 2)
12				
13	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained	Please refer to the
14			in order to protect confidentiality before, during, and after the trial	Protocol (page 36)
15				
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17	Declaration of	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____23-24_____
18	interests			
19				
20	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that	Please refer to the
21			limit such access for investigators	Protocol (page 35)
22				
23	Ancillary and post-	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial	Please refer to the
24	trial care		participation	Protocol (page 28)
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27	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals,	_____20-21_____
28			the public, and other relevant groups (eg, via publication, reporting in results databases, or other data	
29			sharing arrangements), including any publication restrictions	
30				
31		31b	Authorship eligibility guidelines and any intended use of professional writers	_____N/A_____
32				
33		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____N/A_____
34				

35  
36 **Appendices**

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1	Informed consent	32	Model consent form and other related documentation given to participants and authorised surrogates	Please refer to the
2	materials			Consent form in
3				the Supplementary
4				files
5				
6	Biological	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular	Please refer to the
7	specimens		analysis in the current trial and for future use in ancillary studies, if applicable	Supplementary
8				materials (page 2)
9				

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11 \*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.  
12 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons  
13 [“Attribution-NonCommercial-NoDerivs 3.0 Unported”](#) license.  
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# BMJ Open

## Effects of adjunctive brexpiprazole on sleep-wake and circadian parameters in youth with depressive disorders: Study protocol for a clinical trial

Journal:	<i>BMJ Open</i>
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<b>Primary Subject Heading</b>:	Mental health
Secondary Subject Heading:	Research methods, Mental health, Medical publishing and peer review
Keywords:	MENTAL HEALTH, PSYCHIATRY, Depression & mood disorders < PSYCHIATRY, Neurobiology < NATURAL SCIENCE DISCIPLINES

SCHOLARONE™  
Manuscripts

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2 1 **Effects of adjunctive brexpiprazole on sleep-wake and circadian parameters in youth with depressive**  
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4 2 **disorders: Study protocol for a clinical trial**

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9 5 Joanne S Carpenter<sup>1</sup>, Natalia Zmicerevska<sup>1</sup>, Jacob J Crouse<sup>1</sup>, Alissa Nichles<sup>1</sup>, Alexandra Garland<sup>1</sup>, Yun Ju  
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Word Count: 4,190 (without Abstract, Article Summary, Tables 1 and 2)

## ABSTRACT

### Introduction

Sleep-wake and circadian disturbance is a key feature of mood disorders with a potential causal role and particular relevance to young people. Brexpiprazole is a second-generation antipsychotic medication with demonstrated efficacy as an adjunct to antidepressant treatment for Major Depressive Disorder (MDD) in adults, with preliminary evidence suggesting greater effectiveness in subgroups of depressed patients with sleep disturbances. This clinical trial aims to evaluate the relationships between changes in sleep-wake and circadian parameters and changes in depressive symptoms following adjunctive brexpiprazole treatment in young adults with MDD and sleep-wake disturbance.

### Methods and analysis

This study is designed as a 16 week (8 weeks active treatment, 8 weeks follow up) mechanistic, open-label, single-arm phase IV clinical trial and aims to recruit 50 young people aged 18 to 30 with MDD and sleep-wake cycle disturbance through an early intervention youth mental health clinic in Sydney, Australia. At baseline, participants will undergo multidimensional outcome assessment and subsequently receive 8 weeks of open-label treatment with brexpiprazole as adjunctive to their stable psychotropic medication. Following 4 weeks of treatment, clinical and self-report measures will be repeated. Ambulatory sleep-wake monitoring will be conducted continuously for the duration of treatment. After 8 weeks of treatment, all multidimensional outcome assessments will be repeated. Follow-up visits will be conducted 4 and 8 weeks after trial completion (including sleep-wake, clinical, and self-report assessments). Circadian rhythm biomarkers including salivary melatonin, cortisol, and core body temperature will be collected during an in-lab assessment. Additionally, metabolic, inflammatory, and genetic risk markers will be collected at baseline and after 8 weeks of treatment.

### Ethics and dissemination

This trial protocol has been approved by the Human Research Ethics Committee of the Sydney Local Health District (X19-0417 and 2019/ETH12986, Protocol Version v 1-3, dated 25.02.2021). The results of this study,

1  
2 62 in de-identified form, will be disseminated through publication in peer-reviewed journals, scholarly book  
3  
4 63 chapters, presentation at conferences and publication in conference proceedings.  
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## 8 65 **Trial Registration**

10 66 Australian New Zealand Clinical Trials Registry (ANZCTR) Number: ACTRN12619001456145p, Date 22  
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13 67 October, 2019.  
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## 17 69 **KEYWORDS:**

19 70 Mental health, adjunctive brexpiprazole, sleep-wake cycle, youth depression, body clock  
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22 71  
23

## 24 72 **ARTICLE SUMMARY**

### 26 73 **Strengths and limitations of this study**

- 29 74 • Use of a comprehensive battery that includes ecologically valid and laboratory based circadian  
30 assessments (alongside genetic, metabolic, and inflammatory markers) may provide greater insights  
31 75 into the antidepressant mechanisms of adjunctive brexpiprazole.  
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33 76
- 35 77 • Participants will receive a psychoeducational session about sleep and circadian rhythms, including  
37 information on how to improve their sleep-wake cycle based on their individual actigraphy data.  
38 78
- 40 79 • This trial focuses on ascertainment of the current 24-hour sleep-wake cycle and will not examine  
41 possible factors that may contribute to sleep/circadian disruption in the long term (e.g., stressors) or  
42 80 the physiologic properties of sleep.  
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44 81
- 46 82 • Some extraneous factors that influence the sleep-wake cycle and/or circadian rhythms (e.g., ambient  
48 temperature, natural light exposure) are not measured in this study.  
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## 84 INTRODUCTION

85 In young adults, major depressive disorder (MDD) is highly prevalent, recurrent, and comorbid with other  
86 mental and physical conditions, generating a substantial burden of disease and disability [1, 2]. While  
87 multiple psychological and pharmacological treatments are commonly provided, a large proportion of  
88 patients fail to respond to first-line psychotherapy or antidepressant treatments [3-10], and augmentation  
89 with a second generation antipsychotic is often recommended in these treatment-resistant cases [11, 12].  
90 Sleep-wake cycle disturbances are common features of depressive disorders, including insomnia [13-15],  
91 hypersomnia [16, 17], abnormal sleep duration [13, 14], and abnormal timing of 24-hour patterns of  
92 rest/activity [18, 19]. Moreover, abnormalities in biological circadian rhythms (e.g., melatonin) have been  
93 reported [20, 21], suggesting that in some cases sleep disturbances are accompanied or underpinned by  
94 disturbances of the underlying circadian system [22, 23].

95  
96 The human circadian system is controlled by a master oscillator in the brain's hypothalamus (suprachiasmatic  
97 nucleus) which projects to circuits that govern bio-behavioural processes altered in depression (e.g., mood,  
98 vigilance, 24-hour sleep-wake cycle). The circadian system is primarily entrained by bright light, and its  
99 functioning can be disrupted by factors including aberrant light exposure and irregular sleep-wake  
100 behaviours [24, 25]. Adolescents and young adults are particularly vulnerable to circadian perturbations due  
101 to significant developmental changes in circadian rhythms across this age period [26], and sleep-wake phase  
102 delays are common in young people with depressive disorders [27]. Recently, we reported delayed and  
103 disrupted circadian rhythms in a subgroup of young people with depressive disorders (who also presented  
104 with greater symptom severity) [28]. During adolescence there is a phase shift in the circadian rhythm of the  
105 sleep-wake cycle, such that adolescents typically develop a bio-behavioural preference for going to sleep  
106 later and waking later (a manifestation of changes in the biology of the circadian system) [29, 30].  
107 Furthermore, there is some evidence that correction of circadian abnormalities is associated with  
108 antidepressant effects of treatments targeting the circadian system such as Agomelatine [31] and light  
109 therapy [32].

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2 110  
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4 111 Brexpiprazole is a second-generation antipsychotic with demonstrated efficacy by multiple randomised  
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6 112 controlled trials as an adjunct to antidepressant treatment in MDD in adults [33-36]; however the  
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8 113 mechanism of antidepressant action is unknown [37]. The pharmacodynamic properties of brexpiprazole,  
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11 114 together with evidence from preclinical studies, suggest that there may be specific effects on anxiety,  
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13 115 cognition, and sleep [37, 38]. Further, there is preliminary evidence to suggest that brexpiprazole may  
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15 116 have greater effectiveness in subgroups of depressed patients with sleep disturbances, anxiety, or  
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17 117 irritability [22, 39]. As an adjunctive treatment in MDD patients with inadequate response to  
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20 118 antidepressant treatment, brexpiprazole has been reported to lead to clinical improvement of sleep  
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22 119 disturbances (e.g., insomnia) and depressive symptoms, as well as improvement of daytime alertness and  
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24 120 functioning [40]. This pattern of changes is consistent with effects on circadian rhythms, with potential  
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26 121 influences on the entire 24-hour pattern of rest/activity, rather than simply on sleep period (in isolation).  
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29 122 To improve the personalisation of treatment selection for mood disorders, a greater understanding of the  
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31 123 mechanisms of antidepressant action of specific compounds is needed.  
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35 125 The goal of this clinical trial is to investigate whether the effect of brexpiprazole on depressive symptoms  
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37 126 is associated with changes in 24-hour sleep-wake or circadian parameters in young people with MDD.  
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40 127 While disturbances in electrophysiological measures of sleep (e.g., REM sleep) have been considered to  
41  
42 128 represent biomarkers for depression [41-44], this trial focuses instead on the investigation and  
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44 129 measurement of bio-behavioural changes associated with the circadian system (e.g., rest/activity,  
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46 130 melatonin, cortisol, and core body temperature rhythms), rather than changes in electrophysiological  
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49 131 sleep architecture (beyond the scope of this study).  
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51 132

## 53 133 **METHODS AND ANALYSIS**

### 55 134 **Study objectives**

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1  
2 135 The primary objective of this study is to determine if changes in depressive symptoms following adjunctive  
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4 136 brexpiprazole treatment are correlated with changes in sleep-wake or circadian parameters in youth with  
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6 137 depressive disorders.

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11 139 The secondary objective is to determine if changes in social and occupational functioning following  
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13 140 adjunctive brexpiprazole are correlated with changes in sleep-wake or circadian parameters in youth with  
14  
15 141 depressive disorders.

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20 143 The tertiary objectives of this study are to determine if changes in depressive symptoms or changes in  
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22 144 sleep-wake or circadian parameters following adjunctive brexpiprazole treatment are associated with a  
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24 145 range of multidimensional outcome measures in youth with depressive syndromes [45] (e.g., other mental  
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26 146 illness symptoms, self-harm and suicidal thoughts and behaviours, physical health, alcohol/substance use,  
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28  
29 147 and genetic markers).

### 31 148 32 33 149 **Trial design**

34  
35 150 This investigator-initiated, mechanistic study involving 50 young people with depressive disorders and  
36  
37 151 sleep-wake cycle disturbances is designed as a 16-week (8 weeks active treatment, 8 weeks follow-up)  
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40 152 open-label, single-arm, phase IV clinical trial.

### 41 42 153 43 44 154 **Participants**

45  
46 155 Participants aged 18-30 years with a diagnosis of MDD according to DSM-5 criteria on a current  
47  
48 156 antidepressant treatment of either selective serotonin reuptake inhibitor (SSRI) or serotonin-  
49  
50 157 norepinephrine reuptake inhibitor (SNRI) with a disrupted sleep-wake cycle will be recruited through the  
51  
52 158 youth mental health clinics associated with the Brain and Mind Centre (BMC), University of Sydney. All  
53  
54 159 participants will provide written informed consent. The research team will make explicit to any potential  
55  
56 160 participants both verbally and in writing (in the Participant Information Statement) that participation is  
57  
58 161 voluntary and will not affect the patient's care.

1  
2 162  
3  
4 163 The inclusion criteria for this trial are: (i) aged 18-30, (ii) diagnosis of MDD as per DSM-5 (Structured  
5  
6 164 Clinical Interview for DSM; SCID[46]) criteria, (iii) current major depressive episode of moderate severity  
7  
8  
9 165 as defined by a Quick Inventory of Depressive Symptomatology [47] rating  $\geq 11$  at two assessments two  
10  
11 166 weeks apart, (iv) failure to respond to at least one adequate (minimum four weeks) trial of  
12  
13 167 pharmacological treatment, (v) current antidepressant treatment with an SSRI or SNRI (including  
14  
15 168 citalopram, fluoxetine, paroxetine, sertraline, escitalopram, venlafaxine, desvenlafaxine, or duloxetine)  
16  
17 169 for at least 6 weeks, at a stable dose for two weeks prior to study commencement, and (vi) a perturbed  
18  
19  
20 170 sleep-wake cycle as evidenced by: delayed sleep onset; delayed sleep offset; disrupted sleep; high day-  
21  
22 171 to-day variability of sleep-wake cycle; non-restorative sleep; or daytime fatigue.

23  
24 172  
25  
26 173 Exclusion criteria are: (i) any adjunctive antipsychotic treatment for current episode in the past month, (ii)  
27  
28 174 use of medications which affect sleep, melatonin, circadian rhythms, or alertness (e.g., agomelatine,  
29  
30  
31 175 modafinil), (iii) primary psychotic disorder, (iv) acute suicidal behaviour (score of 6 on Comprehensive  
32  
33 176 Assessment of At-Risk Mental States item 7.3 [48], (v) evidence of a medical condition (primary,  
34  
35 177 respiratory, neurological) that could contribute to sleep-wake dysfunction, (vi) significant alcohol or  
36  
37  
38 178 substance misuse or dependence (assessed via DSM-5 SCID[46] and World Health Organisation Alcohol,  
39  
40 179 Smoking and Substance Involvement Screening Test [49, 50], (vii) shift work or (viii) recent transmeridian  
41  
42 180 travel (i.e., participants will be required to wait three days for each jet lag hour before entering the study),  
43  
44 181 (ix) previous hypersensitivity to brexpiprazole, (x) taking CYP2D6 or CYP3A4 inhibitors (or other  
45  
46 182 contraindicated medications listed in the Rexulti product information), and (xi) pregnancy or lactation.

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49 183

#### 50 51 184 **Study course and procedure**

52  
53 185 Patients presenting for mental health care who may be eligible for the study will be screened by phone before  
54  
55 186 being invited to participate and attending an enrolment visit. The enrolment visit will formally assess  
56  
57  
58 187 eligibility criteria and confirm the presence of MDD as per DSM-5 (SCID)[46]. Participants will be provided  
59  
60

1  
2 188 with an actigraphy device (non-invasive wrist-worn device used to objectively measure rest/activity patterns)  
3  
4 189 and will be given instructions to wear the device for the following two-week period.  
5

6 190  
7  
8  
9 191 *Visit 1 (Baseline):* Within two weeks of completing the diagnostic and screening assessments, data from  
10  
11 192 the actigraphy device will be downloaded and reviewed. A further assessment of depressive symptom  
12  
13 193 severity (QIDS Clinician-Rated; QIDS-CR)[47] will be conducted to ensure participants meet all inclusion  
14  
15 194 criteria. Bloods will be collected for assessment of metabolic and inflammatory measures and genomic  
16  
17 195 analysis. Clinical and self-report assessments will be conducted, as well as circadian assessments in which  
18  
19  
20 196 participants will remain in the sleep lab overnight. The following morning, participants will attend a 1-  
21  
22 197 hour psychoeducation session about sleep and circadian rhythms covering the following topics: i) sleep  
23  
24 198 and circadian education with tailored discussion based on their personal actigraphy data; ii) individualized  
25  
26 199 plan for progressive sleep rescheduling; and iii) lifestyle factors and behaviours impacting on sleep (e.g.,  
27  
28  
29 200 exercise, light, sleep environment, sleep regulation, foods, stress, anxiety, mood).  
30

31 201  
32  
33 202 Once all baseline clinical and self-report assessments have been conducted, and the medical assessment  
34  
35 203 completed by the study doctor to confirm inclusion and exclusion criteria, participants will be issued with  
36  
37 204 the study medication to receive 8 weeks of open-label pharmacotherapy with brexpiprazole (REXULTI®-  
38  
39  
40 205 Lundbeck) as adjunctive to their stable psychotropic medication (treatment as usual). Brexpiprazole will  
41  
42 206 be provided to participants at Visit 1 (Baseline) and Visit 2 (Week 4) for the following four weeks and will  
43  
44 207 be titrated from 1 mg once daily in week 1, to 2 mg once daily in weeks 2-8.  
45

46  
47 208  
48  
49 209 Patients will receive 2mg/day, once daily as tablets, for oral use. The brexpiprazole dosage will be steadily  
50  
51 210 increased from 1mg/day during week 1, to 2mg/day during weeks 2-8 (up-titration). This is the dosage and  
52  
53 211 titration regime recommended for adjunctive use in major depression by the Federal Drug Administration  
54  
55 212 (USA). Several previous clinical trials have used this titration regime from 1mg to 2mg [34, 40, 51], and a  
56  
57  
58 213 dose of 2mg has been shown to be effective in reducing depressive symptoms [33]. As doses higher than  
59  
60

1  
2 214 2mg have been shown to increase incidence of akathisia [37], a maximum dose of 2mg will be used in the  
3  
4 215 present study to minimise side effects.  
5  
6 216  
7  
8  
9 217 *Monitoring visits:* Participants will be contacted by telephone on a weekly basis for the duration of the 8-  
10  
11 218 week treatment period to monitor adverse events and adherence. Any changes in concomitant  
12  
13 219 medications will also be investigated and recorded. In addition, participants will be provided with a  
14  
15 220 medication diary and asked to complete during the study to monitor adherence. More detailed  
16  
17  
18 221 information about potential side-effects will be further assessed by the study doctor at visits 2, 3, 4 and 5  
19  
20 222 using the UKU Side Effect Rating Scale [52], Abnormal Involuntary Movement Scale (AIMS) [53] and the  
21  
22 223 Simpson-Angus Scale (SAS) [54] for evaluation of extrapyramidal symptoms (EPS).  
23  
24  
25 224  
26  
27 225 *Visit 2 (Week 4):* Following four weeks of the treatment phase, participants will return for clinical and self-  
28  
29 226 report assessments to assess changes in clinical and functional measures.  
30  
31 227  
32  
33 228 *Visit 3 (Week 8):* Following eight weeks of the treatment phase, participants will return to complete clinical  
34  
35 229 and self-report assessments and will also complete a second circadian (overnight) in-lab assessment.  
36  
37  
38 230 Bloods will be collected at this visit for follow-up metabolic and inflammatory markers. Participants will  
39  
40 231 continue to be provided the brexpiprazole for up to 12 months following completion of the treatment  
41  
42 232 phase as clinically indicated, at the discretion of their treating clinician. Analyses will account for whether  
43  
44 233 participants have continued or discontinued the medication during the follow-up period.  
45  
46  
47 234  
48  
49 235 *Visit 4 and 5 (Follow-up visits 1 and 2, 12 and 16 weeks respectively):* Twelve and sixteen weeks after  
50  
51 236 commencing treatment (i.e., four and eight weeks after completing the eight-week treatment period  
52  
53 237 respectively), participants will return to complete clinical and self-report assessments. Participants will be  
54  
55 238 provided with an actigraphy device to wear for two weeks prior to these assessments.  
56  
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240 Participants will be reimbursed for their time and the cost of transportation to and from the research sites.

**Outcomes**

243 Outcome measures are summarized in Table 1.

**Primary outcomes**

246 The primary endpoint will be the correlation between change in sleep-wake and circadian parameters and  
 247 change in depressive symptoms from baseline to week eight. Sleep items in the primary depressive symptom  
 248 measures (QIDS-CR total score, QIDS-Self Report (QIDS-SR) total score, The Montgomery-Åsberg Depression  
 249 Rating Scale (MADRS) total score) will be removed in analyses to provide a measure of depressive symptoms  
 250 not biased by changes in sleep-wake parameters.

**Secondary outcomes**

253 The secondary endpoint will be correlation between change in sleep-wake and circadian parameters and  
 254 change in functioning from baseline to week eight.

**Tertiary outcomes**

257 Tertiary endpoints will be correlation between change in sleep-wake and circadian parameters and other  
 258 multidimensional outcome measures based on assessments of symptoms, self-harm and suicidal thoughts  
 259 and behaviours, physical health, and alcohol/substance use. Further tertiary endpoints will be comparison of  
 260 primary endpoints between Clinical Stages [55-58], illness trajectories [59], and genetic variants with  
 261 potential relevance to mood disorders and/or circadian rhythms (e.g. CLOCK, BMAL1).

**Table 1. Primary, secondary, and tertiary outcome measures.**

Primary Outcome Measures	Secondary Outcome Measures	Tertiary Outcome measures
(Correlation between change in sleep-wake and circadian parameters and change in		

depressive symptoms from baseline to week eight)	(Correlation between change in sleep-wake and circadian parameters and change in functioning from baseline to week eight)	(Correlation between change in sleep-wake and circadian parameters and other multidimensional outcome measures)
<p><b>Primary depressive symptom measures:</b></p> <ul style="list-style-type: none"> <li>• QIDS-CR total score (minus sleep items)</li> <li>• QIDS-Self Report (QIDS-SR) total score (minus sleep items)</li> <li>• The Montgomery-Åsberg Depression Rating Scale (MADRS) total score (minus sleep items)</li> </ul> <p><b>Sleep-wake and circadian variables:</b> Actigraphy parameters (in the two-week period prior to baseline and prior to week eight):</p> <ul style="list-style-type: none"> <li>• Sleep onset time</li> <li>• Sleep offset (wake) time</li> <li>• Total sleep time (duration)</li> <li>• Wake after sleep onset (estimation of number of minutes awake during the sleep period)</li> <li>• Sleep efficiency (% of sleep period estimated as sleep)</li> <li>• Inter-daily stability</li> <li>• Intra-daily variability</li> </ul> <p><b>In-lab circadian measures:</b></p> <ul style="list-style-type: none"> <li>• Dim Light Melatonin Onset (DLMO) timing</li> <li>• Phase angle (time lapse) between DLMO and habitual sleep</li> <li>• Core body temperature nadir</li> <li>• Evening cortisol area under the curve</li> </ul> <p><b>Self-report measures:</b></p> <ul style="list-style-type: none"> <li>• Non-restorative sleep score (based on the Pittsburgh Sleep Quality Index (PSQI), and Munich Chronotype Questionnaire (MCTQ))</li> <li>• <i>Pittsburgh Sleep Quality Index</i> (PSQI) total score</li> <li>• Epworth Sleepiness Score (ESS) total score</li> <li>• Insomnia Severity Index (ISI) total score</li> <li>• Morningness -Eveningness Questionnaire (MEQ) total score*</li> <li>• Seasonal Pattern Assessment Questionnaire (SPAQ) total score*</li> </ul>	<p><b>Functioning measures:</b></p> <ul style="list-style-type: none"> <li>• Social and Occupational Functioning Assessment Scale (SOFAS) rating</li> <li>• The Work and Social Adjustment Scale (WSAS) total score</li> <li>• Adapted Schuster Social Support Scale (SSSS) total score</li> <li>• Not in Education, Employment, or Training (NEET) status</li> <li>• Number of days 'out of role' (unable to perform usual activities) in the past 30 days</li> </ul>	<p><b>Symptom measures:</b></p> <ul style="list-style-type: none"> <li>• Young Mania Rating Scale (YMRS) total score</li> <li>• Brief Psychiatric Rating Scale (BPRS) total score and subscale scores</li> <li>• Overall Anxiety Severity Impairment Scale (OASIS) total score</li> <li>• Altman Self-Rating Mania scale (ASRM) total score</li> <li>• Prodromal Questionnaire (brief version) (PQ-16) total score</li> <li>• DSM-5 Primary Care Post-Traumatic Stress Disorder screen (PC-PTSD-5) total score</li> <li>• Adapted Eating Disorder Examination (EDE) total score</li> <li>• Clinical Global Impressions scale (CGI) severity and improvement scores</li> </ul> <p><b>Self-harm and suicidal thoughts and behaviours:</b></p> <ul style="list-style-type: none"> <li>• Suicidal risk (score from Suicidal Ideation Attributes Scale (SIDAS) and Columbia- Suicide Severity Rating Scale (C-SSRS) items)</li> <li>• Adapted Brief Non-Suicidal Self-Injury Assessment Tool (B-NSSI-AT) total score</li> </ul> <p><b>Physical Health:</b></p> <ul style="list-style-type: none"> <li>• Body Mass Index (BMI) calculated from height and weight</li> <li>• Waist circumference</li> <li>• International Physical Activity Questionnaire (IPAQ) total score</li> <li>• Metabolic blood markers including triglycerides, cholesterol (total, Low Density Lipoprotein (LDL), High Density Lipoprotein (HDL)), and Homeostasis Model of Insulin Resistance (HOMA2-IR) calculated from fasting glucose and insulin measures</li> <li>• Inflammatory blood markers including Interleukin-1<math>\beta</math> (IL-1<math>\beta</math>), Interleukin-6 (IL-6), Tissue Necrosis Factor (TNF-<math>\alpha</math>), C-Reactive Protein (CRP)</li> </ul> <p><b>Alcohol and substance Use:</b></p>

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<p>*Baseline scores will be used rather than change scores as these are trait measures</p>		<ul style="list-style-type: none"> <li>• World Health Organisation Alcohol, Smoking, and Substance Involvement Screening Test (WHO ASSIST) score for tobacco, and cannabis</li> <li>• Alcohol Use Disorders Identification Test-Consumption (AUDIT C) total score</li> <li>• WHO ASSIST alcohol-related impairment</li> <li>• Age of onset of alcohol use</li> </ul> <p><b>Comparison of primary endpoints between:</b></p> <ul style="list-style-type: none"> <li>• Clinical Stages</li> <li>• Illness Trajectories</li> <li>• Genetic variants with potential relevance to mood disorders and/or circadian rhythms (e.g., CLOCK, BMAL1).</li> </ul>
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**Assessments**

Assessments used here are based on the multidimensional assessment and outcomes framework [45] and include clinical and self-report ratings of mental health symptoms, social and occupational functioning, self-harm, suicidal thoughts and behaviours, physical health, alcohol and substance use, illness type, stage and trajectory, as well as circadian parameters and metabolic, inflammatory and genetic markers. Our recent research [45, 60-62] indicates the capacity of the multidimensional outcomes framework to further our understanding of the pathophysiological mechanisms and illness progression in this cohort, as well as to inform more personalized and measurement-based models of care.

Diagnostic assessments

The presence of MDD and any comorbidity will be evaluated using the Structured Clinical Interview for DSM-5 Axis I Disorders (SCID) [46] (30-75 minutes to complete).

Mental risk assessment

Acute suicidal behaviour will be assessed by relevant subscale of the Comprehensive Assessment of At-Risk Mental States (CAARMS) [48] (5 minutes to complete).

1  
2 282 Clinical assessments

3  
4 283 The clinical interview is expected to take around 35 minutes to complete.

5  
6 284 1. *Clinical-rated Quick Inventory of Depressive Symptomatology (QIDS-CR)* [47]: assesses the nine  
7  
8 285 criterion symptom domains designated by the DSM to diagnose a MDE.

9  
10  
11 286 2. *Montgomery-Åsberg Depression Rating Scale (MADRS)* [63]: will also be used to assess depressive  
12  
13 287 symptoms, to allow for direct comparisons with previous studies of brexpiprazole in MDD.

14  
15 288 3. *Young Mania Rating Scale (YMRS)* [64]: an 11-item, multiple-choice diagnostic questionnaire used to  
16  
17 289 measure severity of manic episodes.

18  
19  
20 290 4. *Brief Psychiatric Rating Scale (BPRS)* [65]: used to measure psychiatric symptoms (e.g., depression,  
21  
22 291 anxiety, hallucinations).

23  
24 292 5. *Social and Occupational Functioning Assessment Scale (SOFAS)* [66]: used to assess functioning on a  
25  
26 293 0-100 scale (lower scores suggesting greater impairment).

27  
28  
29 294 6. *Clinical Global Impressions scale (CGI)* [67]: used to measure of clinical improvement.

30  
31 295 7. Participants will also be rated on previously established *clinical stage* [55-58] and *illness trajectory*  
32  
33 296 [59] models on the basis of information collected throughout the clinical interview. The clinical staging  
34  
35 297 framework differentiates those in the earliest phases of mental health problems with non-specific  
36  
37 298 clinical presentations (stage 1a; 'help-seeking') from those at greater-risk with more specific, sub-  
38  
39 299 threshold presentations (stage 1b; 'attenuated syndromes') and those who have already reached a  
40  
41 300 threshold for a progressive or recurrent disorder meeting diagnostic criteria (stage 2, 3, or 4). The  
42  
43 301 illness trajectory model is a novel tripartite framework based on three proposed pathophysiological  
44  
45 302 pathways leading to youth-onset mental disorders: (i) neurodevelopmental-psychosis, (ii) circadian-  
46  
47 303 bipolar spectrum, and (iii) hyperarousal-anxious depression[68-70].

48  
49  
50  
51 304 8. *World Health Organisation (WHO) Alcohol, Smoking and Substance Involvement Screening Test (WHO-*  
52  
53 305 *ASSIST)* [49, 50]: a reliable, culturally adaptable, valid screener for problematic or risky substance use.

54  
55  
56 306  
57  
58 307 Self-report assessments

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1  
2 308 The self-report questionnaires are tailored to the individual (using skip logic) so the amount of time taken  
3  
4 309 to complete the questionnaire varies, but we estimate the assessment will take 45 minutes to complete.  
5  
6 310 1. *Demographics and Mental Health History*: including details of work and education, physical health  
7  
8 311 (height, weight, waist circumference), history of mental health, and family history  
9  
10  
11 312 2. *International Physical Activity Questionnaire (IPAQ) - short version [71, 72]*: 7-item questionnaire  
12  
13 313 providing internationally comparable data on health-related physical activity.  
14  
15 314 3. *Alcohol Use Disorders Identification Test – Consumption (AUDIT-C) [73]*: includes three short  
16  
17 315 questions that estimate alcohol consumption in a standard, meaningful, non-judgmental manner.  
18  
19 Additional questions assessing age of onset of alcohol consumption will also be used.  
20 316  
21  
22 317 4. *Suicidal Ideation Attributes Scale (SIDAS) [74]*: 5-item self-report questionnaire assessing the  
23  
24 318 frequency, controllability, closeness to attempt, distress, and interference with daily activities on a  
25  
26 319 10-point Likert scale over the past month.  
27  
28  
29 320 5. *Columbia-Suicide Severity Rating Scale (C-SSRS) [75]*: The scale comprises 3 sections: suicidal  
30  
31 321 ideation, intensity of ideation, and suicidal behaviour. A self-rating adaptation will be used in  
32  
33 322 combination with the SIDAS.  
34  
35 323 6. *Brief Non-Suicidal Self-Injury Assessment Tool (B-NSSI-AT) [76]*: designed to assess primary (such as  
36  
37 324 form, frequency, and function) and secondary (including but not limited to NSSI habituation;  
38  
39 contexts in which NSSI is practiced; and NSSI perceived life interference, treatment, and impacts)  
40 325  
41 NSSI characteristics.  
42 326  
43  
44 327 7. *Quick Inventory of Depressive Symptomatology – self-report (QIDS-SR) [77]*: a self-rating (SR) version  
45  
46 328 includes 16 questions with equivalent weightings (0-3) for each symptom item that assesses the nine  
47  
48 criterion symptom domains designated by the DSM-IV to diagnose a MDE.  
49 329  
50  
51 330 8. *Overall Anxiety Severity Impairment Scale (OASIS) [78]*: 5-item self-report measure used to assess  
52  
53 331 severity and impairment associated with any anxiety disorder or multiple anxiety disorders.  
54  
55 332 9. *Altman Self-Rating Mania Scale (ASRM) [79]*: 5-item self-rating scale designed to assess the presence  
56  
57 333 and/or severity of manic symptoms.  
58  
59  
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- 1  
2 334 10. *Primary Care Post-Traumatic Stress Disorder Screen for DSM-5 (PC-PTSD-5)* [80]: 5-item screen  
3  
4 335 designed for use in primary care settings to identify respondents with probable PTSD.  
5  
6 336 11. *Prodromal Questionnaire (PQ-16)* [81]: self-report screen for use in secondary mental health care  
7  
8 337 services to select subjects for psychosis risk.  
9  
10  
11 338 12. *Eating Disorder Examination (EDE)* [82, 83]: comprises a range of health-related and demographic  
12  
13 339 questions, including present height and weight, and a detailed and comprehensive assessment of  
14  
15 340 symptoms, particularly binge eating. In this study, three eating disorder behaviours are assessed:  
16  
17 341 binge eating, purging, and strict dieting or fasting.  
18  
19  
20 342 13. *Sleep questions*: 7 questions regarding time falling asleep, waking up during weekdays and  
21  
22 343 weekends, hours of sleep, feelings when waking up. Sleep timing items are based on the Pittsburgh  
23  
24 344 Sleep Quality Index (PSQI) and Munich Chrono Type Questionnaire (MCTQ), while sleep quality items  
25  
26 345 are based on expert consensus in the literature.  
27  
28  
29 346 14. *Work and Social Adjustment Scale (WSAS)* [84]: 5-item scale of functional impairment attributable  
30  
31 347 to an identified problem.  
32  
33 348 15. *Schuster Social Support Scale (SSSS)* [85]: 15-item measure of social support used to examine an  
34  
35 349 individual's social relationships with others (relatives, friends, spouse) and the associated impact on  
36  
37 350 their emotional functioning  
38  
39  
40 351 16. *Additional sleep questionnaires*: participants will complete the BMC sleep-wake self-report  
41  
42 352 questionnaire battery including questions regarding ethnicity, caffeine consumption, menstrual  
43  
44 353 cycle, visual impairments, and non-restorative sleep, as well as the *Pittsburgh Sleep Quality*  
45  
46 354 *Inventory (PSQI)* [86], *Epworth Sleepiness Scale (ESS)* [87], *Insomnia Severity Index (ISI)* [88], *Horne-*  
47  
48 355 *Ostberg Morningness-Eveningness Questionnaire (MEQ)* [89], and the *Seasonal Patterns Assessment*  
49  
50 356 *Questionnaire (SPAQ)* [90].  
51  
52  
53 357

#### 54 358 **Sleep wake assessments**

55  
56 359 24-hour sleep-wake and circadian rest-activity parameters will be measured by actigraphy recordings.  
57  
58 360 Actigraphy is a non-invasive tool to objectively measure activity profiles used to estimate sleep and circadian  
59  
60

1  
2 361 patterns based on validated algorithms. Participants will be asked to complete a sleep diary and to wear an  
3  
4 362 actigraph (GENEActiv device; Activinsights, Kimbolton, UK) on the non-dominant wrist for at least 10 days  
5  
6 363 prior to commencing the study, and continuously for the 8-week treatment phase. The device is comfortable  
7  
8  
9 364 and easy to use, battery operated wrist-worn device, similar in appearance to Fitbit, designed to record and  
10  
11 365 provide data on movement, light, temperature and sleep patterns. The device will provide objective  
12  
13 366 monitoring of participants' 24-hour circadian rhythm, including their sleep onset and duration, rise time, any  
14  
15 367 night-time sleep interruptions, and activity patterns (see Table 1). The device allows for the outputting of  
16  
17 368 real-time raw measurement data for up to a month without charging. Instructions will be provided to  
18  
19  
20 369 participants on how to use the device upon their recruitment into the study. Two-week actigraphy recordings  
21  
22 370 will also be completed at the 12- and 16-week follow up assessments. GENEActiv devices have been validated  
23  
24 371 against several types of accelerometry-based activity monitors [91-94] as well as for sleep-wake scoring [95,  
25  
26 372 96]. For decades, actigraphy monitors like the GENEActiv devices have been used extensively in research to  
27  
28  
29 373 measure sleep and activity patterns in diverse clinical settings including sleep disorders, medical illnesses  
30  
31 374 (e.g., neurodegenerative diseases) and various major mental disorders [19, 97, 98].  
32

### 33 375 34 35 376 **In-lab circadian assessment**

36  
37  
38 377 Circadian rhythms will be measured in an evening/overnight recording period, including 24-hour rhythms  
39  
40 378 of salivary melatonin, salivary cortisol, and core body temperature (Table 1). Circadian assessments will  
41  
42 379 be performed in accordance with established dim light melatonin onset protocols [99-102].  
43

### 44 380 45 46 381 **Metabolic and inflammatory markers**

47  
48  
49 382 The following markers will be collected at baseline and 8-weeks follow up visits: (i) Triglycerides, (ii)  
50  
51 383 Cholesterol (including total, High Density Lipoprotein (HDL), and Low-Density Lipoprotein (LDL)), (iii)  
52  
53 384 Fasting glucose, (iv) Fasting insulin, (v) Interleukin (IL)-1 $\beta$ , (vi) IL-6, (vii) Tissue Necrosis Factor (TNF)- $\alpha$ , (viii)  
54  
55 385 C-Reactive Protein (CRP). Height, weight, and waist circumference will be recorded. Insulin resistance will  
56  
57  
58 386 be estimated based on paired fasting plasma glucose and insulin levels [103] by the updated homeostatic  
59  
60 387 model assessment (HOMA2-IR) using iHOMA2 software V.8.8 [104].

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2 388  
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4 389 **Genetics**  
5  
6 390 Additional blood (30mL) will be collected at baseline for assessment of genetic markers as per procedures  
7  
8 391 from the University of Queensland Human Studies Unit.  
9  
10  
11 392 The schedule of trial assessments is summarized in Table 2 and the participant timeline is presented in  
12  
13 393 Figure 1.

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15 39416  
17  
18 395 **Table 2. Schedule of assessments**

	Enrolment Visit	Visit 1 (Baseline)	Visit 2 (Week 4)	Visit 3 (Week 8)	Visit 4 (Follow-up 1)	Visit 5 (Follow-up 2)
<i>Study week</i>		<i>0</i>	<i>4</i>	<i>8</i>	<i>12</i>	<i>16</i>
Informed Consent	✓					
Inclusion/Exclusion Criteria	✓	✓				
Diagnostic Assessment (SCID)	✓					
Mental Risk Assessment (CAARMS)	✓	✓	✓	✓	✓	✓
Demographics and Mental Illness History		✓				
Clinical Assessment (QIDS- CR, MADRS, YMRS, BPRS, SOFAS)		✓	✓	✓	✓	✓
Self-report Assessment		✓	✓	✓	✓	✓
Sleep-wake Assessment (actigraphy monitoring)		✓	✓	✓	✓	✓
In-lab Circadian Assessment		✓		✓		
Blood Sample Collection (Metabolic and Inflammatory Markers)		✓		✓		
Safety, side-effects, and adherence assessment			✓	✓	✓	✓
IP dispensing		✓	✓	✓*	✓*	✓*
IP return			✓	✓		

43 396 \* If clinically indicated, at the discretion of the treating clinician  
44  
45

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48 398 **Safety and side-effects monitoring**

49  
50 399 Studies have shown that brexpiprazole is generally well tolerated, with no unexpected or severe side  
51  
52 400 effects [33, 36, 105, 106]. Safety and tolerability of the investigational product (IP) will be closely  
53  
54 401 monitored throughout the trial. For the duration of the 8-week treatment period, weekly phone calls will  
55  
56 402 be conducted to monitor safety and elicit information regarding side effects and potential adverse events.  
57  
58 403 Any changes in concomitant medications will also be investigated and recorded. In addition, participants  
59  
60

1  
2 404 will be provided with a medication diary and asked to complete during the study to monitor tolerability  
3  
4 405 and adherence. According to the IP information, participants will be advised to not drive a car, operate  
5  
6 406 machinery, or do other dangerous activities until they know how the IP affects them, as it may induce  
7  
8  
9 407 drowsiness in some subjects.

10  
11 408  
12  
13 409 Further formal assessment of side effects and potential adverse events following the end of the treatment  
14  
15 410 phase will be conducted at the two follow-up visits (visit 4 and 5). At the baseline visit, participants will be  
16  
17  
18 411 informed that any serious negative side effects should be reported to the study doctor immediately and will  
19  
20 412 be provided with the relevant contact details to do so. All Adverse Events will be assessed for causality and  
21  
22 413 symptom severity according to the study protocol and followed up by the study doctor if required. In the  
23  
24 414 occurrence of a Serious Adverse Event, appropriate diagnostic and therapeutic measures will be taken and  
25  
26  
27 415 the participant will be kept under observation for as long as is medically indicated. The Principal Investigator  
28  
29 416 will then determine if the seriousness of the event warrants the removal of the participant from the study or  
30  
31 417 abandonment of the study. For serious side effects or medical problems, the patient may be taken  
32  
33 418 immediately to Royal Prince Alfred Hospital for treatment. The Principal Investigator will ensure that follow-  
34  
35  
36 419 up of the participant is appropriate to the nature of any event, and that it continues until resolution.

37  
38 420  
39  
40 421 Throughout the trial the study doctor will monitor participants for pregnancy. It is not currently included  
41  
42 422 in the protocol, but the trial Standard Operating Procedures manual explains that the study doctor will  
43  
44 423 give relevant contraception advice to participants based on the current IP information.

#### 45 46 47 424 48 49 425 **Sample size calculation**

50  
51 426 Sample size was determined based on a study of circadian changes in response to agomelatine [31] where  
52  
53 427 a coefficient of 0.54 was found for the correlation between change in DLMO and change in depressive  
54  
55  
56 428 symptoms. We conservatively estimated that the coefficient for brexpiprazole would be smaller (~0.35;  
57  
58 429 i.e., medium effect size), as effects on the circadian system may be less direct. Assuming  $\alpha=0.05$  and 80%  
59  
60 430 power for a one-tailed correlation analysis, a sample size of  $n=49$  is required to detect this effect.

1  
2 431  
3  
4 432 **Data analysis plan**

5  
6 433 Correlations will be performed between change scores (i.e., Visit 2 score minus Visit 1 score) for sleep and  
7  
8 434 circadian measures, and change scores for depressive symptoms. The intention-to-treat principle will be used  
9  
10  
11 435 for missing data (last observations carried forward). Before analysis, plots with outlier and normality statistics  
12  
13 436 will be generated for all variables to identify outliers and issues with variable distribution. Extreme outliers  
14  
15 437 ( $\pm 3$  z-scores) will be checked against source data and testing notes to verify whether they are the result of  
16  
17 438 an error in data entry or a specific issue during testing (e.g., equipment failure), with errors rectified. If not  
18  
19  
20 439 the result of data entry error, outliers will be curtailed. Pearson's or Spearman's correlations will be selected  
21  
22 440 to perform analyses based on normative or non-normative data distribution (significance level  $\alpha=0.05$ ).  
23  
24 441 Correlations will also be examined between other change scores to assess secondary and tertiary endpoints.  
25  
26 442 Further tertiary endpoints will be assessed by partial correlations comparing categorical variables.  
27  
28  
29 443

30  
31 444 **Patient and public involvement**

32  
33 445 Clinical professionals working with young people with mental health problems were invited to comment on  
34  
35 446 the study design and procedures. Findings will be disseminated to scientific, clinical, and wider communities.  
36  
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38 447  
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40 448 **Ethics and dissemination**

41  
42  
43 449 This trial has been approved by the Human Research Ethics Committee of the Sydney Local Health District  
44  
45 450 (X19-0417 and 2019/ETH12986, Protocol Version v 1-3, dated 25.02.2021). The study will be conducted in  
46  
47 451 compliance with all stipulations of the protocol, the conditions of ethics committee approval, the NHMRC  
48  
49 452 National Statement on Ethical Conduct in Human Research and the Good Clinical Practice guidelines. The  
50  
51 453 results of this study will be disseminated as widely as possible into the scientific and broader community. This  
52  
53  
54 454 will include publication in peer-reviewed journals, scholarly book chapters, presentation at conferences and  
55  
56 455 publication in conference proceedings. Publications arising from this project will be deposited into an open  
57  
58 456 access institutional repository, where possible. Results will also be disseminated into the wider community in  
59  
60

1  
2 457 a format appropriate for a lay audience, through links including the BMC website and social media, as well as  
3  
4 458 newsletters.

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### 9 460 **Figure 1. Study flow chart**

10  
11 461 Legend: This figure illustrates the study design and participant timeline from referral to the last follow up  
12  
13 462 visit, including withdrawal and safety procedures.

### 14 15 16 463 17 18 464 **TRIAL STATUS**

19  
20 465 Protocol ID: BMC-YMH-005-2018, Version: v 1-3, dated 25/02/2021.

21  
22 466 The trial has not commenced recruitment.  
23  
24  
25

### 26 467 **AUTHOR CONTRIBUTIONS**

27  
28 468 JSC and IBH conceived the study, led the proposal and protocol development. JSC wrote the trial protocol.

29  
30 469 AG drafted the first version of the manuscript. NZ drafted the final version of the manuscript with input from  
31  
32  
33 470 other authors. JSC, AG, AN, NZ, YJSS, CW, CR, JJC, CMM, FML, DK and EMS were all involved with modifications  
34  
35 471 to the design of the study and with drafting of this paper. All authors have read and approved the final  
36  
37 472 manuscript.  
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42  
43 474 This investigator-initiated trial with Lundbeck compound is supported by Lundbeck Australia Pty Ltd.

44  
45 475 (award/grant number is not applicable).  
46  
47  
48 476  
49

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51  
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53  
54 479 Leadership Fellowship (GNT2008197).  
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58

### 59 481 **COMPETING INTERESTS**

60

1  
2 482 Professor Ian Hickie is the Co-Director, Health and Policy at the Brain and Mind Centre (BMC) University of  
3  
4 483 Sydney, Australia. The BMC operates an early-intervention youth services at Camperdown under contract to  
5  
6 484 headspace. Professor Hickie has previously led community-based and pharmaceutical industry-supported  
7  
8  
9 485 (Wyeth, Eli Lilly, Servier, Pfizer, AstraZeneca) projects focused on the identification and better management  
10  
11 486 of anxiety and depression. He is the Chief Scientific Advisor to, and a 5% equity shareholder in, InnoWell Pty  
12  
13 487 Ltd. InnoWell was formed by the University of Sydney (45% equity) and PwC (Australia; 45% equity) to deliver  
14  
15 488 the \$30 M Australian Government-funded Project Synergy (2017-20) and to lead transformation of mental  
16  
17  
18 489 health services internationally through the use of innovative technologies.

19  
20 490  
21  
22 491 Associate Professor Elizabeth M Scott is the Medical Director, Young Adult Mental Health Unit, St Vincent's  
23  
24 492 Hospital Darlinghurst, Discipline Leader of Adult Mental Health, School of Medicine, University of Notre  
25  
26  
27 493 Dame, Research Affiliate, The University of Sydney and Consultant Psychiatrist. She has received honoraria  
28  
29 494 for educational seminars related to the clinical management of depressive disorders supported by Servier  
30  
31 495 and Eli-Lilly pharmaceuticals. She has participated in a national advisory board for the antidepressant  
32  
33 496 compound Pristiq, manufactured by Pfizer. She was the National Coordinator of an antidepressant trial  
34  
35 497 sponsored by Servier.

36  
37  
38 498  
39 499 Other authors declare no competing interests.

40  
41 500

#### 42 43 501 **DATA AVAILABILITY STATEMENT**

44  
45 502 As this trial has not commenced recruitment, no data is available at present. Once the dataset is generated,  
46  
47  
48 503 de-identified data may be made available from the corresponding author upon reasonable request.

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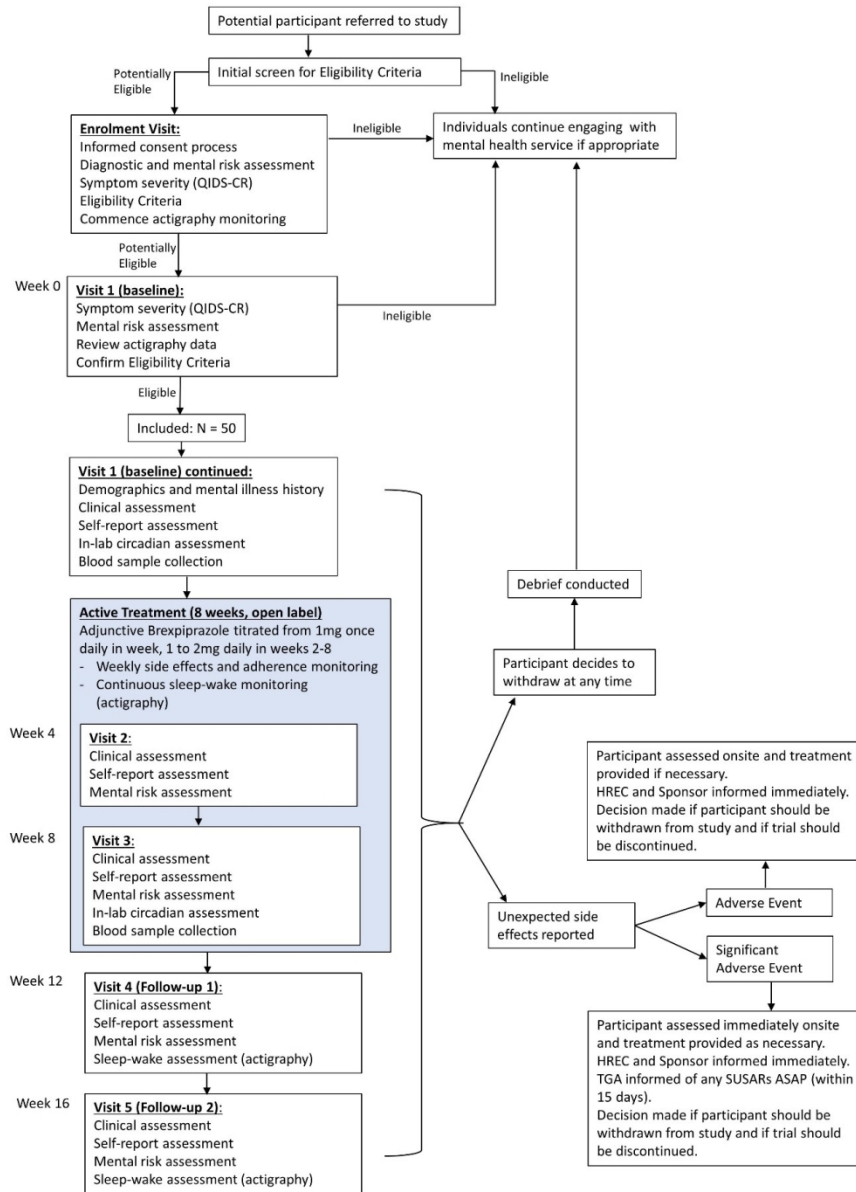


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For peer review only



This figure illustrates the study design and participant timeline from referral to the last follow up visit, including withdrawal and safety procedures.

155x209mm (220 x 220 DPI)



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description	Addressed on page number
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	___ 1 ___
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	___ 3 ___
	2b	All items from the World Health Organization Trial Registration Data Set	___ 3 ___
Protocol version	3	Date and version identifier	___ 2; 21 ___
Funding	4	Sources and types of financial, material, and other support	___ 23 ___
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	___ 1; 22-23 ___
	5b	Name and contact information for the trial sponsor	___ 1 ___
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Please refer to the Protocol (page 37)
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	___ N/A ___



1 **Introduction**

2

3 Background and 6a Description of research question and justification for undertaking the trial, including summary of relevant \_\_\_ 4-5 \_\_\_  
 4 rationale studies (published and unpublished) examining benefits and harms for each intervention  
 5

6 6b Explanation for choice of comparators N/A as one arm  
 7 study  
 8

9 Objectives 7 Specific objectives or hypotheses \_\_\_ 5-6 \_\_\_  
 10

11 Trial design 8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),  
 12 allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) \_\_\_ 6 \_\_\_  
 13  
 14

15 **Methods: Participants, interventions, and outcomes**

16

17 Study setting 9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will \_\_\_ 6 \_\_\_  
 18 be collected. Reference to where list of study sites can be obtained  
 19

20 Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and \_\_\_ 7 \_\_\_  
 21 individuals who will perform the interventions (eg, surgeons, psychotherapists)  
 22

23 Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be \_\_\_ 7-9 \_\_\_  
 24 administered  
 25

26 11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose \_\_\_ 19 \_\_\_  
 27 change in response to harms, participant request, or improving/worsening disease)  
 28

29 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence \_\_\_ 9; 18-19 \_\_\_  
 30 (eg, drug tablet return, laboratory tests)  
 31

32 11d Relevant concomitant care and interventions that are permitted or prohibited during the trial \_\_\_ 7 \_\_\_  
 33

34 Outcomes 12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood \_\_\_ 9-12 \_\_\_  
 35 pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, \_\_\_ 9-12 \_\_\_  
 36 median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen  
 37 efficacy and harm outcomes is strongly recommended  
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1	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	____ 18 ____ Please also refer to Figure 1
2				
3				
4				
5	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	____ 19-20 ____
6				
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8	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	____ 6 ____
9				

11 **Methods: Assignment of interventions (for controlled trials)**

13 Allocation:

15	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	N/A as not a controlled trial
16				
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20	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A as not a controlled trial
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25	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A as not a controlled trial
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27				
28	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A as not a controlled trial
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31		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A as not a controlled trial
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35 **Methods: Data collection, management, and analysis**

37	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	____ 12-17 ____
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1		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Please refer to Figure 1
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4	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	____20____ Please also refer to the Protocol (page 35)
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9	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	____20____
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13		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	____N/A____
14				
15		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	____20____
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19	<b>Methods: Monitoring</b>			
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21	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Please refer to the Protocol (page 11)
22				
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26		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Please refer to the Protocol (page 28)
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29	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	____19____
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33	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Please refer to the Protocol (page 34)
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37	<b>Ethics and dissemination</b>			
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39	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	____21____
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1	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	____21____ Please also refer to the Protocol (page 36)
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6	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	____6____
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10		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Please refer to the Supplementary materials (page 2)
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14	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Please refer to the Protocol (page 36)
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17	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	____23-24____
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20	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Please refer to the Protocol (page 35)
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23	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Please refer to the Protocol (page 28)
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27	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	____20-21____
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31		31b	Authorship eligibility guidelines and any intended use of professional writers	____N/A____
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33		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	____N/A____
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36 **Appendices**  
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1	Informed consent	32	Model consent form and other related documentation given to participants and authorised surrogates	Please refer to the
2	materials			Consent form in
3				the Supplementary
4				files
5				
6	Biological	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular	Please refer to the
7	specimens		analysis in the current trial and for future use in ancillary studies, if applicable	Supplementary
8				materials (page 2)
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10  
11 \*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.  
12 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons  
13 "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)" license.  
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