

1. PROTOCOL FULL TITLE

Cognitive Remediation in Bipolar (CRiB2): a randomised trial assessing efficacy and mechanisms of cognitive remediation therapy compared to treatment as usual.



Trial Identifiers

ISRCTN:	ISRCTN10362331		
REC Number:	22/LO/0210		
IRAS Number:	310423		
Protocol Version Number:	5.5	Date:	25/10/2024

Co-Sponsors

Name:	King's College London and South London and Maudsley NHS Foundation Trust
Address:	De Crespigny Park, Denmark Hill, London, SE5 8AF
Telephone:	02078487306
Email:	Professor Bashir Al-Hashimi, Vice President (Research and Innovation) / vpri@kcl.ac.uk

Chief Investigator

Name:	Professor Allan Young
Address:	Institute of Psychiatry, Psychology & Neuroscience, King's College London, De Crespigny Park, Denmark Hill, London, SE5 8AF
Telephone:	02078485895
Email:	Allan.young@kcl.ac.uk

Co-Investigators

Name:	Dr Rebecca Strawbridge
Position/ Role:	Post-doctoral Research Associate
Address:	Institute of Psychiatry, Psychology & Neuroscience, King's College London, De Crespigny Park, Denmark Hill, London, SE5 8AZ
Telephone:	02078485305
Email:	Becci.strawbridge@kcl.ac.uk

Name:	Professor Dame Til Wykes
Position/ Role:	Professor of Psychology
Address:	Institute of Psychiatry, Psychology & Neuroscience, King's College London, De Crespigny Park, Denmark Hill, London, SE5 8AF
Telephone:	02078480596
Email:	Til.wykes@kcl.ac.uk

Name:	Dr Matteo Cella
Position/ Role:	Senior Lecturer & Clinical Psychologist
Address:	Institute of Psychiatry, Psychology & Neuroscience, King's College London, De Crespigny Park, Denmark Hill, London, SE5 8AF
Telephone:	020 7848 5001
Email:	matteo.cella@kcl.ac.uk

Name:	Dr Kimberley Goldsmith
Position/ Role:	Senior Trial Statistician
Address:	Institute of Psychiatry, Psychology & Neuroscience, King's College London, De Crespigny Park, Denmark Hill, London, SE5 8AF
Telephone:	020 7848 0059
Email:	kimberley.goldsmith@kcl.ac.uk

Name:	Dr Dimosthenis Tsapekos
Position/ Role:	Trial Manager
Address:	Institute of Psychiatry, Psychology & Neuroscience, King's College London, De Crespigny Park, Denmark Hill, London, SE5 8AF
Telephone:	02078485305
Email:	dimosthenis.tsapekos@kcl.ac.uk

Name:	Samuel Swidzinski
Position/ Role:	PPI Lead
Address:	Institute of Psychiatry, Psychology & Neuroscience, King's College London, De Crespigny Park, Denmark Hill, London, SE5 8AF
Email:	samuel.swidzinski@kcl.ac.uk

Name:	Professor Steve Marwaha
Position/ Role:	Birmingham Principal Investigator
Address:	Institute for Mental Health, 52 Pritchatts Road, University of Birmingham, B15 2TT
Telephone:	0121 414 3665
Email:	s.marwaha@bham.ac.uk

Name:	Dr Elizabeth Newton
Position/ Role:	Birmingham Clinical Lead
Address:	Bipolar Service, Tall Trees, Uffculme Site, Queensbridge Road, Kings Health , Birmingham,
Telephone:	01213013370
Email:	Elizabeth.newton3@nhs.net

Name:	Professor Paul Harrison
Position/ Role:	Oxford Principal Investigator
Address:	Department of Psychiatry, Warneford Hospital, Oxford, OX3 7JX
Telephone:	01865 618329
Email:	paul.harrison@psych.ox.ac.uk

Name:	Professor Catherine Harmer
Position/ Role:	Affect Lead (joint)
Address:	Department of Psychiatry, Warneford Hospital, Oxford, OX3 7JX
Telephone:	01865 618326
Email:	catherine.harmer@psych.ox.ac.uk

Name:	Professor Michael Browning
Position/ Role:	Affect Lead (joint)
Address:	Department of Psychiatry, Warneford Hospital, Oxford, OX3 7JX
Telephone:	01865 618316
Email:	michael.browning@psych.ox.ac.uk

Name:	Dr David Cousins
Position/ Role:	Newcastle Principal Investigator
Address:	Newcastle Magnetic Resonance Centre
Telephone:	01912 081250
Email:	david.cousins@ncl.ac.uk

Name:	Dr Stephen Barton
Position/ Role:	Newcastle Clinical Lead
Address:	Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust, St. Nicholas Hospital, Jubilee Road, Gosforth, Newcastle
Telephone:	01912 468606
Email:	stephen.barton@cntw.nhs.uk

1. Study Synopsis

TITLE OF CLINICAL TRIAL:	Cognitive Remediation in Bipolar (CRiB2): a randomised trial assessing efficacy and mechanisms of cognitive remediation therapy compared to treatment as usual.
Protocol Short Title/ Acronym:	CRiB2
Study Phase If Not Mentioned In Title:	Phase II
Sponsor Name:	King's College London & South London and Maudsley NHS Foundation Trust
Chief Investigator:	Professor Allan Young
Medical Condition Or Disease Under Investigation:	Bipolar Disorder (type I or type II)
Purpose Of Clinical Trial:	To investigate the efficacy and explore putative mechanisms of a partly-computerised cognitive remediation (CR) therapy for people with bipolar disorder.
Primary Objective:	The principal research question is whether the CR intervention provides significant and durable effects on psychosocial functioning over treatment as usual (TAU) for people with bipolar disorder.
Secondary Objective(s):	<ul style="list-style-type: none"> - Whether CR provides immediate benefits on psychosocial functioning over TAU - Whether CR induces immediate and durable changes in global cognition and individual cognitive domains, subjective cognitive complaints, affective symptom severity, sleep quality, and self-defined patient goal attainment - Whether CR leads to immediate changes in biomarker levels, and whether these changes are associated with long-term cognitive improvement - Whether CR drives immediate changes in global cognition, metacognitive skills, and mood instability, and whether these changes are associated with long-term improvement in functional outcomes.
Trial Design:	The study is a multi-site, single-blind RCT comparing CR+TAU to TAU alone for euthymic bipolar patients.

<p>Endpoints:</p>	<p>Throughout the protocol, week 0 refers to randomisation timepoint; all other references to “week” timepoints anchor from week 0 randomisation.</p> <p>Week 0: Baseline assessment, pre-intervention</p> <p>Weeks 1-12 post-randomisation: Intervention period</p> <p>Week 13 post-randomisation: Post-intervention assessment</p> <p>Week 25 post-randomisation: Follow-up assessment</p>
<p>Sample Size:</p>	<p>250 individuals with bipolar disorder: 125 will be randomised to CR intervention (& TAU); 125 to TAU alone.</p>
<p>Summary Of Eligibility Criteria:</p>	<p>Diagnosis of bipolar disorder, type I or type II;</p> <p>Aged between 18-65 at study entry;</p> <p>No diagnosis of degenerative neurological disorder, or current substance abuse/dependence;</p> <p>At time of study entry, eligible individuals will have been free of acute symptoms and in stable mood (euthymia) for at least one month.</p>
<p>Intervention (Description, frequency, details of delivery):</p>	<p>Cognitive Remediation intervention (CIRCuiTS computerised program, Reeder & Wykes, 2010): Participants will receive 30-40 hours of CR over the course of 12-weeks. Face-to-face sessions (up to 1 hour long) will be held at least once per week, but participants will be encouraged to attend up to 3 sessions per week if feasible; an alternative arrangement of twice-weekly remote sessions will be offered, and all individuals will be provided unlimited access to use the program in their own time, should they wish to additionally practice independently. This intervention aims to tailor towards individual needs. Guided by previous studies, we will consider a minimum dose of 20 CR hours to be considered to have undertaken the intervention.</p> <p>Participants in the intervention arm will also receive treatment as usual in addition to CR.</p>
<p>Comparator Intervention:</p>	<p>Participants will receive treatment as usual, with no intervention from the research team.</p>
<p>Maximum Duration Of Treatment Of A Participant:</p>	<p>12 weeks intervention, plus 12-weeks follow-up. We estimate that the maximum number of treatment hours engaging in face-to-face CR alongside a therapist will be 40 hours over the 12-week intervention period. This will be supplemented by independent homework practice, as agreed between the participant and the therapist.</p>
<p>Version And Date Of Final Protocol:</p>	<p>Version 2.0 – 04/04/2022, approved on 14/04/2022</p>

The electronic version of this document is the latest version. It is responsibility of the individual to ensure that any paper material is the current version. Printed material is uncontrolled documentation.

Version And Date Of Protocol Amendments:	See below, Revision History.
---	------------------------------

2. Revision History

Document ID – (Document Title) revision X.Y	Description of changes from previous revision	Effective Date
Protocol CriB2 0.01 – 0.15	New draft Protocol, edits throughout	29/07/2021 – 12/12/2021
Protocol CRiB2 1.0	Changes as per Sponsor’s review	24/01/2022
Protocol CRiB2 2.0	Changes as per REC’s review & additional modifications	04/04/2022
Protocol CRiB2 2.5	Changes for substantial amendment 1 (addition of an extra site in Newcastle and sample increase to 250; replacement of Ethica with Qualtrics for affective fluctuation data collection; optional blood sample component; and addition of PIC sites for primary care patient identification)	22/07/2022
Protocol CRiB2 3.0	Changes for non-substantial amendment 1 (removal of protocol specification for 1 in-person CR session per week; specification of blood-based biomarkers; and updated power calculation based on sample increase)	10/01/2023
Protocol CRiB2 3.5	Changes for substantial amendment 2 (addition of the optional EEG study component; increase of the timeframe for saliva sample collection from 1 to 3 days after W0 and W13 study visits; and addition of PIC sites for secondary/tertiary care patient identification)	31/05/2023
Protocol CRiB2 4.0	Changes for substantial amendment 3 (change of the EEG device and addition of the Oxford site to the optional EEG component)	25/09/2023

The electronic version of this document is the latest version. It is responsibility of the individual to ensure that any paper material is the current version. Printed material is uncontrolled documentation.

Protocol CRiB2 4.5	Changes for substantial amendment 4 (addition of a new questionnaire to evaluate satisfaction with Cognitive Remediation therapy; replacement of the NIHR logo with updated version in all study documents)	25/07/2024
Protocol CRiB2 5.0	Changes for substantial amendment 5 (addition of an optional study component examining participant perspectives of cognitive remediation; 12-month extension of the study duration)	16/09/2024
Protocol CRiB2 5.5	Changes for non-substantial amendment 4 (removal of the 'English language capacity' exclusion criterion)	25/10/2024

3. Glossary of terms

AE: adverse event

AR: adverse reaction

BD: bipolar disorder

BRC: biomedical research centre

CAR: cortisol awakening response

CI: chief investigator

CIRCuiTS: CR computerised programme (specific CR intervention used in this trial)

CMHT: community mental health team

CR: cognitive remediation

CRF: clinical research facility

CRiB2: cognitive remediation in bipolar efficacy and mechanism trial

CTQ: childhood trauma questionnaire (Bernstein et al., 2003)

DHEA: dehydroepiandrosterone

DMEC: data monitoring and ethics committee

DSM-5: diagnostic and statistical manual of mental disorders 5th edition

EDC: electronic data capture

EEG: electroencephalography

EQ5D-3L: EuroQol 5 dimension health-related quality of life scale – 3 levels (Fryback & Hanmer, 2005)

FAST: functional assessment short test (primary outcome of psychosocial functioning) (Rosa et al., 2007)

GAS: goal attainment scale (Turner-Stokes, 2009)

GCP: good clinical practice

HAMA: Hamilton anxiety rating scale (Hamilton, 1959)

HAMD: Hamilton depression rating scale (Hamilton, 1960)

HTA: human tissue act

IME: important medical event

IS: identification code

IRAS: integrated research application system

ISRCTN: international Standard Randomised Controlled Trial Number

KCL: King's College London

KCTU: King's clinical trials unit

MAI: metacognitive awareness inventory (Schraw & Dennison, 1994)

The electronic version of this document is the latest version. It is responsibility of the individual to ensure that any paper material is the current version. Printed material is uncontrolled documentation.

MEQ: morningness-eveningness questionnaire (Horne & Östberg, 1976)
MINI-7: Mini international neuropsychiatric interview (version 7 for DSM-5) (Sheehan et al, 1998)
MoCA-T: Montreal cognitive assessment (telephone version) (Nasreddine et al., 2005)
MSI-BPA: Maclean screening instrument for borderline personality disorder (Zanarini et al., 2003)
NHS: national health service (UK)
NIHR: national institute for health research
PANAS: positive and negative affect scale (Thompson, 2007)
PDQ: perceived deficits questionnaire (Fehnel et al., 2016)
PI: principal investigator
PIS: participant information sheet
PSQI: Pittsburgh sleep quality index (Buysse et al., 1989)
REC: research ethics committee
RCT: randomised controlled trial
SAE: serious adverse event
SAP: statistical analysis plan
SAR: serious adverse reaction
SD: standard deviation
SOP: standard operating procedure
STOP-BANG: Obstructive Sleep Apnea questionnaire (Chung et al., 2016)
SUSAR: suspected unexpected serious adverse reaction
TAU: treatment as usual
TIDieR: template for intervention description and replication guidelines
TMG: trial management group
TMT: trail making test (Heaton, 2004)
TOPF: test of premorbid functioning (Wechsler, 2011)
TSC: trial steering committee
UAR: unexpected adverse reaction
VPA: verbal paired associates
WAI-SR: working alliance inventory – short revised (Hatcher & Gillaspay, 2006)
WAIS-IV: Wechsler abbreviated scale of intelligence 4th version (Wechsler, 2014)
WMS-IV: Wechsler memory scale 4th version (Wechsler, 2009)
UK: United Kingdom
YMRS: Young mania rating scale (Young et al., 1978)

4. Protocol Contents

1. PROTOCOL FULL TITLE	1
1. STUDY SYNOPSIS	6
2. REVISION HISTORY	8
3. GLOSSARY OF TERMS	9
4. PROTOCOL CONTENTS	11
5. BACKGROUND & RATIONALE	13
6. TRIAL OBJECTIVES AND DESIGN	16
6.1. TRIAL OBJECTIVES	16
6.1.1. Primary post-randomisation efficacy endpoints	17
6.1.2. Secondary post-randomisation efficacy endpoints	17
6.1.3. Post-randomisation mechanistic endpoints	17
6.1.4. Tertiary endpoints	18
6.2. TRIAL DESIGN	18
6.3. TRIAL FLOWCHART	19
7. TRIAL INTERVENTION	21
7.1. THERAPY/INTERVENTION DETAILS	21
7.2. INTERVENTION TIMELINE	22
7.3. INTERVENTION ADHERENCE	22
7.4. CONCOMITANT TREATMENTS (USUAL CARE)	23
8. RESEARCH ENVIRONMENT	23
9. SELECTION AND WITHDRAWAL OF PARTICIPANTS	23
9.1. INCLUSION CRITERIA	23
9.2. EXCLUSION CRITERIA.....	24
9.3. SELECTION OF PARTICIPANTS	25
9.4. RANDOMISATION PROCEDURE / CODE BREAK.....	25
9.5. BLINDING PROCEDURES	26
9.6. WITHDRAWAL OF PARTICIPANTS.....	26
9.7. EXPECTED DURATION OF TRIAL	27
10. TRIAL PROCEDURES	29
10.1. BY VISIT	29
10.2. LABORATORY TESTS	33
11. ASSESSMENT OF SAFETY	35
11.1. ASSESSMENT OF THERAPY SAFETY	35
11.2. SPECIFICATION, TIMING AND RECORDING OF SAFETY PARAMETERS.....	35
11.3. PROCEDURES FOR RECORDING AND REPORTING ADVERSE EVENTS	35
11.4. ADVERSE EVENTS THAT DO NOT REQUIRE REPORTING.....	36
11.5. STOPPING RULES.....	37
12. STATISTICS	37
12.1. SAMPLE SIZE.....	37
12.2. ANALYSIS.....	37

The electronic version of this document is the latest version. It is responsibility of the individual to ensure that any paper material is the current version. Printed material is uncontrolled documentation.

13. TRIAL STEERING COMMITTEE	38
14. DATA MONITORING.....	38
15. DIRECT ACCESS TO SOURCE DATA AND DOCUMENTS	39
16. ETHICS & REGULATORY APPROVALS.....	39
17. QUALITY ASSURANCE	40
18. DATA HANDLING	40
19. DATA MANAGEMENT	41
20. PUBLICATION POLICY.....	41
21. INSURANCE / INDEMNITY	41
22. FINANCIAL ASPECTS.....	42
23. SIGNATURES.....	42
24. REFERENCES.....	43

5. Background & Rationale

Bipolar disorder (BD) is one of the most disabling health related conditions, contributing at least 2% to the total disability adjusted life-years of non-communicable diseases worldwide in 2005 (Prince et al, 2007). Bipolar disorder typically first occurs at the beginning of adult life, when life-long relationship and occupational trajectories are established, potentially causing serious and long-lasting social and functional impairment. The cost to society is also considerable, in terms of lost productivity and in the direct costs related to health care. In the United Kingdom, the annual social and economic cost of the disorder has been estimated as £2 billion in 2002 (Gupta & Guest, 2002). More recently, the annual NHS cost of bipolar disorder was estimated at £342 million, with inpatient admissions accounting for 60%, outpatient and community mental health for 26.7%, and medication in primary care for 7.4% of the overall direct health care costs (Young et al, 2011). Secondary preventative treatment would reduce the personal burden of the illness, and fewer future admissions would provide a significant cost saving to the NHS. At present, bipolar disorder is regarded as a chronic illness, and research has shown that individuals with psychiatric diagnoses have better recovery when they receive combined pharmacological and psychological treatments (Pampallona et al., 2004). Further research is required to develop and investigate useful psychological interventions that are cost-effective and could be provided routinely in health services.

One potential target for therapy is cognition. Bipolar disorder is associated with widespread cognitive deficits, which are present not only during mood episodes, but also after remission of symptoms. Evidence is convincing that there is a significant association between cognition and functioning in BD, with cognitively impaired patients showing significantly poorer levels of psychosocial or community functioning, functional capacity or quality of life (Burdick et al., 2014; Jensen et al., 2016), as well as greater difficulties in occupational functioning (Tsapekos et al., 2021a). Preliminary findings are consistent with a pattern of deterioration in cognitive function as the illness progresses and cognitive impairment is a factor that may predict increased recurrence of episodes (Daban et al., 2006). This is similar to the pattern of findings in schizophrenia research, for which a new psychological treatment targeting cognition has shown promising results: cognitive remediation therapy (CR). This intervention has demonstrated many positive findings for cognition in people with a diagnosis of schizophrenia, as well as improved psychosocial functioning, including work and social functioning, quality of life and severity of psychiatric symptoms (Wykes et al, 2007; Wykes et al., 2011; Vita et al., 2021). In a meta-analysis of CR for different disorders, Anaya et al. (2012) demonstrated a beneficial effect of CR in patients with mood disorders. Since then, CR has been increasingly recognised for its potential in bipolar disorder (Tsapekos et al., 2019). For example, a small number of pilot trials using CR or functionally targeted therapy based on CR principles have reported benefits in executive functioning and quality of life for people with bipolar disorder (Bernabei et al. 2020; Lewandowski et al., 2017; Torrent et al., 2013).

Our recently completed CRiB feasibility trial (CRiB1; Strawbridge et al. 2016) employed a CR programme delivered to individuals with bipolar disorder using an evidence-derived manualised programme (CIRCuiTS) that is therapist-led and partly computerised. Participants (n=60) were randomised to receive CR and treatment as usual (TAU) or TAU only. Those who received CR showed

greater cognitive and functional improvements after the intervention that were maintained 12 weeks later (medium to high effect sizes at both timepoints) (Strawbridge et al., 2021).

In summary, with compelling evidence from schizophrenia research showing that CR can improve cognition and functioning, and initial findings from BD research pointing towards comparable benefits, the crucial next step is to establish the efficacy of CR and investigate its mechanisms of action in an appropriately powered trial. Providing robust evidence that improving cognition can facilitate functional recovery in people with BD could have substantial implications for clinical practice and the quality of care provided to patients with BD, as well as it could prospectively reduce the costs associated with care provision.

Efficacy

The results from this study as well as systematic reviews of the topic (Bellani et al., 2019; Tsapekos et al. 2019) indicate that the therapeutic effects of CR are pronounced in studies that employ a systematic cognitive training programme with a focus on metacognition and transfer of cognitive gains to everyday life, delivered in individual rather than group format and with a sufficient time intensity. The only UK trial conducted to date was our CRiB1 pilot trial, however this type of CR has reliably conferred benefits in UK trials in people with psychosis. An adequately powered trial of CR, including these therapeutic ingredients, is now needed to establish its efficacy in individuals with bipolar disorder.

The current study (CRiB2) is the first appropriately powered (in addition to robustly designed) RCT testing the efficacy of this feasible and acceptable evidenced CR package compared with TAU in individuals with bipolar disorder. CR will be delivered over a 12-week period, using a combination of routes (i.e., face-to-face and remote sessions plus individual practice), amounting to 20-40 hours of therapy engagement in total. Efficacy will be assessed immediately after the 12-week intervention (week 13 post-randomisation) and at the end of a 12-week follow up period (week 25 post-randomisation) using a blinded-rater assessment of psychosocial functioning.

Mechanisms

CRiB2 also integrates an exploratory mechanistic component to indicate how CR might exert its therapeutic effects on cognition and functioning.

One potential biomarker of cognitive improvement to be explored in CRiB2 is cortisol. **Cortisol** is important for the regulation of cognitive processes, with several studies reporting causal associations between change in cortisol levels and cognitive functioning (Strawbridge & Young 2016). Indeed, other cognitive interventions (e.g., mifepristone) directly influence cortisol regulation. Higher baseline cortisol levels were correlated with greater cognitive benefit from mifepristone and cortisol decrease was a factor associated with cognitive benefits (Young et al. 2004, 1999, Watson et al. 2012). Therefore, cognitive remediation interventions potentially exert a cognitive effect by influencing cortisol production. We hypothesise that CR will generate changes in cortisol regulation from enhanced top-down regulation of the hypothalamic-pituitary-adrenal axis (Arnsten 2015) and that these changes will be causally associated with improved cognitive

functioning. Therefore, the trial will investigate whether changes in **cortisol** levels at treatment end (week 13) are associated with improved global cognitive functioning at follow-up (week 25).

Other potential biomarkers to be explored in CRiB2 are **inflammatory markers and growth factors** in plasma. A cross-sectional analysis of the CRiB1 sample demonstrated that several of these markers, including interleukin-6 (IL-6), interleukin-7 (IL-7), interleukin-16 (IL-16), brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor C (VEGF-C), placental growth factor (PIGF), macrophage inflammatory protein-1 β (Mip-1 β), tumour necrosis factor- β (TNF- β), and basic fibroblast growth factor (bFGF), were associated with cognitive performance at baseline (Strawbridge et al., 2021). These are candidate markers of cognitive improvement in bipolar disorder and affecting their plasma levels might be one of the mechanisms cognitive remediation interventions exert their effect on behavioural outcomes. Although an exploratory analysis, we do expect that changes in plasma-based **inflammatory markers and growth factors** (i.e., IL-6, IL-7, IL-16, BDNF, VEGF-C, PIGF, Mip-1 β , TNF- β , and bFGF; Strawbridge et al., 2021) at treatment end (week 13) will be associated with improved global cognitive functioning at follow-up (week 25).

In terms of mechanisms underlying functional improvement, an exploratory analysis of CRiB1 data indicated that post-treatment benefits in **global cognition** accounted for more than one third (35%) of the therapy effect on psychosocial functioning at follow-up (Tsapekos et al., 2021b). This was one of the first studies supporting the theoretical assumption that CR-induced changes in cognition are translated into functional improvements in people with BD, consistent with previous evidence suggesting an indirect effect of cognition on functional outcomes in people with schizophrenia (Reeder et al., 2017; Wykes et al., 2012). The characteristics of our CR paradigm may explain how cognitive changes exert an effect on psychosocial functioning since CIRCuiTS prompts the development and use of strategies to compensate for cognitive difficulties, while a substantial part of therapy time is devoted to how participants can transfer newly acquired strategies and cognitive skills to daily-life activities.

Secondly, **metacognition** might explain the effect of CR on functioning. Metacognitive skill development includes improving understanding of one's own capabilities; strengths, weaknesses, strategies that can enable higher-level cognitive and functional task successes. We and others (Tsapekos et al. 2020; Douglas et al. 2019) have suggested that building metacognitive skills could be responsible for greater everyday life benefits, as identified for those with psychosis (Cella et al. 2015). However, only CIRCuiTS (described below), incorporates a focus on metacognitive development as a key tool to improve functioning in daily life. An exploratory analysis from CRiB1 provided a preliminary indication of the role of metacognitive awareness as a mediator of the CR effect on functioning. We found that changes in participants' awareness of their cognitive strengths and weaknesses by week 13 partially mediate the effect of CR on functioning at week 25.

Thirdly, regulatory networks described above for cortisol are also likely critical to the regulation of affect (Arnsten 2015) and impairment of these networks can be associated with **affective instability**. Affective instability is a characteristic feature of BD that is associated with adverse outcomes such as functional impairment (Marwaha et al. 2014). Cognitive control processes regulate affective responses (Ochsner & Gross 2005) which suggests that CR's mechanism of action may include enhanced cognitive control, leading to reduced affective instability, thus improving psychosocial functioning.

Hence, CRiB2 will examine whether post-treatment (week 13) changes in **metacognition** and **affective instability**, (in addition to changes in **global cognitive performance**) are associated with improved psychosocial functioning at follow-up (week 25).

6. Trial Objectives and Design

6.1. Trial Objectives

CRiB2 aims to establish whether CR provides significant and durable benefits for the lives of people with bipolar disorder. The primary objective is to test the efficacy of CR for improving psychosocial functioning in people with bipolar disorder, compared to TAU. The primary outcome measure will be the Functional Assessment Short Test (FAST) 25 weeks after randomisation (12 weeks post-intervention), reflecting a prioritisation of longer-term outcomes evaluating psychosocial functioning. The FAST at week 13 (immediately post-intervention) will measure short-term efficacy, a secondary objective. We hypothesise an improvement in FAST in those randomised to CR+TAU (compared with those randomised to TAU) at both time points.

Secondary objectives comprise examination of the effects of CR on cognition (global and individual cognitive domains), subjective cognitive complaints (Perceived Deficits Questionnaire; PDQ), affective symptom severity (Hamilton Depression Rating Scale; HAMD, & Young Mania Rating Scale; YMRS), sleep quality (Pittsburgh Sleep Quality Index; PSQI), patient-defined goal attainment (Goal Attainment Scale; GAS) and health related quality of life (EuroQol 5 Dimension – 3 Levels; EQ5D-3L), all at both week 13 and week 25. We hypothesise that these outcomes will be improved at week 25 (and week 13) post-randomisation in those randomised to CR compared with those randomised to TAU.

Mechanistic objectives/outcomes are as follows:

1. We will investigate whether reducing cortisol secretion is a mechanism of CR action by assessing change in cortisol (week 13 levels, adjusted for week 0) between those randomised to CR versus TAU and the association between cortisol change and global cognition composite score at week 25. We hypothesise that CR will reduce levels of cortisol (in contrast to no changes in the TAU group) and that these cortisol reductions will be associated with subsequently improved cognitive function.
2. We will investigate whether a recommended composite measure of global cognitive performance (as per Strawbridge et al. 2020) (week 13 score, adjusted for week 0) mediates the association between CR (versus TAU) and the subsequent primary outcome of psychosocial functioning (FAST) at week 25. We hypothesise that CR will improve global cognition (over and above TAU) and that these cognitive improvements will be associated with subsequently improved functioning.
3. We will investigate whether metacognitive skills improvement is a mechanism of CR action by assessing its mediating effects, evaluated by the Metacognitive Awareness Inventory (MAI) and the Torres' method (week 13 scores, adjusted for week 0) on functioning (FAST) at week 25. We hypothesise that CR will improve metacognition (over and above TAU) and that these metacognitive improvements will be associated with subsequently improved functioning.

4. We will investigate whether reduced affect fluctuation as a putative mechanism of CR action by assessing change in mood symptom instability (Pulcu et al., 2021), evaluated by the Positive and Negative Affect Schedule (PANAS; variability in bidaily mood scores across 7 days in week 13-14, adjusted for variability in daily mood scores across the 7 days in week 0-1) between those randomised to CR versus TAU and the association between affect fluctuation changes and psychosocial functioning at week 25. We hypothesise that CR will reduce fluctuation in PANAS scores between these two timepoints (in contrast to no changes in the TAU group) and that this reduction in affect fluctuation will be associated with subsequently improved functioning.

Tertiary objectives are exploratory/mechanistic and will not be presented in primary publications of results. These include a) the examination of potential CR effects moderation by early-life trauma (Childhood Trauma Questionnaire; CTQ), anxiety symptom severity (Hamilton Anxiety Rating Scale; HAMA), chronotype (Morningness-eveningness questionnaire; MEQ), borderline personality disorder traits (MacLean Screening Instrument for Borderline Personality Disorder; MSI-BPD), and sleep spindle density (through home-based sleep electroencephalography [EEG] assessment; optional at the London and Oxford site only) at week 0 (baseline), b) the examination of the role of therapeutic alliance (Working Alliance Inventory – Short Revised; WAI-SR), rated during therapy at week 3 and week 12, as a factor potentially modifying the effect of CR on functioning, c) the examination of the ratio of cortisol to dehydroepiandrosterone (DHEA) as a factor potentially underlying the effect of CR on cognition, d) the examination of plasma-based inflammation and growth factors as candidate markers of cognitive improvement following CR, and e) the examination of participant feedback on the content and the delivery of CR using a combination of quantitative and qualitative approach ('Perspectives of CR' sub-study).

6.1.1.Primary post-randomisation efficacy endpoints

- Psychosocial functioning (FAST) at week 25 (end of 12-week follow-up period)

6.1.2.Secondary post-randomisation efficacy endpoints

- Psychosocial functioning (FAST) at week 13 (end of 12-week treatment period)
- Global cognition composite score and individual cognitive domain scores (processing speed, working memory, verbal learning and memory, executive function) at week 13 and week 25. The measures used for these are delineated below in section 10.1.
- Cognitive complaints (PDQ) at week 13 and week 25
- Attainment of patient-defined goals (GAS) at week 13 and week 25
- Sleep quality (PSQI) at week 13 and week 25
- Health related quality of life (EQ5D-3L) at week 13 and week 25
- Interviewer-rated depression (HAMD) and mania (YMRS) symptom severity at week 13 and week 25.

6.1.3.Post-randomisation mechanistic endpoints

- Cortisol awakening response (CAR) and basal cortisol level in saliva samples at week 13

The electronic version of this document is the latest version. It is responsibility of the individual to ensure that any paper material is the current version. Printed material is uncontrolled documentation.

- Global cognition composite score at week 13
- Metacognitive awareness (MAI), knowledge and experience (Torres' method) at week 13
- Affect fluctuation (PANAS) at week 13

6.1.4. Tertiary endpoints

- Pre-randomisation: potential (exploratory) treatment effect moderators of premorbid IQ (TOPF), childhood trauma (CTQ), interviewer-rated anxiety (HAMA), chronotype (MEQ), traits of borderline personality disorder (MSI-BPD), and sleep spindle density (EEG; optional for London and Oxford site only) at week 0 on primary outcome at week 25.
- Post-randomisation: potential (exploratory) treatment effect modification of therapeutic alliance (WAI-SR) rated during therapy, at week 3 and week 12 (average score) on primary outcome at week 25.
- Post-randomisation: potential (exploratory) treatment effect mediation of the cortisol-DHEA ratio at week 13 on secondary outcome (global cognition composite score) at week 25.
- Post-randomisation: potential (exploratory) treatment effect mediation of inflammatory markers and growth factors at week 13 on secondary outcome (global cognition composite score) at week 25.
- Post-therapy completion: participant perspectives of CR therapy content and delivery (optional for all sites) after week 13.

6.2. Trial Design

A multisite, single-blind (outcome assessor) randomised controlled trial (RCT) investigating cognitive remediation therapy (CR) for people with bipolar disorder who are currently in a euthymic state, as indicated by stable mood and absence of acute symptoms for at least one month. We will recruit 250 people with bipolar disorder, half of which will be randomised to a 12-week course of computerised CR (CIRCuiTS), aiming to include 30-40 hours of therapy. Participants will be recruited across 4 sites: London (n ~ 100), Birmingham (n ~ 60), Oxford (n ~ 40), and Newcastle (n ~ 50). After all baseline data are collected and complete, participants will be randomised by accessing the bespoke study web-based randomisation system created and hosted by King's College Clinical Trial Unit (KCTU) in a 1:1 ratio into TAU or CR+TAU arms; further details pertaining to randomisation procedures can be found below in Section 9.4. The intervention period lasts for 12 weeks (outcomes assessed at week 13 post-randomisation) and the follow-up period lasts for 12 weeks (week 25 post-randomisation; primary outcome endpoint). The researchers conducting cognitive assessments will be blind to group status of each participant (i.e., intervention or treatment-as-usual arm); further details about blinding can be found below in Section 9.5.

6.3. Trial Flowchart

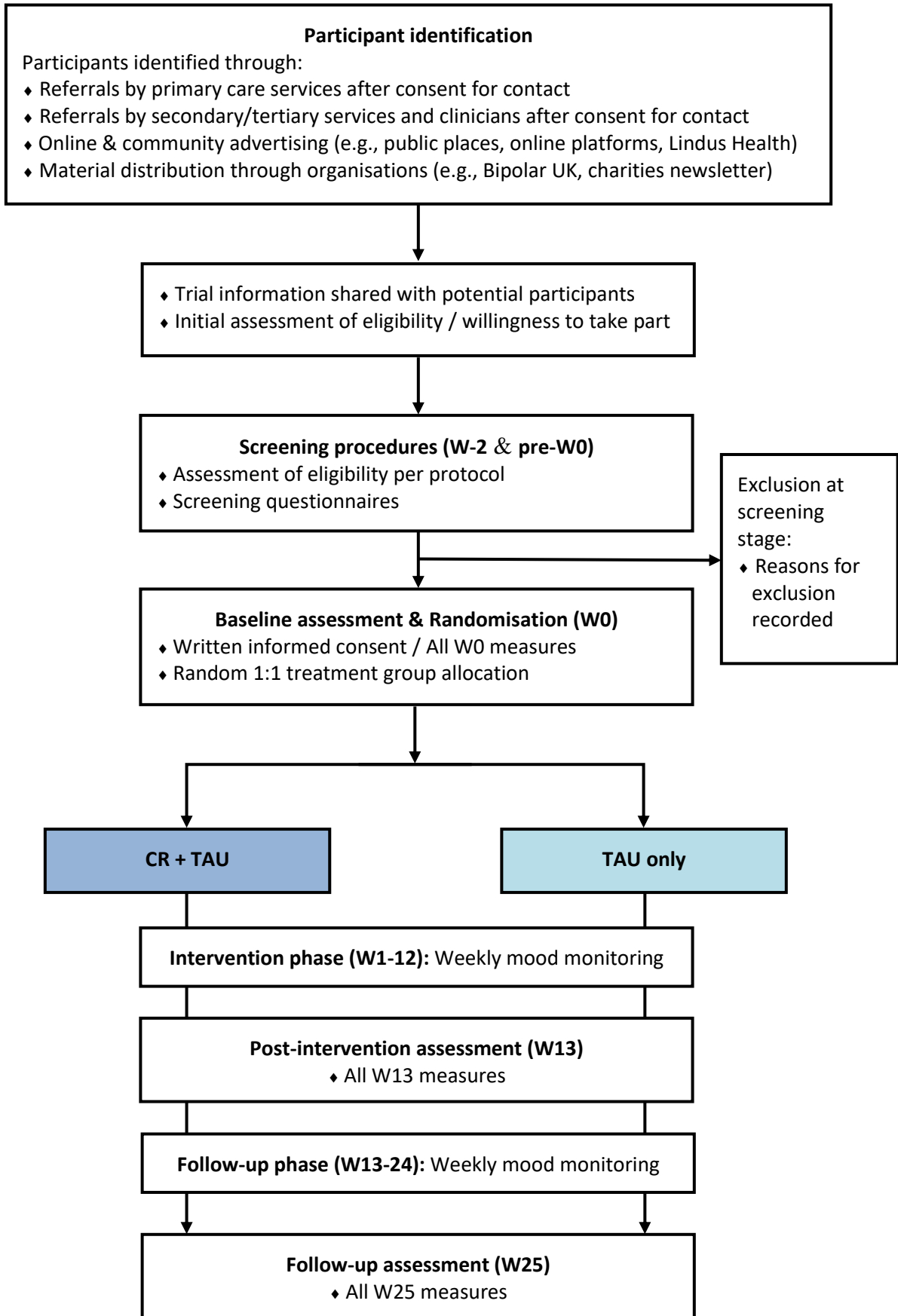


Table 1: Summary of study procedures and measures.

Procedures/Measures	Screening (W-2)	Baseline (W0)	Intervention (W1-12)	Post (W13)	Follow-up (W25)	All (W1-24)
<i>Administrative</i>						
Eligibility assessment	x					
Informed consent		x				
Randomisation		x				
CR delivery			x			
Blinding				x	x	
<i>Eligibility</i>						
Patient information	x					
MINI 7	x	x ^a				
TOPF / MoCA-T	x					
HAMD / YMRS	x	x		x	x	
STOP-BANG ^c	x					
<i>Interview-based</i>						
Sociodemographic		x		x	x	
Illness history		x				
Service use		x		x	x	
<i>Baseline only</i>						
CTQ / HAMA / MEQ / MSI-BPD		x				
EEG ^c		x				
<i>Efficacy outcomes</i>						
Cognitive battery (Hotel test, WMS-IV, WAIS-IV ^b , TMT, FAS)		x		x	x	
FAST / GAS		x		x	x	
PDQ / PSQI / EQ5D-3L		x		x	x	
<i>Mechanistic outcomes</i>						
Saliva/blood sample		x		x		
PANAS		x		x		
MAI / Torres		x		x	x	
<i>Therapy-related</i>						
WAI-SR			x (W3, W12)			
CR satisfaction/feedback				x		
<i>Monitoring</i>						
Adverse Events		x		x	x	x
Mood monitoring						x

^a MINI comorbidity data not required prior to inclusion (e.g., anxiety disorders) will be assessed at W0 instead of W-2. ^b preselected tests rather than whole scales: WMS-IV Verbal Paired Associates I & II; WAIS-IV Digit Span & Coding. ^c optional at London and Oxford site only. *Notes:* CR: Cognitive Remediation Therapy; CTQ: Childhood Trauma Questionnaire; EEG: Electroencephalogram; EQ5D-3L: EuroQoL-5 Dimensions – 3 Levels; FAS: F-A-S letters verbal fluency test; FAST: Functioning Assessment Short Test; GAS: Goal Attainment Scale; HAMA: Hamilton Anxiety Rating Scale; HAMD: Hamilton Depression Rating Scale; MAI: Metacognitive Awareness Inventory; MEQ: Morningness-Eveningness Questionnaire; MINI 7: Mini International Neuropsychiatric Interview for DSM-5; MoCA-T: Montreal Cognitive Assessment-Telephone version; MSI-BPD: MacLean Screening Instrument for Borderline Personality Disorder; PANAS: Positive and Negative Affect Schedule; PDQ: Perceived Deficits Questionnaire; PSQI: Pittsburgh Sleep Quality Index; STOP-BANG: Obstructive Sleep Apnea questionnaire; TMT: Trail Making Test; TOPF: Test of Premorbid Functioning; MVAS: Maudsley Visual Analogue Scale; W: week; WAIS: Wechsler Adult Intelligence Scale, 4th edition; WAI-SR: Working Alliance Inventory-Short Revised; WMS-IV: Wechsler Memory Scale, 4th edition; YMRS: Young Mania Rating Scale.

The electronic version of this document is the latest version. It is responsibility of the individual to ensure that any paper material is the current version. Printed material is uncontrolled documentation.

7. Trial Intervention

7.1. Therapy/Intervention Details

This section relates to the Cognitive Remediation Therapy (CR) intervention (n=125); for details of usual care, please see section 7.4. Information about CR are presented here according to the TiDieR guidelines for intervention description and replication (Hoffman et al., 2014).

Participants in the intervention arm will receive a 12-week course of therapist-led CR using the online software 'Computerised Interactive Remediation of Cognition – Interactive Training for Schizophrenia' (CIRCuiTS; www.circuitstherapy.com). CIRCuiTS is a manualised CR approach (Reeder & Wykes, 2010), developed according to the basic principles of CR (e.g., errorless learning, scaffolding, positive feedback develop of strategies; Wykes & Reeder, 2005). Apart from offering rigorous cognitive training with computerised tasks to enhance cognition, this approach emphasises strategy use, metacognitive skill development, and transfer of cognitive skills to daily life activities to facilitate functional recovery.

CIRCuiTS tasks are set in a virtual village where participants can practice 36 different cognitive tasks, each one with at least 12 gradually increasing levels of difficulty. Progress to higher difficulty levels depends on the accuracy scores achieved, with progression occurring only when the 80% proficiency threshold is achieved. This is to facilitate errorless learning and to maintain treatment engagement and high levels of positive feedback for the participant. Cognitive tasks in CIRCuiTS are differentiated between abstract tasks and exercises. Abstract tasks are targeting specific cognitive functions, such as speed of processing (e.g., finding the exit on a maze route), while exercises are designed as more complex ecologically valid tasks simulating real-life activities, such as social interactions, travelling, shopping or work, implicating multiple cognitive functions (e.g., planning the calendar of a working day). Exercises take place in different locations within the CIRCuiTS village (e.g., a train journey initiates at the train station) which provides a social context for task practice. This allows participants to consider the transfer of strategies and metacognitive processes from the software tasks to real-life activities.

CR will be delivered by postgraduate level therapists with supervision from an experienced clinical psychologist. All therapists will have completed training in the theoretical framework of CIRCuiTS and the delivery of CR using the CIRCuiTS software. Supervision will be routinely provided in a group format (held fortnightly) to discuss therapist cases, adherence and implementation challenges, and best practice to facilitate transfer. Group supervision sessions will be supplemented by individual sessions to discuss training needs, personal issues and professional development. In CIRCuiTS, the role of the therapist is critical for prompting strategy use and promoting the metacognitive components of the therapy. Therapists support participants to select and apply strategies, identify strengths and shortcomings in their own cognitive functioning, and set real-life cogSMART goals (i.e., specific, measurable, attainable, realistic, and timely goals that are related to cognitive improvement) which are reviewed throughout the therapy. Cognitive difficulties and their impact on people's lives is formulated considering the metacognitive competencies (i.e., metacognitive knowledge and regulation), as well as non-cognitive factors (e.g., procrastinating, anxiety, fatigue or sleeping difficulties) (Cella et al., 2015). Therapists are important to facilitate the transfer of

cognitive gains and new learning to daily life functioning through examples, role-playing, and in vivo practicing.

CR will be flexibly provided to participants over the course of 12 weeks. Therapy delivery involves one-on-one sessions with the therapist (usually 1 hour long), either in person or remotely (i.e., telephone or video). Face-to-face sessions will take place at NHS Trust or university facilities at each site, depending on local arrangements between the recruitment sites and the associated universities/NHS Trusts. For King's College London, therapy sessions will be held at the Clinical Research Facility of King's College Hospitals which fulfils all necessary requirements for accommodating therapy sessions (i.e., quiet rooms, computers, internet access). The target for therapy engagement is 2-3 hourly sessions per week aiming for a total of ~30 sessions over 12 weeks. Participants will be encouraged to attend these sessions in person. If not feasible, a blend of face-to-face and remote sessions will be offered. Additionally, all individuals will be provided access to CIRCuiTS for additional independent practice as agreed in communication with the therapist.

Although the same CR paradigm will be offered to all participants in the intervention arm, therapy will be tailored towards the individual needs of each participant. Tailoring refers not only to a delivery format, but also the therapy content in terms of cognitive task selection, implementation of strategies, and individual goal setting.

Fidelity to the therapy approach and the core principles of CR with CIRCuiTS will be initially ensured through the provision of similar training across trial therapists and will continuously evaluated through supervision. Treatment adherence (e.g., session attendance) will be monitored and recorded for all participants in their individual therapy log.

7.2. Intervention timeline

The intervention will begin at W1, 1 week after baseline assessment and randomisation. Data from the CRiB feasibility trial demonstrated that this period is ample for participants and therapists to make contact and schedule the start of therapy. Starting from week 1, the intervention will continue for an interrupted 12-week treatment period (W1-W12). Following post-treatment assessment (W13), there will be a 12-week follow-up (W13-W24) where all participants will continue receiving usual care only and at week 25, a final follow-up assessment will be completed (W25).

7.3. Intervention adherence

Following evidence from a feasibility study in people with schizophrenia (Reeder et al., 2016), it was decided that 20 hours of CIRCuiTS would be the minimum dose for treatment completion. Hence, to be considered adherent, participants must have completed at least 20 hours, as calculated from time spent in face-to-face or remote sessions with the therapist plus time spent on the CIRCuiTS online program outside of these sessions. Engagement in each of these formats will be estimated based on each participant's therapy log records. We are employing strategies for engaging participants in the intervention by initially scheduling sessions tailored to participant

preferences and schedule (e.g., planned number of face-to-face, remote, and independent practice sessions per week) and also sending text reminders when necessary.

7.4. Concomitant treatments (usual care)

All participants will continue receiving TAU including all concomitant interventions and service use. We will monitor and record pharmacological and non-pharmacological therapy use, as well as other use of healthcare services throughout the trial, including any changes, at every assessment time-point (W13 and W25).

8. Research environment

The study will take place in four locations (London, Oxford, Birmingham, Newcastle) with clinical academic sites and services for people with BD, at the convenience of each participant. For the London site, the Clinical Research Facility (CRF) at King's College Hospital will be used as the primary research environment for study procedures. The CRF is a purpose-built facility to support clinical trials in mental health and provides ideal infrastructure for experimental studies and neuropsychological testing (e.g., quiet, private rooms with appropriate space for cognitive testing materials). Similar type facilities will be used in the other research sites (Oxford CRF, Birmingham and Solihull Mental Health NHS Foundation Trust, Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust).

All face-to-face aspects of the research study will be conducted in full compliance with ongoing Covid-19 national and local guidelines. In the event of restrictions to face-to-face contact, our procedures can be adapted to enable the study to continue fully remotely, although this will only take place if considered necessary from this national and local guidance.

9. Selection and Withdrawal of Participants

9.1. Inclusion Criteria

Participants will:

- 1) have a DSM-5 diagnosis of bipolar type I or II (validated using the MINI 7 interview);
- 2) be aged between 18 and 65 years;
- 3) be euthymic according to the Newcastle Euthymia Protocol (Thompson et al. 2005). This euthymia criteria requires participants to score less than 8 on both the Hamilton Rating Scale for Depression (HAM-D) and Young Mania Rating Scale (YMRS) (standardised cut-off scores) covering the previous month. These scoring criteria must be met at both timepoints assessed prior to inclusion – the two timepoints are a first screen 2 weeks before baseline assessment will be scheduled, and the second within 24 hours before informed consent);

4) be able to use a computerised device (defined as having used a computer, a tablet or a smartphone at least once in the prior 4 weeks without any difficulties), even if not currently having access to a computerised device.

9.2.Exclusion Criteria

People meeting any of the following criteria will be excluded:

- 1) Comorbid alcohol/substance use diagnosis in the past 12 months (assessed using the MINI 7 interview);
- 2) Current risk of suicide (assessed using the MINI 5 interview);
- 3) Indications of cognitive decline (assessed using the MoCA-T) or impairing organic neurological disorder (assessed using patient-report, and checked with a medical practitioner);
- 4) Having undertaken a manualised cognitive remediation therapy any time in the past;
- 5) Have an IQ <80 as informed by the Test of Premorbid Functioning (TOPF);
- 6) Currently undergoing a formal psychological therapy or specifically planning changes to treatment (medication or initiation of a new therapy) over the coming 6 months (trial period);
- 7) Not having registered with a primary healthcare professional in the UK (i.e., General Practice) or unwillingness to provide their details for the study to contact;
- 8) Unable to travel to one of the research sites on a regular basis over 25 weeks;
- 9) Unable to provide informed consent to participate, for any other reason.

Participants opting to take part in the optional EEG-assessment at the London and Oxford site will be excluded from the EEG-assessment if they meet any of the following criteria:

- 10) Have a diagnosed or probable sleeping disorder, such as sleep apnea, narcolepsy or REM-sleep-behaviour disorder (assessed using patient-report and the STOP-BANG questionnaire for sleep apnea);
- 11) Have a disorder associated with significantly impaired sleep, such as polyneuropathy or chronic back pain (assessed using patient-report);
- 12) Have an inflammatory condition, a neurological condition, or any other condition likely to interfere with EEG interpretation, such as epilepsy, cerebral palsy or multiple sclerosis (assessed using patient-report);
- 13) Currently use melatonin, benzodiazepines, zopiclone, or zolpidem on a regular basis;
- 14) Had recent (within past 4 weeks) trans meridian travel (across more than 3 time zones);
- 15) Currently perform shift- or night-time work.

Individuals of any sex/gender can take part. Where there is any doubt as to the validity of BD diagnoses, euthymia (as above), current suicide risk or impairing neurological disorder (see below), each potential participant's assessments requires validation with a practising psychiatrist collaborating with the study team (study CI, PI, clinical lead or other clinician within the participating research teams). Informed consent to participate will be obtained before inclusion into the study.

Participants opting to take part in the optional 'Perspectives of CR' component will need to have been previously allocated to the intervention arm and have completed the CR therapy course. A separate informed consent will be obtained for inclusion in this sub-study.

9.3. Selection of Participants

There will be 4 routes for participant selection:

1. Secondary/tertiary care services at each site (e.g., the National Affective Disorders Service, the OPTIMA Mood Disorders Programme, Mood on Track, Birmingham specialist assessment clinic, and Oxford specialist bipolar disorder research clinic).
2. Secondary care services: assessment and liaison, home treatment, CMHT and other services within the local Trusts of each centre. NHS Participant Identification Centres will also facilitate identification of participants from secondary care services across neighbouring boroughs in each site. We also have access to the CRIS electronic records health system, which allows patients in secondary care services across London, Oxfordshire, Buckinghamshire, and Cumbria/Northumberland/Tyne and Wear to be identified. This service allows approved researchers to rapidly screen case notes of service users who have agreed that researchers can access their contact details and limited clinical information and invite them to participate in research projects. We will utilise the SLaM Consent for Contact (C4C) initiative to recruit Trust patients and will follow the related Trust policy.
3. Primary care services i.e. GP mailouts to local patients as coordinated by CRN Portfolio teams.
4. Community offline and online advertisements: posters in the public domain, the Centre for Affective Disorders (KCL) database of people interested in research participation, online advertising via research portals (e.g., NIHR BRC, MQ) and collaboration with Bipolar UK, social media posting, advertising campaigns on various platforms, such as Gumtree, Facebook and Google to publicise the study to interested potential participants. We also aim to collaborate with Lindus Health (<https://www.lindushealth.com/>), a specialist recruitment service assisting clinical trials with running online advertising campaigns and accelerating participant identification.

After potentially eligible individuals are identified through any of these routes, they will be provided with information about the study and a full screening for eligibility will take place subject to verbal consent; for details, see Section 10).

9.4. Randomisation Procedure / Code Break

Following written consent, participants will be randomised in a 1:1 ratio to one of the two treatment arms (TAU, or TAU+CR) within 1-4 hours of completing the baseline assessment. A web-based randomisation system will be designed, using the bespoke KCTU randomisation system. The randomisation system will be created in collaboration with the trial analyst/s and the CI and maintained by the King's Clinical Trials Unit for the duration of the project. It will be hosted on a dedicated server within KCL. The system will employ block randomisation with randomly varying block sizes and will be stratified by site. The details needed for randomisation (study site, month/year of birth, initials and unique patient identity number) will be held in a dedicated

The electronic version of this document is the latest version. It is responsibility of the individual to ensure that any paper material is the current version. Printed material is uncontrolled documentation.

database. Only the trial coordinator (unblinded) will have access to the randomisation system (or their nominated backup in times of absence; the nominated backup will not be another member of the blinded team but will be a team member whose role on the delegation log specifies this role as contingency Trial Manager).

9.5. Blinding Procedures

While it is not possible to blind participants to their study arm, the researchers conducting cognitive post-intervention and follow-up assessments will be blind to group status of each participant (i.e., by explicitly asking participants to not disclose their group allocation). To avoid bias, the high-quality randomisation system, designed and managed by the KCTU, ensures the allocation sequence will be concealed from researchers who have conducted screening assessments; further, researchers conducting assessments will not be involved in therapy delivery procedures. Blinding will be maintained until the last participant completes the follow-up assessment. However, we concede that it is possible for participants to inadvertently disclose their study-arm during study assessments. If a researcher becomes unblinded for an individual participant, a different assessor will replace them for the remaining assessments of this participant (this procedure was trialed successfully in the CRiB feasibility study). See Table 2 for full details of individual- and group-level blinding procedures for individuals involved in the study with different roles.

In addition, data will be collected from each assessor to test the robustness and maintenance of blinding. At both post-intervention endpoints (week 13 and week 25) study assessors will be asked by the trial manager whether they have been explicitly unblinded (at the time of outcome rating) for this participant. Ratio (%) of unblinding will be estimated and reported for both the intervention and the control group.

9.6. Withdrawal of Participants

We will highlight to all participants that they are free to withdraw from the study at any time, without prejudice or consequences for either their clinical care, or involvement in any other research studies. Similarly, therapy can be discontinued at any point, if a participant withdraws from the trial or if a participant decides they no longer wish to continue the intervention. Researchers and therapists will also be available throughout the study course to answer further questions about withdrawal from the trial. The investigator also has the right to withdraw patients from the therapy and/or study in the event of current illness, ARs, SARs, SUSARs associated with the trial or therapy procedures, protocol violations, administrative reasons or other reasons. If a participant loses the capacity to consent to the study, they will be withdrawn. This will be assessed by researchers and therapists during every contact with participants (e.g., phone calls, study appointments).

Should a participant decide to withdraw from the study, all efforts will be made to report the reason for withdrawal as thoroughly as possible. Importantly, therapy discontinuation does not constitute as a withdrawal from the trial. Thus, should a patient withdraw from the intervention only, efforts

will be made to continue to obtain follow-up data, with the permission of the patient; participants who wish to withdraw from therapy will be asked to confirm whether they are still willing to provide the study data already provided for research. Efforts made to collect data for such participants will be made equally regardless of whether they are in the CR or TAU groups.

9.7.Expected Duration of Trial

The total trial duration is 25-26 weeks long: with week 0 comprising the baseline assessment, week 1 the beginning of intervention period, week 12 the end of therapy, week 13 including the post-treatment assessment, followed by a second 12-week follow-up (no intervention) period and a follow-up assessment at week 25. The beginning of the study will be week 0 (baseline assessment) of the 1st participant, estimated April 2022, and the end of the trial will be the last week of the 250th participant's follow-up assessment, estimated to be in December 2024.

Table 2: Information and procedures for blinding individuals to randomisation outcome

Roles	Individual -level	Method of blinding OR justification for unblinding	Group -level	Method of blinding OR justification for unblinding
Trial manager	U	Assigns participants to randomisation groups (is not recruiting or assessing participants)	B	No access to randomisation list or data summarised at group-level
Study participants	U	Only unblinded to their own allocation (we are unable to blind participants to receiving CR)	B	No access to randomisation list or data summarised at group-level
Trial therapists	U	Only unblinded to those seen for therapy (required for providing CR). Information about other therapists' participants may be mentioned in therapy supervision but is minimised.	B	No access to randomisation list or data summarised at group-level
Therapist supervisor	U/P	Usually blinded (not told of group assignments), unless participant details need to be conveyed for safety or wellbeing purposes	B	No access to randomisation list or data summarised at group-level
Data collectors / Outcome assessors	B	Not told of group assignment, participants asked to conceal this but blinding assessed *	B	No access to randomisation list or data summarized at group-level
Trial Statistician	B	No interaction with individual participants	U	Access to full randomisation list required for data monitoring & analysis. NB only unblinded after an initial draft of the SAP has been signed
Senior Statistician	B	No interaction with individual participants	B	No access to full randomisation list **
Principal / Chief Investigators	(U)	Usually blinded, unless participant details need to be conveyed for safety or wellbeing purposes	B	No access to randomisation list or data summarised at group-level
(independent members of) DMEC	B	No interaction with individual participants	U/P	The level of DMEC blinding will be at their discretion but will likely see data split by group at least a partially blinded level.
TSC	B	No interaction with individual participants	B	No access to randomisation list or data summarised at group-level

U = unblinded, B = blinded, P = partially blinded (i.e., see data split by groups labelled as A/B).

* assessment of unblinding as described in 9.5

** after data has all been collected, the database locked, the data have been analysed and a first draft of the statistical report has been prepared, the senior statistician will become unblinded in order to carry out final checks on the analysis code and statistical report.

10. Trial Procedures

10.1. By Visit

The summary table in section 6.3 describes the procedures at each 'visit '(or measurement timepoint) which are also described below. We refer to each timepoint by its week number (W), starting from W-2 (first screen, two weeks before study inclusion at randomisation) through to inclusion and randomisation at W0, through to W25 as the final visit.

Once identified through different recruitment sources (e.g., referral by a clinician who obtained consent for contact, direct express of interest in the study by a person), potential participants will be first contacted regarding the study by a researcher who will send them a copy of the Participant Information Sheet (PIS; via email or post). The researcher will encourage potential participants to spend as much time as they need asking questions about the study (via email or phone call) and consider whether they wish to participate or not.

As a minimum, study information will be provided to potential participants at least 24 hours prior to initial screening. After reading the PIS and having any questions answered, if the participant is happy to take part in the study, an appointment for screening will be arranged.

W-2: First screening session – Usually conducted over the phone, study information will be discussed and verbal consent for screening obtained. If the potential participant is willing, screening will provide an initial determination of eligibility. Specifically, eligibility will be assessed via screening procedures as follows:

- Eligible age range: between 18 and 65 years old.
- Diagnostic interview to confirm a DSM-5 diagnosis of bipolar type I or II: The Mini International Neuropsychiatric Interview, version 7.0 (MINI 7) for DSM-5 (Sheehan et al., 1998) will be administered by trained researchers and reviewed in collaboration with the site's trial psychiatrist to determine a current BD diagnosis (type-I or type-II).
- Intellectual disability: Test of Premorbid Functioning (TOPF; Wechsler, 2011) will be administered, with a threshold of an estimated premorbid IQ of ≥ 80 applying for inclusion.
- Indications of cognitive decline associated with organic/neurological condition: Montreal Cognitive Assessment, telephone version (MoCA-T; Nasreddine et al., 2005), will be administered, with a threshold score of > 12 applying for inclusion.
- Assessment of euthymia: Hamilton Depression Rating Scale 17-item (HAM-D; Hamilton, 1960) and Young Mania Rating Scale (YMRS; Young et al., 1978) will be administered, with euthymia defined as a score ≤ 7 in both scales (covering the prior two weeks).
- Questions assessing other potential exclusion criteria: risk of suicide, comorbid diagnoses, treatment use, computer use, language, healthcare professional contact details, inability to travel, lack of capacity to consent.
- Participants who are willing to take part in the optional sleep EEG-assessment at the London or Oxford site need to be free from sleeping disorders, other disorders associated with impaired sleep, conditions incompatible with EEG use, certain medications affecting sleep,

no recent trans meridian travel and do not perform shift- or night-time work. This will be assessed through patient-report and the STOP-BANG questionnaire for sleep apnea.

pre-W0: Second screening session – If not excluded at W-2 screen, a second screening session will take place two weeks later, within 24 hours of the scheduled (provisionally) baseline assessment. This will validate whether patients are still experiencing a stable euthymic state (using the HAMD for depression and the YMRS for mania). If not, the participant will be invited to re-schedule another W-2 (and pre-W0) screen at a future date. If the participant is willing to take part in the EEG-assessment, it will be confirmed that there was no recent trans meridian travel. If inclusion criteria are met following this, the W0 assessment will take place as scheduled.

W0: Baseline Assessment – Before the assessment begins, written informed consent will be completed by the participant. A copy of the consent form alongside a letter of notification is sent to the contact Healthcare Professional (who also receives an information sheet about the study) for that participant. The letter asks the professional to note on the patient’s health record confirming that they are participating in this interventional study (and if they are receiving CR).

Sociodemographic/illness-history/service use questions

- Date of birth, gender, ethnicity, height, weight, education level (years of education and highest level of education), employment (employment status, number hours worked per week, number of hours missed due to health issues), marital status, living situation, smoking (if yes, number of cigarettes smoked per week)
- Year of mood symptom onset, mental health difficulties before symptom onset, year of BD diagnosis, incorrect diagnosis before BD, BD diagnostic type, number of past episodes (depressive, manic, hypomanic), most recent episode (type, length), time being symptomatic the past year, length of current euthymia, number of past hospital admissions, hospital admissions within the past six months, comorbid mental health diagnoses, comorbid physical conditions, stressful life events within the past 12 months
- Current pharmacological treatments (type, dose, frequency of use, duration of use), current non-pharmacological treatments (type, provider, attendance frequency), past treatments (number of pharmacological, psychological, and other treatments)

Diagnostic interview

- MINI 7 for DSM-5 (Sheehan et al., 1998), for comorbidity data not required for inclusion/exclusion

Cognitive measures

- Hotel test (Manly et al., 2002), for planning, problem solving, and multi-tasking
- Trail Making Test B (TMT-B; Heaton, 2004), for executive control and task switching
- FAS letter fluency test (Tombaugh et al., 1999), for phonemic verbal fluency
- Verbal Paired Associates I test (VPA1) from the Wechsler Memory Scale 4th edition (Wechsler, 2009), for verbal learning

- Verbal Paired Associates II test (VPA2) from the Wechsler Memory Scale 4th edition (Wechsler, 2009), for verbal memory
- Digit Span test from the Wechsler Adult Intelligence Scale 4th edition (Wechsler, 2014), for verbal working memory
- Trail Making Test A (TMT-A; Heaton, 2004), for attention
- Digit-symbol Coding test from the Wechsler Adult Intelligence Scale 4th edition (Wechsler, 2014), for processing speed
- Perceived Deficits Questionnaire (PDQ; Fehnel et al., 2016), for self-reported evaluation of difficulties in attention, retrospective memory, prospective memory, planning and organisation, and overall cognitive functioning

Functional measures

- Functional Assessment Short Test (FAST; Rosa et al., 2007), for domain-specific and general psychosocial functioning
- Goal Attainment Scale (GAS; Turner-Stokes, 2009), for achievement of participant-defined recovery goals
- EuroQol 5 Dimension – 3 Levels (EQ5D-3L; Fryback & Hanmer, 2005), for health-related quality of life

Clinical measures

- Hamilton Depression Rating Scale 17-item (HAM-D; Hamilton, 1960), for depressive symptom severity
- Young Mania Rating Scale (YMRS; Young et al., 1978) for manic symptom severity
- Hamilton Anxiety Rating Scale 14-item (HAM-A; Hamilton, 1959), for anxiety symptom severity
- Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989), for sleep quality
- Childhood Trauma Questionnaire (CTQ; Bernstein et al., 2003), for adverse early life experiences
- Morningness – Eveningness Questionnaire (MEQ; Horne & Östberg, 1976), for chronotype
- MacLean Screening Instrument for Borderline Personality Disorder (MSI-BPD; Zanarini et al., 2003), for BPD traits

Mechanistic measures

- Metacognitive Awareness Inventory (MAI; Schraw & Dennison, 1994), for knowledge and regulation of cognition
- Torres' ratings (Torres et al., 2016), for metacognitive knowledge and experience
- Optional: Blood sample (Strawbridge et al., 2021), for plasma-based inflammatory markers and growth factors

[Note that other measures for mechanistic outcomes, i.e., cortisol, affect fluctuation, and sleep spindle density (through EEG) are conducted after randomisation by necessity, but participants will be notified of their allocation group after cortisol has been collected.]

Subsequently, randomisation will be conducted (as per timing and procedures described in section 9.4). The participant will be notified by telephone of which intervention arm they have been randomised to 1-2 working days (after day 1 cortisol) of randomisation.

W0, days 1-3: On one of the next three days after the baseline assessment – Participants will provide a salivary cortisol sample six times over the day (0, 15, 30, 45, and 60 minutes after waking, and then at 8pm), as per standardised protocols e.g., Bhagwagar et al. (2005).

W0, days 1-7: Seven consecutive days after the baseline assessment – Participants will be completing a bidaily self-assessment of their mood symptoms with the 10-item Positive and Negative Affect Schedule (PANAS; Thompson, 2007), using a secure web platform (Qualtrics; <https://www.qualtrics.com/>). Variability between daily mood ratings throughout the week will subsequently be computed to measure daily affect fluctuation, split into positive and negative mood volatility (the measure of interest; defined as the change in the mean of the mood ratings between ratings) and positive and negative noise (defined as variability in affect that does not persist between ratings; Pulcu et al., 2021). Estimates of volatility and noise over time will be calculated separately for positive and negative affect items using Bayesian Observer model (Pulcu et al., 2021) of the mean affect score (of all positive or all negative items). Participants will be prompted with email reminders and in-application notifications to complete these ratings according to specified parameters (in terms of timing, frequency, and questions' format), standardised across participants.

W0, between days 1-7: If participants decide to take part in the optional home-based EEG assessment at the London or Oxford site, they will be asked to apply an EEG device (ZMax© by Hypnodyne©) for three consecutive nights at home. The device consists of a headband with integrated electrodes. Following a short tutorial on how to mount the headband during their baseline visit, they will take the device home, use it for three consecutive nights, and return it at a time-point convenient for them. They will additionally receive written instructions and a link to a video tutorial (<https://www.youtube.com/watch?v=TRJcleSam28>) that guides them through the process of positioning the headband. Participants will be instructed to contact study staff through email the next morning if they experience any technical difficulties during the night. The headband will be returned either at their next visit at the London or Oxford site, if they are randomized to the CR group, or another day within 7 days chosen by the participant, if they are randomized to the TAU group. In case participants cannot return to the London site (e.g., travel time > 1 hour), study staff can pick the device up or meet them at a location more convenient for them.

W1-12: Intervention period – All participants will continue usual care (TAU) throughout. For those randomised to CR, the CIRCuiTS CR intervention will be delivered for 12 weeks (see section 7

The electronic version of this document is the latest version. It is responsibility of the individual to ensure that any paper material is the current version. Printed material is uncontrolled documentation.

above for detail). Therapeutic alliance will be measured at week 3 and week 12 for participants in the CR group only and their therapists, using the Working Alliance Inventory Short-Revised (WAI-SR; Hatcher & Gillaspay, 2006). Therapists will complete the WAI-SR questionnaires and return them to the trial manager. For CR participants, questionnaires will be given and collected by the trial manager, either in person or via email. Assessors and therapists will not be involved to ensure blinding and unbiased evaluation of therapeutic alliance, respectively. For both participants and therapists, the average score of the two timepoints will be computed and used in analysis, according to previous examinations of therapeutic alliance in the context of CR (Cella & Wykes, 2019).

W13: Post-intervention – All outcome measures listed at W0 are repeated (including the optional provision of a blood sample), with the exception of the diagnostic interview (MINI 7) and baseline-only questionnaires (i.e., CTQ, HAMA, MEQ, and MSI-BPD). The post-intervention assessment will take place during week 13, and on one of the next three days salivary cortisol collection will be repeated similar to W0 (six samples over one day; all participants). The participant-reported mood symptom measure (PANAS) will also be repeated from the day of week 13 after the post-intervention assessment and for 7 consecutive days (all participants) using the Qualtrics platform. Additional data will be collected regarding participant satisfaction of CR using the Cognitive Remediation Satisfaction scale (CRS; Evans et al., 2023) (through correspondence between the participant and an unblinded researcher outside of the main assessment session; CR participants only). After the W13 assessment, an assessment of unblinding will be conducted by the trial manager for the outcome assessor, according to procedures described in section 9.5. Finally, participants opting to take part in the optional sub-study ‘Perspectives of CR’ component will be asked to remotely complete a feedback questionnaire and a semi-structured interview with one of our therapists.

W25: Follow up – All measures listed above in W13 are repeated, except for saliva/blood collection, affect fluctuation measurements (PANAS), and the CR satisfaction questionnaire.

In addition to all the above timepoints/assessments, participants will be asked to complete very brief mood assessments on a weekly basis from W1 to W24, which are not considered trial outcomes and will be only used to monitor mood and wellbeing of participants during the trial. See Section 11.2 for more detail on the monitoring.

10.2.Laboratory Tests

Cortisol, as mentioned above, will be measured on one of the next three days after the W0 and W13 assessments. At these assessments, saliva self-collection packs will be provided to participants. These packs will adhere to UN3373 transportation standards for Category B biological substances (including: i) a sheet with detailed collection instructions; ii) a leak-proof primary receptacle (i.e., a pre-labelled collection tube, also called a Salivette); iii) a leak-proof secondary packaging; and iv) an outer packaging of adequate strength (which will be a pre-addressed/pre-paid outer postal box).

The electronic version of this document is the latest version. It is responsibility of the individual to ensure that any paper material is the current version. Printed material is uncontrolled documentation.

On the day of saliva collection, participants will follow standardised instructions according to our Saliva Collection Standard Operating Procedures (SOPs), collecting six samples across the day at the following times: upon wakening, 15 minutes after waking, 30 minutes after waking, 45 minutes after waking, 60 minutes after waking (providing data required for the cortisol awakening response [CAR]) and then at 8pm (providing evening basal levels). From these samples, cortisol levels will be analysed to estimate the CAR (defined as the mean increase in cortisol secretion levels within the first hour post-awakening) and an area under the curve (AUC) for the full daily assessments (Smyth et al., 2013). Using the same saliva samples (specifically those collected upon awakening and at 8pm), we will estimate the levels of another hormone, the adrenal steroid dehydroepiandrosterone (DHEA). Subsequently, we will calculate the ratio of cortisol to DHEA in order to get an accurate reflection of the degree of “functional” cortisol secretion, given that DHEA counteracts the action of cortisol in the brain (Young et al., 2002). Adherence to the saliva collection protocol will be corroborated with self-report records of times sampled.

For all participants across sites, collection packs will be sent back to the London site, using Royal Mail Tracked delivery, for processing and storage. Saliva samples (regulated under the Human Tissue Act) will be stored in a locked and alarmed freezer (-20°C) within the Clinical Research Facility at King's College Hospital until transfer to the laboratory for analysis. This is considered a suitable long-term storage method for saliva samples where measurement of salivatory cortisol concentration is the targeted outcome (Garde & Hansen, 2005). Samples will not contain any identifiable information and could be linked with participant data only by using the collection pack label, unique to each study participant and corresponding to their participant ID. At the end of the study, saliva samples will subsequently be assayed using standardised assays to quantify salivatory cortisol concentration. In specific, two outcomes will be assessed: i) CAR to estimate mean cortisol secretion within the first hour post-awakening, and ii) AUC to estimate cortisol secretion levels for the full day. After saliva samples have been analysed, any surplus biological material will be disposed of in accordance with the Human Tissue Act 2004 Code of Practice.

Collection of the blood sample will be optional for all participants and will be conducted on the day of W0 and W13 assessments. Blood samples will be collected by a trained clinical nurse following local SOPs. For each participant at each time-point, 6 mL of blood will be drawn. This sample will be immediately processed to obtain plasma after centrifugation. Extracted plasma vials (regulated under the Human Tissue Act) will be stored in a locked and alarmed freezer (-80°C) within the Clinical Research Facility at King's College Hospital until transfer to the laboratory for analysis. Vials will not contain any identifiable information and could be linked with participant data only by using the collection pack label, unique to each study participant and corresponding to their participant ID. At the end of the study, plasma samples will be assayed using high-sensitivity arrays to estimate a panel of candidate inflammatory markers and growth factors (Strawbridge et al., 2021). After plasma samples have been analysed, any surplus biological material will be disposed of in accordance with the Human Tissue Act 2004 Code of Practice.

11. Assessment of Safety

11.1. Assessment of Therapy Safety

Participants receiving CR will be monitored by their therapist, face-to-face, between 1-3 times per week. Because CR is designed flexibly, if negative feedback is indicated about the ways therapy is delivered and its perceived effects, then therapists will be able to tailor the aspects of the intervention that are not optimal. The CR therapist will be responsible for checking with the participant verbally that there are no current negative effects. CR therapists will also record any injuries, notable events or other phenomena that might imply safety concerns. These will be treated identically to all adverse events (see section 11.3). In circumstances where therapists are unsure, this is to be raised at the fortnightly supervision session.

11.2. Specification, Timing and Recording of Safety Parameters

Processes in place to deal with any safety issues include ongoing participant monitoring throughout the intervention period by completion of self-report symptom measures on a weekly basis. Participants will receive reminders to prompt completion of these measures. The researcher responsible for monitoring participants' completion of these self-report measures will also check the scores/ratings of these measures, to monitor wellbeing at each time point. In the event of high scores (representing affective symptoms or risk), for any participant irrespective of group, participants will receive a telephone call from a team member to discuss their wellbeing. If there are wellbeing concerns based on this communication, the participant's named Healthcare Professional will be contacted to further address these issues. We also have access to multiple experienced psychiatrists as part of the research team who can advise and assist if needed. Researchers and CR therapists will always have access to discuss unresolved concerns with the Principal / Chief Investigator of the study. In events where individuals have not completed weekly symptom measures for more than three weeks consecutively, they will also be followed-up by a telephone call to ensure safety. All incidents that qualify as adverse events will also be recorded and the protocol for this followed, as outlined below.

11.3. Procedures for Recording and Reporting Adverse Events

Data on adverse events will be collected with open ended questions (rather than a predefined checklist) and recorded systematically. Even though CR is not a medicinal product, the standard definitions provided by The Medicines for Human Use (Clinical Trials) Regulations 2004 and Amended Regulations 2006 with regards to adverse events will be used, as follows:

Adverse Event (AE): Any untoward medical occurrence in a subject to whom an intervention has been administered including occurrences which are not necessarily caused by or related to that intervention.

Adverse Reaction (AR): Any untoward and unintended response in a subject to an intervention which is related to the intervention administration to that subject.

Unexpected Adverse Reaction (UAR): An adverse reaction the nature and severity of which is not consistent with the information about the intervention in question.

Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR): Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that: results in death; is life-threatening; required hospitalisation or prolongation of existing hospitalisation; results in persistent or significant disability or incapacity; consists of a congenital anomaly or birth defect.

Important Medical Events (IME): Events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require an intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

Any AEs (excepting those specified in this protocol as not requiring reporting; see below section 11.4) that occur throughout the duration of the trial will be recorded in the participant case report form. Investigators will assess whether the AE may be related to study participation and will also assess the severity of the event. All documented AEs reported after a participant signs the consent form will be included in the primary trial report.

All AEs classified as ARs and UARs will be recorded and immediately addressed with the Chief Investigator (certainly no later than 24 hours), as well as be considered in Steering Group Meetings. All SAEs and SARs will be reported immediately (certainly no later than 24 hours) by the Chief Investigator to the Sponsor and the R&D office using a SAE report form. In accordance with the Health Research Authority procedures, only SUSARs will be reported by the Chief Investigator to the Research Ethics Committee for review (sent within 7 days of the reaction for fatal or life-threatening events and 15 days of the reaction for not fatal or life-threatening events).

Although we do not anticipate any SARs or SUSARs (none have been reported in previous CIRCuiTS trials), participants presenting any such reactions will be withdraw from the CR intervention and, if not already done by the participant, these reactions will be brought to the attention of their named healthcare professional. Non-serious ARs may also warrant a referral back to the named healthcare professional, but withdrawal from the trial will depend on risk assessment, circumstances and participant's wishes.

All SAEs that have not resolved by the end of the trial, or that have not resolved upon discontinuation of the subject's participation in the trial, will be followed until: the event resolves, the event stabilises, the event returns to baseline (if a baseline value is available), the event can be attributed to agents other than the trial participation or to factors unrelated to the trial, when it becomes unlikely that any additional information can be obtained. All follow-up information for SAEs that have not resolved by the end of the trial or by the time of participant withdrawal will be reported to the Sponsor.

11.4. Adverse events that do not require reporting

There are no expected SAEs in this study. Therefore, any SAEs will be reported as will ARs, UARs, SARs or SUSARs or IMEs. AEs that do not meet the above criteria but require intervention (e.g., safety concerns communicated to healthcare professional or incidence of acute episode requiring changes to treatment regime) will be reported. The AEs that do not require reporting include (psychiatric or other) symptom onset that does not require treatment changes or mild distress

disclosed by participants where no further action is required (and that are not related to the trial or intervention).

11.5. Stopping Rules

There are no plans for a formal interim analysis or formal stopping rules for the trial. The trial may be prematurely discontinued by the Sponsor or Chief Investigator on the basis of new safety information, in the case of AEs associated with the intervention, or for other reasons given by the Research Ethics Committee. The trial may also be prematurely discontinued due to lack of recruitment or other concerns regarding trial data. This may be highlighted by the DMC who will advise the Trial Steering Committee (TSC), and the TSC will in this case make a recommendation to the Sponsor. Regarding this, the DMC will be conducted as per a DAMOCLES charter (adapted from standardized templates). If the study is prematurely discontinued, active participants will be informed and no further participant data will be collected. The Research Ethics Committee will be informed within 15 days of the early termination of the trial. Participants may discontinue treatment at any time they choose or as recommended by trial researchers (section 9.6).

12. Statistics

This protocol will be published to ensure transparency of primary study analyses and outcome reporting following the trial.

12.1. Sample Size

CRIB1 provided the following for the main outcome measure, the FAST: ES of 0.49 at 25 weeks, correlation of 0.7 between baseline and follow-up and an intraclass correlation coefficient (ICC) of 0.02. We use a two-sided independent samples t-test for the difference between groups, $\alpha=0.05$, and account for the effect of therapist clustering, repeated measures and attrition on the effective sample size to determine the final numbers to use in the t-test calculation (Killip et al 2004, Machin et al 2008). For the CR group, we will have 7 therapists that we estimate will see ~18 participants each, or $n = 125$ in the CR group. This equates to a design effect of $1 + (18 - 1) \times ICC = 1.34$. With 15% attrition, 106 will remain in each arm total, with an effective sample size after allowing for clustering of $106/1.34 = 79$. We then allow for 1 pre- and 2 post-randomisation repeated measurements with a more conservative correlation $\rho = 0.5$ as compared to CRIB1, which gives a multiplication effect of 0.5. Although we will enroll 125 participants to each treatment group, the precision gain from the repeated measures design gives us an effective sample size of 158 per group [$79/0.5 = 158$]. Using G*Power, this gives 90% power to detect an effect size of 0.37, which is smaller than the CRIB1 effect size, i.e. it is a conservative estimation.

12.2. Analysis

A detailed statistical analysis plan will be drafted. Briefly, all statistical analyses will adopt the intention-to-treat principle and will be carried out with our collaborating trial statistician. All analyses will be conducted after data collection has been completed, the data cleaned and the database locked. Variables will be summarised using descriptive statistics (i.e., mean and standard

deviation [SD] or median and interquartile range [IQR] or frequencies and proportions, as appropriate). To ascertain the differences in primary and secondary outcome measures between participants randomised to CR+TAU and TAU alone, mean differences between the groups (and their 95% confidence intervals) in the primary (FAST functioning score, week 25) and secondary outcomes will be estimated using mixed-effects linear regression models with the 13- and 25-week measures of the outcome in question as dependent variables. Models will include a random intercept for participants, time and time by treatment terms (to allow for extraction of mean differences between treatment groups at different time points), baseline measure of the outcome and site as pre-specified baseline covariates. We may assess whether other covariates are predictive of missing data and include these in models, which in using maximum likelihood methods and assuming missing at random, will account for missing data.

Mediation via exploratory mechanistic measures will be assessed either using structural equation modelling or causal mediation analysis (e.g., `paramed` in `stata`) adjusting for baseline measures of the mediator and outcome, site, age, gender, and other potential mediator-outcome confounders (Valeri et al. 2013). For singly measured mediators (i.e., global cognitive performance and metacognitive skill development), we will model the week 13 mediator measures and week 25 outcome measure. The cortisol mediator measured over multiple time points will likely be modelled using a latent growth model within the overall mediation model. The mood instability mediator(s) will likely be modelled in a similar way to the singly measured mediators, using the summary mood variability measure(s) derived from the PANAS measures taken over time (Pulcu et al., 2021). EEG data will be exported in EDF+ format and analysed using established neural networks for automated sleep staging and spindle annotation (Kaulen et al., 2022).

13. Trial Steering Committee

The Trial Steering Committee (TSC) will be comprised of the Chief Investigator (Prof Allan Young) in addition to members independent of the study team. Independent members will comprise >75% of the TSC. Members of the TSC will include independent clinicians (psychiatrist, psychologist), an independent statistician and two service-user representatives. The TSC will meet every 6-10 months, with a total of seven planned meetings over the trial duration. Meetings will be more frequent at key times of the trial (i.e., just before and after recruitment initiation and data collection completion). The TSC's composition and roles accord with published guidance (e.g., <https://www.nihr.ac.uk/documents/research-governance-guidelines/12154>). The TSC will aim to provide oversight of the project, ensuring that it is conducted to a rigorous standard in line with Good Clinical Practice guidelines and other best practice conduct and reporting standards. These include pre-registration of this protocol, comprehensive and transparent reporting, and the pre-plan of statistical procedures via a statistical analysis plan, which will be signed off by the TSC chair.

14. Data Monitoring

CRT is considered a safe therapy, unlikely to impact on risky behaviours, and the participants have been in remission from mood symptoms for at least one month before entering the trial. Although

The electronic version of this document is the latest version. It is responsibility of the individual to ensure that any paper material is the current version. Printed material is uncontrolled documentation.

this is not considered to be a high-risk study, the trial is designed and intended to give definitive effectiveness or safety information and euthymic individuals with a bipolar disorder diagnosis are considered a vulnerable population. Therefore, a formal independent Data Monitoring and Ethics Committee (DMEC) is warranted (Ellenberg, Fleming and DeMets, 2003). The DMEC will be fully comprised of individuals independent of the study team (e.g., psychiatrist, psychologist, statistician), with its conduct adhering also to the Research Governance Guidelines, to ensure quality assured monitoring and safety during the trial.

DMEC oversight meetings will take place shortly before the TSC meetings. Data extracts will be requested by the Trial Statistician prior to each DMEC meeting (see Table 2 for information regarding blinding) and will prepare open and closed DMEC reports including data quality and safety information. A report from the DMEC will be provided to the TSC after each meeting; this may take the form of a letter.

15. Direct Access to Source Data and Documents

The study investigators will permit trial-related monitoring, audits, and REC review by providing the Sponsor and REC direct access to source data and other documents (e.g., case report forms, test reports, etc.) when required.

16. Ethics & Regulatory Approvals

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Mental Capacity Act 2005. This protocol and related documents will be submitted for review to London – Bromley Research Ethics Committee (REC) in Spring 2022 (22/LO/0210). The Chief Investigator will submit a final report at conclusion of the trial to the funder, the REC and the Sponsor.

17. Quality Assurance

Monitoring of this trial will ensure compliance with Good Clinical Practice and scientific integrity will be managed by the study team and overseen from the DMC/TSC. To optimise and maintain quality throughout the trial, TSC monitoring includes $\geq 75\%$ individuals independent from the study team; our procedures also ensure that support and training for undertaking research assessments and handling data. King's Clinical Trials Unit (KCTU) will manage the creation of the eCRF database and randomization system in collaboration with the CI, statisticians, and study team. The Chief Investigator maintains overall trial responsibilities, working closely with a trial manager to ensure the trial is conducted according to the protocol and KCTU standard operating procedures. A trial management group (TMG) consisting of the Chief Investigator, co-investigators, trial manager and trial statisticians will meet monthly during the first year of the trial and quarterly thereafter. The TMG's purpose will be to oversee the smooth running of trial procedures and quality assurance overall. During the planning of the project, the proposal was reviewed by experienced academics, statisticians, and clinicians. The proposal was also reviewed by people affected by bipolar disorder and those with lived experience were consulted using various approaches. The full proposal was formally peer reviewed via the funding application process (to the NIHR Efficacy and Mechanisms funding stream), where the project was judged of sufficient quality and design to obtain funding and was considered worthwhile in terms of future implications regarding benefits to patients and the NHS.

18. Data Handling

The Chief Investigator will act as custodian for the trial data. Patient data will be anonymised as far as possible (see below for detail). All trial data will be stored in line with the Data Protection Act and archived in line with Sponsor requirements. A web based electronic data capture (EDC) system will be designed, using the InferMed Macro 4 system. The EDC will be created in collaboration with the trial analyst/s and the CI and maintained by the King's Clinical Trials Unit for the duration of the project. It will be hosted on a dedicated server within KCL. The CI or delegate will request usernames and passwords from the KCTU. Database access will be strictly restricted through user-specific passwords to the authorised research team members. It is a legal requirement that passwords to the EDC are not shared, and that only those authorised to access the system are allowed to do so. If new staff members join the study, a user-specific username and password must be requested via the CI or delegate (e.g., Trial Manager) from the KCTU team and a request for access to be revoked must be requested when staff members leave the project. Study site staff experiencing issues with system access or functionality should contact the CI or delegate (e.g., Trial Manager) in the first instance. Data extracts from the randomisation system and MACRO EDC will be requested by the trial statistician as needed for preparing data monitoring reports and data queries. This will be done by submitting an extract request to the KCTU via the ctu@kcl.ac.uk address. Data extracts will be held securely on a KCL server or on OneDrive.

19. Data Management

The source data for the trial will be collected on paper CRFs. Participants' data will be stored using a coded identifier, e.g. CR010001, CR010002 (01 representing site and 0001 representing patient sequentially recruited per site) and paper forms of participant data will be stored securely within the recruiting site in locked filing cabinets (in offices locked while empty). This source data will then be entered by recruiting site staff, typically within 14 days of data collection by authorised staff onto the EDC (see above section 19 for an explanation of the EDC system) by going to www.ctu.co.uk and clicking the link to access the MACRO 4 EDC system. A full audit trail of data entry and any subsequent changes to entered data will be automatically date and time stamped, alongside information about the user making the entry/changes within the system.

The EEG data from the optional part at the London and Oxford site will be locally stored on a memory card inside the headband. After return, all data will be transferred to a secure KCL or Oxford server and deleted from the memory card. These servers will be also used for data analysis. All data will be pseudonymized using the study ID as a coded identifier. Hynodyne© does not have access to any data at any point.

Participant initials and month/year of birth will be entered on the EDC, however identifiable information such as NHS number, email addresses, participant names and addresses and full postcodes will not be entered into the EDC. No data will be entered onto the EDC system unless a participant has signed a consent form to participate in the trial.

The study team will undertake appropriate reviews of the entered data [in consultation with the trial statistician] where appropriate for the purpose of data cleaning and will request amendments as required. Following checks of data correctness and completeness, all data can be formally locked for analysis. Upon request, KCTU will provide a copy of the final exported dataset to the CI in .csv format and the CI will onward distribute as appropriate.

We will adhere to NHS confidentiality practices, and to the Research Governance Framework in monitoring and managing the research. As CI, Professor Young will undertake overall responsibility for management of the project.

20. Publication Policy

It is intended that the results of the study will be reported and disseminated at international conferences and in peer-reviewed scientific journals. We intend to publish the study protocol before the end of the first year of recruitment. A primary publication will include all primary and secondary outcomes as per the protocol, and a second publication will explore the mechanistic components of the intervention. Exploratory tertiary outcomes will be explored separately and subsequently.

21. Insurance / Indemnity

Indemnity and insurance are provided through KCL/SlaM schemes.

22. Financial Aspects

This project (NIHR132619) is funded by the Efficacy and Mechanism Evaluation (EME) Programme, an MRC and NIHR partnership. The optional blood sample component and the optional EEG component of the study, delivered at London and Oxford site only, are funded by the International Research Training Group (IRTG), as part of the transCampus collaboration between TU Dresden and King's College London. The optional 'Perspectives of CR' sub-study are funded by King's College London. The views expressed in this publication are those of the authors and not necessarily those of the MRC, NIHR or the Department of Health and Social Care.

23. Signatures

Professor Allan Young



Chief Investigator

19/04/2022

Dr Kimberley Goldsmith



Senior Statistician

19/04/2022

24. References

- Anaya, C., Martinez Aran, A., Ayuso-Mateos, J. L., et al. 2012. A systematic review of cognitive remediation for schizo-affective and affective disorders. *Journal of Affective Disorders*, 142(1), 13-21
- Arnsten AF. 2015. Stress weakens prefrontal networks: molecular insults to higher cognition. *Nature neuroscience*. 18(10), 1376.
- Bellani M, Biagiante B, Zovetti N, Rossetti MG, Bressi C, Perlini C, Brambilla P. 2019. The effects of cognitive remediation on cognitive abilities and real-world functioning among people with bipolar disorder: A systematic review. *Journal of Affective Disorders*, 257, 691–697.
- Bernabei L, Bersani FS, Pompili E, Delle Chiaie R, Valente D, et al. 2020. Cognitive remediation for the treatment of neuropsychological disturbances in subjects with euthymic bipolar disorder: findings from a controlled study. *Journal of Affective Disorders*. 273, 576-585.
- Bernstein, D. P., Stein, J. A., Newcomb, M. D., Walker, E., Pogge, D., Ahluvalia, T., ... & Zule, W. (2003). Development and validation of a brief screening version of the Childhood Trauma Questionnaire. *Child abuse & neglect*, 27(2), 169-190.
- Bhagwagar Z, Hafizi S, Cowen PJ. 2005. Increased salivary cortisol after waking in depression. *Psychopharmacology*, 182(1), 54-7.
- Burdick KE, Russo M, Frangou S, et al. 2014. Empirical evidence for discrete neurocognitive subgroups in bipolar disorder: clinical implications. *Psychological Medicine*, 44(14), 3083-3096.
- Buysse, D.J., Reynolds, C.F., Monk, T.H., Berman, S.R., & Kupfer, D.J. (1989). The Pittsburgh Sleep Quality Index (PSQI): A new instrument for psychiatric research and practice. *Psychiatry Research*, 28(2), 193-213.
- Cella, M., Reeder, C., & Wykes, T. (2015). Lessons learnt? The importance of metacognition and its implications for Cognitive Remediation in schizophrenia. *Frontiers in psychology*, 6, 1259.
- Cella M, Edwards C, Swan S, Elliot K, Reeder C, Wykes T. 2019. Exploring the effects of cognitive remediation on metacognition in people with schizophrenia. *Journal of Experimental Psychopathology*.
- Cella, M., & Wykes, T. (2019). The nuts and bolts of cognitive remediation: exploring how different training components relate to cognitive and functional gains. *Schizophrenia Research*, 203, 12-16.
- Chung, F., Abdullah, H. R., & Liao, P. (2016). STOP-Bang questionnaire: a practical approach to screen for obstructive sleep apnea. *Chest*, 149(3), 631-638.
- Daban, C., Martinez-Aran, A., Torrent, C., et al. 2006. Specificity of cognitive deficits in bipolar disorder versus schizophrenia. A systematic review. *Psychotherapy and Psychosomatics*, 75, 2, 72-84.
- Douglas KM, Peckham A, Porter R, Hammar A. 2019. Cognitive enhancement therapy for mood disorders: A new paradigm? *Australian and New Zealand Journal of Psychiatry*, 53, 1148–1150
- Ellenberg, S., Fleming, T.R., DeMets, D.L.. 2003. *Data Monitoring Committees in Clinical Trials: A practical perspective*. John Wiley & Sons: England
- Evans, J., Tinch-Taylor, R., Csipke, E., Cella, M., Pickles, A., McCrone, P., ... & Wykes, T. (2023). Satisfaction with cognitive remediation therapy: its effects on implementation and outcomes using the cognitive remediation satisfaction scale. *Schizophrenia*, 9(1), 67.
- Fehnel, S., Forsyth, B., DiBenedetti, D., Danchenko, N., François, C., & Brevig, T. (2016). Patient-centered assessment of cognitive symptoms of depression. *CNS Spectrums*, 21(1), 43-52. doi:10.1017/S1092852913000643
- Fryback, D. G., & Hanmer, J. (2005). The Measurement and Valuation of Health Status Using EQ5D: A European Perspective. Evidence from the EuroQol BIOMED Research Program. *Quality of Life Research*, 14(2), 571-573.
- Garde, A. H., & Hansen, Å. M. (2005). Long-term stability of salivary cortisol. *Scandinavian Journal of Clinical and Laboratory Investigation*, 65(5), 433-436.
- Gupta, R. D., & Guest, J. F. (2002). Annual cost of bipolar disorder to UK society. *The British Journal of Psychiatry*, 180(3), 227-233.

- Hamilton, M. (1959). The assessment of anxiety states by rating. *Br J Med Psychol*, 32(1), 50-55. doi:10.1111/j.2044-8341.1959.tb00467.x
- Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery, and Psychiatry*, 23(1), 56.
- Hatcher, R. L., & Gillaspay, J. A. (2006). Development and validation of a revised short version of the Working Alliance Inventory. *Psychotherapy Research*, 16(1), 12-25.
- Heaton, R. K. (2004). *Revised comprehensive norms for an expanded Halstead-Reitan Battery: Demographically adjusted neuropsychological norms for African American and Caucasian adults, professional manual*. Psychological Assessment Resources.
- Hoffmann, T. C., Glasziou, P. P., Boutron, I., Milne, R., Perera, R., Moher, D., ... & Michie, S. (2014). Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *BMJ*, 348.
- Horne, J. A., & Östberg, O. (1976). A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. *International journal of chronobiology*.
- Jensen JH, Knorr U, Vinberg M, Kessing LV, Miskowiak KW. (2016). Discrete neurocognitive subgroups in fully or partially remitted bipolar disorder: Associations with functional abilities. *Journal of Affective Disorders*, 15(205), 378-386.
- Kaulen, L., Schwabedal, J. T., Schneider, J., Ritter, P., & Bialonski, S. (2022). Advanced sleep spindle identification with neural networks. *Scientific Reports*, 12(1), 1-10.
- Lewandowski KE, Sperry SH, Cohen BM, Norris LA, Fitzmaurice GM, Ongur D, Keshavan MS. 2017. Treatment to Enhance Cognition in Bipolar Disorder (TREC-BD): Efficacy of a Randomized Controlled Trial of Cognitive Remediation Versus Active Control. *Journal of Clinical Psychiatry*, 78(9), e1242-e1249.
- Manly, T., Hawkins, K., Evans, J., Woldt, K., & Robertson, I. H. (2002). Rehabilitation of executive function: facilitation of effective goal management on complex tasks using periodic auditory alerts. *Neuropsychologia*, 40(3), 271-281.
- Marwaha S, Broome MR, Bebbington PE, Kuipers E, Freeman D. 2014. Mood instability and psychosis: analyses of British national survey data. *Schizophrenia Bulletin*, 40, 269–277
- Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., ... & Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society*, 53(4), 695-699.
- Ochsner KN, Gross JJ. 2005. The cognitive control of emotion. *Trends Cogn Sci* 9, 242–249
- Pampallona, S., Bollini, P., Tibaldi, G., Kupelnick, B. Munizza, C. 2004. Combined pharmacotherapy and psychological treatment for depression: A systematic review. *Archives of General Psychiatry*, 61, 7, 714-9.
- Prince, M., Patel, V., Saxena, S., et al. 2007. No health without mental health. *The Lancet*, 370, 9590, 859-877.
- Pulcu, E., Saunders, K., Harmer, C., Harrison, P., Guy, G., Geddes, J., & Browning, M. (2021). Measuring Mood Instability Using a Generative Model of Affect. *Biological Psychiatry*, 89(9), S113-S114.
- Reeder, C., & Wykes, T. 2010. *Computerised Interactive Remediation of Cognition – Training for Schizophrenia (CIRCuiTS)*. King's College London: UK.
- Reeder, C., Pile, V., Crawford, P., Cella, M., Rose, D., Wykes, T., ... & Callard, F. (2016). The feasibility and acceptability to service users of CIRCuiTS, a computerized cognitive remediation therapy programme for schizophrenia. *Behavioural and Cognitive Psychotherapy*, 44(3), 288-305.
- Reeder, C., Huddy, V., Cella, M., Taylor, R., Greenwood, K., Landau, S., & Wykes, T. (2017). A new generation computerised metacognitive cognitive remediation programme for schizophrenia (CIRCuiTS): a randomised controlled trial. *Psychological Medicine*, 47(15), 2720-2730.
- Rosa, A. R., Sánchez-Moreno, J., Martínez-Aran, A., Salamero, M., Torrent, C., Reinares, M., . . . Ayuso-Mateos, J. L. (2007). Validity and reliability of the Functioning Assessment Short Test (FAST) in bipolar disorder. *Clinical Practice and Epidemiology in Mental Health*, 3(1), 5.

- Schraw, G., & Dennison, R. S. (1994). Assessing metacognitive awareness. *Contemporary Educational Psychology, 19*(4), 460-475.
- Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., ... & Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (MINI): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry, 59*(20), 22-33.
- Smyth, N., Hucklebridge, F., Thorn, L., Evans, P., & Clow, A. (2013). Salivary cortisol as a biomarker in social science research. *Social and Personality Psychology Compass, 7*(9), 605-625.
- Strawbridge R, Fish J, Halari R, Hodsoll J, Reeder C, Macritchie K, et al. 2016. The Cognitive Remediation in Bipolar (CRiB) pilot study: study protocol for a randomised controlled trial. *Trials, 17*, 371.
- Strawbridge R, Tsapekos D, Hodsoll J, Mantingh T, Yalin N, McCrone P, et al. 2021. Cognitive Remediation Therapy for Patients with Bipolar Disorder: A Randomised Proof-of-Concept Trial. *Bipolar Disorders, 23*(2), 196-208.
- Strawbridge, R., Carter, R., Saldarini, F., Tsapekos, D., & Young, A. H. (2021). Inflammatory biomarkers and cognitive functioning in individuals with euthymic bipolar disorder: exploratory study. *BJPsych Open, 7*(4).
- Strawbridge R, Young AH. 2016. *HPA-axis and cognitive dysfunction in mood disorders*. Chapter 13. In: Cognitive Impairment in Major Depressive Disorder. Cambridge.
- Thompson, J. M., Gallagher, P., Hughes, J. H., Watson, S., Gray, J. M., Ferrier, I. N., & Young, A. H. (2005). Neurocognitive impairment in euthymic patients with bipolar affective disorder. *The British Journal of Psychiatry, 186*(1), 32-40.
- Thompson, E. R. (2007). Development and validation of an internationally reliable short-form of the positive and negative affect schedule (PANAS). *Journal of Cross-cultural Psychology, 38*(2), 227-242.
- Tombaugh, T. N., Kozak, J., & Rees, L. (1999). Normative data stratified by age and education for two measures of verbal fluency: FAS and animal naming. *Archives of Clinical Neuropsychology, 14*(2), 167-177.
- Torrent, C., del Mar Bonnin, C., Martínez-Arán, A., et al. 2013. Efficacy of functional remediation in bipolar disorder: a multicenter randomized controlled study. *American Journal of Psychiatry, 170*, 8, 852-859.
- Torres, I. J., Mackala, S. A., Kozicky, J. M., & Yatham, L. N. (2016). Metacognitive knowledge and experience in recently diagnosed patients with bipolar disorder. *Journal of Clinical and Experimental Neuropsychology, 38*(7), 730-744.
- Tsapekos, D., Seccomandi, B., Mantingh, T., Cella, M., Wykes, T., & Young, A. H. (2019). Cognitive enhancement interventions for people with bipolar disorder: A systematic review of methodological quality, treatment approaches, and outcomes. *Bipolar Disorders, 22*(3), 216-230.
- Tsapekos, D., Strawbridge, R. C., Cella, M., Wykes, T. H., & Young, A. (2020). Do we really need a “new” cognitive therapy for bipolar disorder? Paradigm refinements and treatment mechanisms for cognitive remediation. *Bipolar Disorders, 22*(3), 213-215.
- Tsapekos, D., Strawbridge, R., Cella, M., Wykes, T., & Young, A. H. (2021a). Predictors of psychosocial functioning in euthymic patients with bipolar disorder: A model selection approach. *Journal of Psychiatric Research, 143*, 60-67.
- Tsapekos, D., Strawbridge, R., Cella, M., Young, A. H., & Wykes, T. (2021b). Does cognitive improvement translate into functional changes? Exploring the transfer mechanisms of cognitive remediation therapy for euthymic people with bipolar disorder. *Psychological Medicine, 1*-9.
- Turner-Stokes, L. (2009). Goal attainment scaling (GAS) in rehabilitation: a practical guide. *Clinical Rehabilitation, 23*(4), 362-370.
- Vita, A., Barlati, S., Ceraso, A., Nibbio, G., Ariu, C., Deste, G., & Wykes, T. (2021). Effectiveness, Core Elements, and Moderators of Response of Cognitive Remediation for Schizophrenia: A Systematic Review and Meta-analysis of Randomized Clinical Trials. *JAMA Psychiatry*.
- Watson, D., Clark, L. A., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: The PANAS scales. *Journal of Personality and Social Psychology, 54*(6), 1063–1070. <https://doi.org/10.1037/0022-3514.54.6.1063>

- Wykes, T., Reeder, C. et al. 2007. Cognitive remediation therapy in schizophrenia: a randomised controlled trial. *British Journal of Psychiatry*, 190, 421-427.
- Wykes, T., Huddy, V., Cellard, C., et al. 2011. A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes. *American Journal of Psychiatry*, 168(5), 472-485.
- Young, R. C., Biggs, J. T., Ziegler, V. E., & Meyer, D. A. (1978). A Rating Scale for Mania: Reliability, Validity and Sensitivity. *British Journal of Psychiatry*, 133(5), 429-435. doi:10.1192/bjp.133.5.429
- Young, A. H., Rigney, U., Shaw, S., et al. 2011. Annual cost of managing bipolar disorder to the UK healthcare system. *Journal of Affective Disorders*, 133, 3, 450-456.
- Young AH, Sahakian BJ, Robbins TW, Cowen P. 1999. The effects of chronic administration of hydrocortisone on cognitive function in normal male volunteers. *Psychopharmacology*, 145, 260–266.
- Young AH, Gallagher P, Watson S, Del-Estal D, Owen BM, Ferrier IN. 2004. Improvements in neurocognitive function and mood following adjunctive treatment with mifepristone (RU-486) in bipolar disorder. *Neuropsychopharmacology*, 29, 1538–1545.
- Young, A. H., Gallagher, P., & Porter, R. J. (2002). Elevation of the cortisol-dehydroepiandrosterone ratio in drug-free depressed patients. *American Journal of Psychiatry*, 159(7), 1237-1239.
- Watson S, Gallagher P, Porter RJ, Smith MS, Herron LJ, Bulmer S et al. 2012. A randomized trial to examine the effect of mifepristone on neuropsychological performance and mood in patients with bipolar depression. *Biological Psychiatry*, 72(11), 943-9.
- Wechsler, D. (2009). *Wechsler memory scale—Fourth Edition (WMS-IV) technical and interpretive manual*. Pearson Assessments.
- Wechsler, D. (2011). *Test of premorbid functioning. UK version (TOPF UK)*. UK: Pearson Corporation.
- Wechsler, D. (2014). *Wechsler adult intelligence scale—Fourth Edition (WAIS-IV)*. San Antonio, Texas: Psychological Corporation.
- Wykes, T., & Reader, C. (2005). *Cognitive Remediation Therapy for Schizophrenia: Theory & practice*. London: Routledge, pp: 315.
- Wykes, T., Reeder, C., Huddy, V., Taylor, R., Wood, H., Ghirasim, N., . . . Landau, S. (2012). Developing models of how cognitive improvements change functioning: mediation, moderation and moderated mediation. *Schizophrenia Research*, 138(1), 88-93.
- Zanarini, M. C., Vujanovic, A. A., Parachini, E. A., Boulanger, J. L., Frankenburg, F. R., & Hennen, J. (2003). A screening measure for BPD: The McLean screening instrument for borderline personality disorder (MSI-BPD). *Journal of Personality Disorders*, 17(6), 568-573.