RESEARCH PROTOCOL

Evaluating the Effectiveness of Imagery enhanced Cognitive Therapy

PROTOCOL TITLE: Evaluating the effectiveness of imagery focussed cognitive therapy in patients suffering from bipolar disorders: An exploratory trial

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR   ABR form, General Assessment and Registration form, is the application
              form that is required for submission to the accredited Ethics Committee (In
              Dutch, ABR = Algemene Beoordeling en Registratie)

AE   Adverse Event

CCMO   Central Committee on Research Involving Human Subjects; in Dutch:
              Centrale Commissie Mensgebonden Onderzoek

CV   Curriculum Vitae

DSMB   Data Safety Monitoring Board

EU   European Union

GCP   Good Clinical Practice

IC   Informed Consent

ImCT   <u>Imagery based Cognitive Therapy</u>

CBT   <u>Cognitive Behavioural Therapy</u>

METC   Medical research ethics committee (MREC); in Dutch: medisch ethische
              toetsing commissie (METC)

(S)AE   (Serious) Adverse Event

Sponsor   The sponsor is the party that commissions the organisation or performance
              of the research, for example a pharmaceutical
              company, academic hospital, scientific organisation or investigator. A party
              that provides funding for a study but does not commission it is not
              regarded as the sponsor, but referred to as a subsidising party.

SUSAR   Suspected Unexpected Serious Adverse Reaction

Wbp   Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)

WMO   Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-
              wetenschappelijk Onderzoek met Mensen

SUMMARY

Rationale: Bipolar disorder is a severe, chronic mental illness with currently limited treatment options, both cognitive behavioural therapy (CBT) and pharmacological treatment have modest effects. There is consensus for the need to improve effectiveness of cognitive behavioural therapy (CBT) for patients suffering from bipolar disorders. As for many other mental disorders specific treatments have been improved using imagery, and imagery appears to play a causal role in mood variability in bipolar disorders, adding imagery interventions to CBT might aid this aim. This feasibility study elaborates on a pilot study by Holmes (Holmes et al., 2016) and an audit (Hales et al., 2018) by comparing a new imagery enhanced cognitive behavioural therapy (ImCT) to psychoeducation treatment to evaluate the effectiveness of ImCT with an aim to inform a large planned RCT evaluating ImCT.

Objective: This study aims to evaluate the effectiveness of a new imagery enhanced cognitive behavioural therapy (ImCT) for patients suffering from bipolar disorders, by comparing ImCT to psychoeducation, one of the most regularly applied psychological interventions for bipolar disorder.

Study design: This study is a randomised feasability trial, comparing ImCT intervention to psychoeducation. In addition to the between group design, we will also use a within-group design were ImCT or psychoeducation is preceded by and compared to baseline condition.

Study population: Patients between 18 and 68 years old, suffering from bipolar disorders, in care at a specialised centre for bipolar disorders (Centrum Bipolair) from a large psychiatric hospital (GGzE), having regular contact with their psychiatrist on medication advise.

Intervention: One group receives a new imagery enhanced cognitive behavioural therapy (ImCT), successfully piloted in a case series design in previous research (Holmes et al., 2016). The other group receives psychoeducation treatment. Both interventions consist of 12 hours active treatment and both interventions are carried out conform existing protocols. During the course of the study both groups keep receiving their regular consultation with a psychiatrist (to advise, monitor and if necessary adjust) for mood stabilising medication.

Main study parameters/endpoints: The primary outcome variable is changes in mood variability. The secondary outcome variables are changes in levels of depression, mania, anxiety, general level of functioning and level of hopelessness, number of relapses into mania and depression and changes in imagery characteristics.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Risks for patients participating in this study are minimal. ImCT intervention has been successfully tested in a pilot study (Holmes et al., 2016) and an audit (Hales et al., 2018), suggesting this intervention is able to decline mood variability in patients suffering from bipolar disorder, and is also well tolerated and well received by patients. The

psychoeducation intervention closely resembles care as usual but is during this study delivered more structured by using a protocol. All patients, during the baseline period, during both treatments and during the follow-up period have regular appointments with their psychiatrist, who prescribes, monitors and adjusts mood stabilising medication. Should patients relapse into mania or depression, they will receive standard care as usual. Both interventions, ImCT and psychoeducation treatment are carried out conform existing protocols. The extra burden for patients, is the weekly questionnaires (20 minutes), and the questionnaires at T0-T4 (45 minutes), as daily mood monitoring is advised in current guidelines and part of care as usual.

1. INTRODUCTION AND RATIONALE

The DSM 5 defines bipolar disorder as a chronic and severe condition characterised by episodes of extreme moods, mania (or hypomania) and depression (Association, 2013). Bipolar disorder afflicts 1.9% to 2.4% of the general population (Regeer et al., 2004; ten Have, Bijl, & Nolen, 2002). In addition, bipolar disorder is associated with high inter episode distress and with ongoing mood swings (mood variability), high suicide risk, and high co-morbidity with other mental health problems especially anxiety (McElroy et al., 2001; Simon et al., 2004). Current interventions consist of pharmacotherapy and psychological interventions, predominantly psycho-education and cognitive behaviour therapy (CBT). Despite these interventions, 50% of patients do not recover within one year, only 25% achieve full recovery (Leahy, 2007) , and 60% relapse again within two years (Geddes & Miklowitz, 2013). There is a consensus for the need to update CBT interventions and increase its effectiveness, aiming at not only managing symptoms, but also at targeting perpetuating or precipitating factors.

In a recent experimental study, O'Donnel and colleagues (O'Donnell, Di Simplicio, Brown, Holmes, & Burnett Heyes, 2017) showed that mental imagery might play a causal role in mood changes in patients suffering from bipolar disorders. Their findings are in line with ideas of Holmes and colleagues, proposing that mental imagery can act as an "emotional amplifier", thus driving mood changes (Holmes, Coughtrey, & Connor, 2008; Ng, Di Simplicio, & Holmes, 2016). Furthermore, experimental research showed that imagery has a greater effect on emotion (Holmes & Mathews, 2005; Holmes, Mathews, Dalgleish, & Mackintosh, 2006) and behaviour (Libby, Shaeffer, Eibach, & Slemmer, 2007) than verbal cognitions.

Mental imagery is considered a transdiagnostic feature of mental disorders (DiSimplicio et al., 2016; Holmes, Arntz, & Smucker, 2007) and added imagery interventions, enhanced the effectiveness of several cognitive behavioural interventions For example updating appraisals of imagery has helped improve effectiveness of CBT for social phobia (Wild & Clark, 2011), targeting vividness of imagery during exposure and EMDR helped improve CBT treatment in patients suffering from PTSD (Ehlers, Clark, Hackmann, McManus, & Fennell, 2005). These findings suggest that adding imagery interventions might also improve CBT for bipolar disorder.

In 2016 Holmes and colleagues (Holmes et al., 2016) introduced a brief imagery-based cognitive intervention (ImCT) for patients suffering from bipolar disorder, using techniques aimed at both, quality of the imagery and appraisals of the imagery. ImCT is a promising intervention as it allows for flexible fine-tuning to target specific elements of imagery. ImCT incorporates an elaborate micro-formulation of imagery (teasing out both

qualitative aspects of imagery as well as appraisals), followed by metacognitive intervention, imagery rescripting or positive imagery and competing task (or a combination of these), tailoring the intervention depending on the outcome of the micro formulation. Holmes and colleagues (Holmes et al., 2016) conducted a pilot study using a non-concurrent baseline design, with a series of A-B replication. Fourteen patients with bipolar disorder were randomly assigned to 4, 5, or 6 weeks baseline after which they received ImCT (in total 10 to 14 sessions). Outcome measures were weekly measures of mood (mania, depression, and anxiety) and changes in targeted imagery. In addition, daily mood measures were collected using a smart phone text messaging to accurately measure mood variability. Result showed that patients reported an increase in mood stability, as well as improvements on weekly, and pre- and post-measures of mood and target imagery. Moreover, it is important to note that this study concluded that daily measurements were feasible. All in all, ImCT appears promising for bipolar disorder and invites further evaluation.

In the present research proposal, we elaborate on the previous ImCT pilot study (Holmes et al., 2016), comparing its effectiveness in patients with bipolar disorder to psychoeducation treatment. As noted before psychoeducation treatment is one of the most regularly applied psychological intervention for bipolar disorder. In advance of a large upcoming RCT in the UK it is necessary to derive more precise estimates of retention rates, especially on daily monitoring, and information on general feasibility as well as first data comparing ImCT to an appropriate control condition. We propose a randomised controlled feasibility study, comparing the effects of ImCT to psychoeducation in patients suffering from bipolar disorder in patients who standard have regular appointments with their psychiatrist, prescribing, monitoring and adjusting mood stabilising medication in a specialized bipolar treatment centre.

2. OBJECTIVES

Primary Objective and secondary objectives:

The present research project elaborates on a pilot study by Holmes and colleagues (2016) and an audit (Hales et al., 2018) using a new cognitive behavioural therapy enhanced with imagery techniques (ImCT), with an aim to improve the effectiveness of CBT for patients suffering from bipolar disorder. The pilot study (Holmes et al., 2016) found promising treatment effects but a controlled feasibility study is needed to test whether this treatment is more effective than regular treatment. Therefore, this research projects examines the effect of this new ImCT treatment, by comparing this intervention to psychoeducation treatment, one of the most regularly applied psychological intervention for bipolar disorder. The current

study will provide new insights for an upcoming large RCT evaluating the effectiveness of ImCT in the UK.

Our primary objective is to estimate the effects of ImCT compared to psychoeducation on mood variability. We hypothesise that (1) mood variability (primary outcome variable) will show stronger decreases in BD patients receiving ImCT at end of the intervention (T2), at follow-up measurement 8 weeks after concluding the interventions (T3) and at follow-up measurement 16 weeks after concluding the interventions (T4) than psychoeducation. Additionally, the effects of both treatments separately are also compared to baseline period preceding both treatments.

Our secondary objective is to estimate the effect of ImCT compared to psychoeducation on 1) level of depression, mania and anxiety and 2) general functioning and level of hopelessness (secondary outcome variables), 3) number of relapses into mania or depression and 4) changes in imagery characteristics. We hypothesise that (2a) symptoms of depression, mania and anxiety decrease and (2b) general functioning increase and level of hopelessness decrease (secondary outcome variables) more strongly in BD patients receiving ImCT than psychoeducation at T2, T3 and T4. Additionally, the effects of both treatments separately are also compared to baseline period preceding both treatments. We also hypothesise that 3) number of relapses into mania or depression after the end of ImCT are lower in the ImCT condition during the follow up period (T4) than in the psychoeducation condition. Finally, we hypotheses that 4) imagery characteristics will change more and problematic imagery decreases in the BD patients receiving ImCT at T2, T3 and T4, compared to baseline.

Note that, our primary outcome variable, mood variability, is measured in two ways. First, at baseline (T0), pre-intervention (T1), T2, T3 and T4. Second, mood variability is measured daily, during the four weeks baseline, during the intervention, and during the follow-up period (in total 16 weeks post intervention), in both the ImCT and psychoeducation conditions. Further note that the secondary outcome variables (2a), level of depression, mania and anxiety, are measured weekly throughout the duration of the study in both conditions and the secondary outcome variables (2b) general functioning and level of hopelessness and (4) changes in imagery are only measured at T0, T1, T2, T3 and T4. All measures are administered using an online secure server called Research Manager.

3. STUDY DESIGN

The present research proposal concerns a randomised feasibility trial, comparing ImCT intervention to psychoeducation. In addition to the between group design, the study also uses a within-group design, were ImCT and psychoeducation is preceded by a four-week baseline condition. Note that during this baseline period and throughout the study, all patients will maintain their regular appointments with their psychiatrist or specialised nurse practitioner, who will prescribe, monitor and adjust mood stabilising medication conform guidelines. The within-group design allows participants baselines to act as their individual control periods with no intervention (Barlow, Nock, & Hersen, 2009; Bonsall, Wallace-Hadrill, Geddes, Goodwin, & Holmes, 2012; Holmes et al., 2016). The study will take place within a specialised centre for bipolar disorders within a large psychiatric hospital (GGzE). All participants start after 4 weeks of baseline with either ImCT or psychoeducation treatment The duration of the study for participants will be 32 weeks for participants in the ImCT condition and 26 weeks for participants in the psycho-education condition. The difference in duration between the conditions is due to treatment length, that is, 12 weeks weekly 1-hour sessions for ImCT and 6 weeks weekly 2-hour sessions for the psychoeducation treatment. Note that all participants will have had 12 hours face-to-face contact in both conditions.
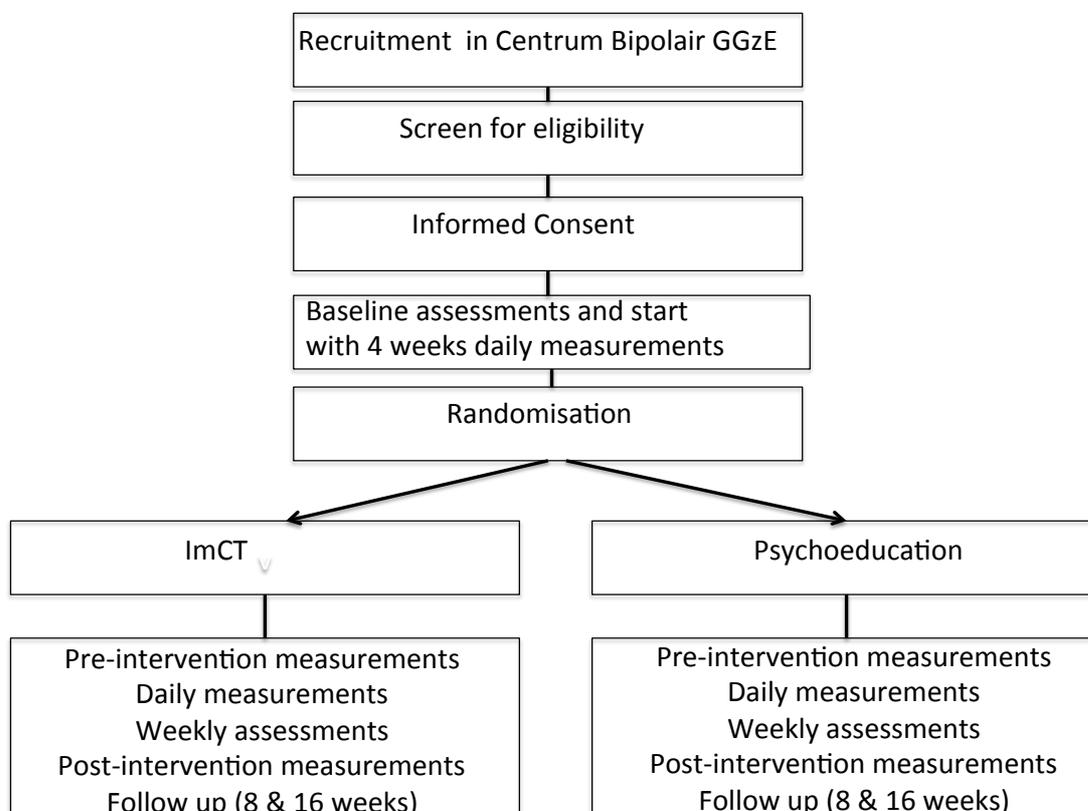
4. STUDY POPULATION

4.1 Population (base)

Participants will be recruited from a specialised centre for bipolar disorders of a large psychiatric hospital (GGzE, Centrum Bipolaire stoornissen). All patients who are referred to this service and all patients who 1) did not receive the current or a largely comparable psychoeducation program 1 year prior to start of the study and 2) who did not receive CBT-treatment tailored for bipolar disorder and with or without imagery interventions 1 year prior, are given written and oral information and informed consent forms and are invited to participate in this study. Currently there are 400 patients attending this service, at least 300 of those have not had psychoeducation or CBT in the last year. On average 70 new patients are referred to this specialised centre each year. Patients attending this service are aged between 18 and 65 years old, both male and female, mostly white European.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Aged 18-68
- Sufficient Dutch language ability to permit the assessment to be completed.
- Diagnosis of BD (I or II or unspecified) according to DSM-5 (clinicians assessment).
- Willing to complete daily and weekly monitoring throughout the duration of the study.
- Successful completion of the daily monitoring in the 4 weeks active run-in phase.
- Willing to be randomised to either ImCT or psychoeducation condition
- Able to attending 12 consecutive weekly sessions ImCT or 6 weekly two hours sessions psychoeducation/TAU.

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Learning difficulties, organic brain disease or severe neurological impairment.
- Have received either 1) psychoeducation similar to the presently used psychoeducation program, or 2) CBT tailored at bipolar disorder with or without imagery interventions within the last year prior to the start of the study.
- Current severe substance or alcohol misuse (clinicians assessment).

- Current manic episode as diagnosed by DSM-5

- Current active psychotic symptoms

- Presence of active suicidal risk as indicated by a score of 2 or more on item 12 (i.e. frequent thought and/or plans to end their life) of the QIDS (Rush et al., 2003) confirmed by convergent clinical opinion.

- Taking part in concurrent treatment studies investigating pharmacological or psychological treatment for BD.

4.4 Sample size calculation

To estimate the sample size needed for the between group design of this study, we used the study's primary outcome variable, mood variability, which is measured using the Affect Lability Scale (ALS-18).

The primary outcome variable for the between subjects design of the study, is the ALS-18, which was used in the audit (Hales et al., 2018) and in the pilot study by Holmes (Holmes et al., 2016). The effect sizes they found using the ALS-18 were $d = 0.8$ and $d = 0.99$ (see Table 1 below). We expect similar effect sizes in our study, that is $d = 0.9$ (the mean of the prior mentioned studies). Studies on the effect of psychoeducation have shown only moderate effects on medication adherence, knowledge of bipolar disorder and attitudes, but no or limited effect on mood variability or relapse, ranging from no effect (Bond & Anderson, 2015; Kurdal, Tanriverdi, & Savas, 2014) to a minimal effect (maximum of $d = 0.3$, but only in patients with less than 7 episodes), (Gumus, Buzlu, & Cakir, 2015; Morriss et al., 2016). We therefore expect an effect size of $d = 0.6$ (i.e., $d = 0.9$ minus $d = 0.3$). Based on prior mentioned effects of the ALS-18 we calculated the sample size needed, to power this study at 80% to detect an effect size of Cohen's $d = 0.6$ using a significance level of .05 two tailed T-tests using G*power 3.1.9.3 The calculated sample size needed is 45 in each group. The study of Holmes et al. (2016) showed a drop out 1 out of 15. After consulting with the research group from the audit and pilot study we expect a similar drop out rate in the current study. We therefore need a sample size of 48 in each group, 96 in total.

Table 1: Mean (SD) ALS-18 scores before and after ImCT in the pilot study of (Holmes et al., 2016)

Pre-Treatment	End of Treatment	4 week FU	12 week FU	24 week FU	Time	Pairwise differences, Bonferroni corrected pairwise t-test
46.36 (11.26)	35.54 (10.49)	35.43 (10.92)	36.36 (12.58)	34.71 (12.74)	F(4.48)= 6.75, p<.001	Pre vs 4w t(12)= 3.77, p =.027, d=0.99; pre vs 12w

						$t(12)=3.58$, $p=.038$, $d =.84$; pre vs 24w $t(12)=4.62$, $p =.006$, $d = 0.97$

Next to the ALS-18 as primary measure, we also use daily mood variability scores, using the NIMH-LCM, for the within subjects-design. Here the assessment are comparted between baseline (4 weeks is 28 measuring points) conditions and both treatment conditions (at least 6 weeks is 42 measuring points). As we use 70 measuring points in total only a small number of cases suffices to calculate and test differences scores. That is, for such a case series analyses, a sample size of 4 or more is sufficient (Barlow et al., 2009). Moreover, Bulte and Onghena (Bulte & Onghena, 2009) stress that to achieve a large effect size ($d = 1.5$) and a study powered at 80%, a study would need a minimum of 4 participants with a minimum of 20 measurements per person. Our study meets those requirements.

Finally, it is important to note that this is a feasibility study following an audit on ImCT (Hales et al., 2018), and a pilot study on ImCT (Holmes et al., 2016), and precedes and plans to inform a large upcoming (N = 350) RCT on ImCT in the UK next year. The National Institute for Health Research recommend sample sizes for a feasibility study of 30 in total (15 per arm) or a range of 24 to 50 in total (12 to 25 per arm) (Julious, 2005; Lancaster, Dodd, & Williamson, 2004; Sim & Lewis, 2012). Our study also meets those requirements.

5. TREATMENT OF SUBJECTS

5.1   Investigational product/treatment

Both ImCT and psychoeducation interventions are preceded by a period of 4 weeks baseline, in which they start to monitor their mood both daily and weekly, start or continue sessions with a psychiatrist (see below). Both groups will either start or continue to have regular sessions with their psychiatrist throughout the study, aimed at advice on pharmacotherapy, monitoring and if necessary adjustment of pharmacotherapy.

Description of ImCT:
The participants receive ImCT for a period of 12 weeks, 12 sessions of 60 minutes. This intervention consists of an in-depth identification (4 sessions) of images followed by imagery interventions, (6 sessions) and a consolidation phase (2 sessions) developed by Holmes, Young, Hales and DiSimplico and described in the ImCT manual (in press). The in-depth

identification consists of identifying problematic imagery, constructing a micro-formulation with the participant along the lines of regular CBT. In this micro-formulation, first triggers of problematic imagery are identified, then both quality and appraisals of this image are identified. Subsequent maladaptive behaviour and possible links with earlier experiences are described, as well as other maintaining factors. The imagery intervention consists of metacognitive imagery intervention, rescripting of imagery, promoting positive imagery or competing imagery tasks (or a combination of these). In addition, relapse prevention strategies are practiced before the end of this intervention. To increase treatment integrity, therapist in the ImCT condition receive weekly supervision from the Imagery Research group (from Oxford, London and Stockholm) via skype. Therapists are qualified psychologist carefully trained in ImCT.

Detailed description of psychoeducation:
The psycho-education lasts for a period of 6 weeks, consisting of 6 2-hour sessions. Psycho-education is offered in groups, using the format described in by Postma and colleagues (Postma, Honig, & van Gent, 2008). In the first three sessions patients are receiving information on bipolar disorder, symptoms, prevalence, aetiology and mood stabilisers. The remaining sessions focus on (early) recognition of mood variations, and management or coping strategies. Finally, medication adherence strategies and relapse strategies are discussed. Nursing staff who run the psychoeducation groups are experienced in running these groups and carefully trained in the psychoeducation method according to guidelines from Trimbos.

5.2   Use of co-intervention (if applicable)

Both groups (ImCT and psychoeducation) maintain their regular consults with a psychiatrist or specialised nurse practitioner and receive advice and guidance on medication, which is monitored and adjusted conform guidelines (Goodwin et al., 2016; Kupka et al., 2015) throughout this study. These guidelines recommend using a mood stabiliser, with specific recommendation for additions in episodes of mania and depression. Where possible the above-mentioned guidelines will be adhered to unless individual circumstances warrant deviations from this. Consultation with the psychiatrist or specialised nurse practitioner will start (or continue should patients already be in care) during the baseline period, intervention period and follow-up period.

6. METHODS

6.1 Study parameters/endpoints

6.1.1 Main study parameter/endpoint

To assess the primary endpoint of this study (1), decrease of mood variability, mood variability is measured using the Affect Lability Score Short Version (ALS-18) (Oliver & Simons, 2004) at baseline (T0), pre- intervention (T1) and post intervention (T2), and at follow-up measurements at 8 (T3) and 16 weeks (T4) after treatment discontinuation in both the ImCT and psychoeducation conditions. The ALS-18 is a self-report scale measuring lability in affect and consists of 18 items. Ratings are made on a 4-point scale with a maximum score of 72. Scores range from A= very characteristic of me (4 points), to D= very uncharacteristic of me (1 point).

In addition we monitor changes in mood variability using the National Institute of Mental Health Life Chart Methodology (NIMH-LCM) Prospective Self-Rating (Denicoff et al., 2000). Participants rate their mood (both mania and depression) on a 9-point Likert scale, ranging from -4 (severe depression, admission required due to severe dysfunction) to 0 (stable mood) to +4 (severe mania, admission required due to severe dysfunction). Daily measurements are calculated during a 4-week baseline prior to start of either ImCT or psychoeducation, during the invention and until follow up at 16 weeks. This method is advised given that traditional self-report mood ratings over a single time point are scarcely representative of mood variability in bipolar disorder.

6.1.2 Secondary study parameters/endpoints (if applicable):

The following parameters are used for the following secondary objectives:

To assess (2a) level of depression, mania and anxiety and (2b) general functioning and hopelessness (3) number of relapses into mania or depression decline/increase, we administer the following measures:

- Level of depression, using the Quick Inventory of Depressive Symptoms (QIDS-SR) (Rush et al., 2003). The QIDS-SR is a 16-item self-report rating scale in which the nine DSM 5 symptoms of major depression are incorporated. Answers are rated on a four-point Likert scale (0-3). The QIDS-SR is administered weekly throughout the duration of the study.

- Level of mania, using the Altman Self-Rating Mania Scale (ASRM-NL) (Altman, Hedekker, & Peterson, 1997). The ASRM-NL is a 5 item self-report instrument to measure severity of mania symptoms. This is administered weekly throughout the duration of the study.

- Level of anxiety, using the Beck Anxiety Inventory (BAI) (Osman, Barrios, Aukes, Osman, & Markway, 1993). The BAI is a 21-item self-report questionnaire used for measuring the severity of anxiety. Answers are rated on a 4-point Likert scale (0-3). This is administered weekly throughout the duration of the study.

- Level of general functioning and coping: Participants rate their level of functioning using the Longitudinal Interval Follow up Evaluation – Range of Impaired Functioning Tool (Leon et al., 1999). This is a brief scale for people suffering from affective disorders, measuring four different functional areas (employment, interpersonal relations, satisfaction and recreation) on a 5-point Likert scale (low rating implies higher functioning). This is administered at T0, T1, T2, T3 and T4.

- Level of hopelessness: participants rate their hopelessness using the Beck Hopelessness Scale (Beck, Brown, & Steer, 1997), The BHS is a 20 item self-report scale measuring three aspects of hopelessness: feelings about the future, motivation and expectations. The BHS demonstrates good internal consistency (alpha = .93) and has high reliability in psychiatric samples (Beck et al., 1997). The BHS is administered at T0, T1, T2, T3 and T4.

- To assess number of relapses into mania and depression, scores on the above measures (ASRM for mania and QIDS-SR for depression) are used. Scores on the ASRM of 5 or more indicate a relapse into mania, a score of 10 or more on the QIDS a relapse into depression. This is measured using the weekly scores on the ASRM and QIDS-SR during the weekly measures in the follow up period (until 16 weeks after the end of either ImCT or psychoeducation).

To assess if (4) problematic imagery the following measures will be used:

- The Visual Analogue Scales of Imagery Characteristics (VAS-Imagery) have been tailored to BD populations. The scales range from 0-9. Examples are "How real / vivid / absorbing / preoccupying / compelling have your image(s) been over the past week"; "To which extent could you understand the role that the image(s) play in your mood instability?"; "To which extent could you find positive / helpful way of using the image(s)?". Target imagery is measured weekly throughout the duration of the study. Imagery characteristics are measured weekly throughout the duration of the study in both ImCT and psychoeducation treatment conditions.

- Mental Imagery and Coping with Bipolar Disorder Questionnaire (MICQ-BD) is a 14 item self-report instrument assessing patient's response to mental imagery on a five-point Likert scale, ranging from "not at all" to "a lot". In a pilot study Holmes (2016) calculated the internal consistency (alpha = .70) of this measure to be satisfactory (DiSimplicio et al., 2016). General imagery is measured at T0, T1, T2, T3 and T4.
- General Imagery (frequency of imagery, quality of imagery and appraisals of imagery) using the Dutch Imagery Survey, DImS): measured at T0, T1, T2, T3 and T4 using a 42-item online Imagery Survey recently validated in a student sample (Van den Berg, in preparation), and patient samples (Van den Berg, in preparation).

6.2 Randomisation, blinding and treatment allocation

An independent central research assistant will randomize participants to treatment condition (ImCT or psychoeducation) after checking all in- and exclusion criteria. Randomization will be based on block randomization with (N=10) per block to guarantee a balance between conditions over time and stratified for mood stabilising medication (either mood stabilising medication, or no mood stabilising medication), so that mood stabilising medication is controlled per arm. Stratification for mood stabilising medication is necessary because not using mood stabilizing medication can seriously affect the primary outcome variable. We roughly estimate that 15 percent of the participants in GGzE will have no mood stabilising medication, but there are no firm data available. Blinding of participants and therapists to treatment condition is not possible in this kind of psychotherapy trial, but the assessments will be blind to treatment condition as they are filled in online.

6.3 Study procedures

6.3.1 Screening procedures

Patients are recruited from a specialised centre for bipolar disorders in psychiatric hospital (Centrum Bipolair GGzE). The responsible lead clinician (regie behandelaar) identifies eligible patients and subsequently give these patients the information letter as well as oral information about the study and asks permission to hand over their contact information to the researcher should they consider participating. Once patients have indicated to the researcher, their nurse, psychiatrist or psychologist they would like to participate in this study, the researcher makes an appointment with the patient. During this appointment the researcher checks if the identified patient meets the inclusion criteria, and if patients still agrees with participation in the study and they are given the informed consent letter. After one week in which patients can consider their participation in this study, the researcher makes another appointment with the participant during which both the researcher and

participant sign the informed consent letter. At this time, the researcher asks for the email address of the participants in order for the online questionnaires to be accessible for the patient.

6.3.2   Study Assessment Moments

Psychoeducation groups at Centrum Bipolar start once in every six weeks. At four weeks prior to the start of each psychoeducation group the identified participants start with the online measures at baseline (T0), and both daily and weekly online measurements which participants receive by email. Note here that the patients that participate in this study will not wait longer than the patients that choose not to participate. Participants continue to fill in both the daily and weekly online measures for four weeks (the baseline period). After four weeks all participants fill in the measures pre-intervention (T1), and are allocated randomly to either the ImCT or psychoeducation condition, which will then commence. During the intervention period (12 weeks for the ImCT condition, and 6 weeks for the psychoeducation treatment condition) all participants continue to fill in both the daily and weekly online measures. At the end of the intervention, all participants fill in the post-intervention measures (T2) online. Subsequently, all participants continue to fill in both daily and weekly online measures until the end of the study (at follow up at 16 weeks). In addition, participants fill in the post-intervention online measures at follow up at 8 weeks (T3) and 16 weeks (T4) after the end of intervention.

6.3.3   Assessment Procedures

All measures are administered online. However, there is an option to fill in the questionnaires on paper, should this prove difficult for participants. The daily measures will take a 2 to 3 minutes, the weekly measures will take approximately 20 minutes. The measures at baseline (T0), pre-intervention (T1), post-intervention (T2) and at 8 and 16-weeks follow-up (T3 and T4) will take approximately 45 minutes. Patients and therapist will not be informed about the results of assessments until the end of the study (16 weeks after the end of intervention).

6.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

6.4.1 Specific criteria for withdrawal (if applicable)

If patients experience relapse (mania or depression) and require a hospital admission for longer than one week, they will be excluded from this trial.

6.5   Replacement of individual subjects after withdrawal

Should patients withdraw from the study they will not be replaced.

6.6   Follow-up of subjects withdrawn from treatment

If patients are withdrawn from the study, they will continue with care as usual from the specialised centre for bipolar disorders of the GGzE.

6.7 Premature termination of the study

The study will be terminated if a large number of patients in ImCT condition drop-out or deteriorate. This, however, is not expected as the treatment has been piloted before and found highly effective and to have low drop-out rate.

7. SAFETY REPORTING

7.1   Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

7.2   AEs, SAEs and SUSARs

7.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the trial procedure or the experimental intervention. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

7.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that:
- Results in death;
- Is life threatening (at the time of the event);
- Requires hospitalisation or prolongation of existing inpatients' hospitalisation;

- Admissions due to relapse episode mania or depression (part of routine care)
- Results in persistent or significant disability or incapacity;
- Is a congenital anomaly or birth defect; or
- Any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events, except for the following SAEs:
- Relapse episode mania or depression as relapse is one of the secondary objectives of this study.

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

7.3   Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study within the Netherlands, as defined in the protocol

7.4   [Data Safety Monitoring Board (DSMB) / Safety Committee]

In this study a DSMB is not needed, as the interventions consists of either care as usual, or a variation on care as usual. Relapse episodes (mania or depression) are expected as part of the condition. Appropriate care for this is in place and considered care as usual.

8. STATISTICAL ANALYSIS

First, descriptive analyses will be used to establish mean scores, standard deviations and to identify outliers. Missing data from our primary outcome variable, will be listwise deleted. In our other outcome variables, data will only be included if pre- and post-measures are completed.

Second, the data will be checked with respect to violation of assumptions (such as error independency, non-normal distributions) for variance-based models.

Primary outcome variable: mood variability:

To assess if there is a stronger decrease in mood variability in the ImCT intervention condition as compared to the psychoeducation condition, multivariate repeated measures analyses are applied. Dependent variables are the scores on the ALS-18 (baseline, T0; pre-treatment, T1; post-treatment, T2; 8-weeks follow-up, T3; 16-weeks follow-up, T4) with treatment condition (ImCT, psychoeducation) as between subjects variable.

In addition, to assess reductions in mood variability during the interventions (ImCT, psychoeducation) compared to mood variability during the baseline period, daily mood measures with the National Institute of Mental Health Life Chart Methodology (NIMH-LCM) Prospective Self-Rating of mood (both mania and depression) are assessed, using a case series design, were participants baseline ratings can act as their own control (Arntz, Sofi, & van Breukelen, 2013). Changes in mood variability are investigated using sequence analysis with R-software (package TraMineR version 1.8-10); (Gabadinho, Ritschard, Muller, & Studer, 2011) on the daily scores. Sequences consist of a series of subsequent states (daily scores) and similarities between sequences are calculated with the Optimal Matching technique (OM). Sequences will be defined as day scores from 28 days prior to starting the interventions, until 112 days after the end of interventions. Rather homogenous groups of trajectories (clusters) will be derived from the distance matrix that result from the OM technique. To this end, cluster analysis will be applied. Shannon entropy of transversal state of the scores on each day will be calculated and plotted (Gabadinho et al., 2011). Entropy is a measure of diversity of states (a measure of mood variability) within sequences and varies between zero (all sequences in the same state) to 1 (maximum diversity). To explore the relationship between diversity in states (mood variability) and background characteristics, this longitudinal entropy will be regressed on co-variates (gender, medication). Also, sequences of scores at the start of treatment will be compared to subsequences during treatment and during the follow-up period to explore change over time.

Secondary outcome variables: depression, anxiety, mania, general functioning and coping, hopelessness, number of relapses into mania or depression, and changes in imagery:

To assess if (2a) level of depression, mania and anxiety, (2b) general functioning and coping, and hopelessness increase/decline more in the ImCT intervention compared to psychoeducation treatment two types of multivariate repeated measures analyses are applied, both with treatment condition (ImCT, psychoeducation treatment) as independent, between groups variable. In the first type of analyses, the dependent variables are the scores of the weekly measures for depression, anxiety and mania (QIDS-SR, BAI, ASRM). In the second type of analyses, time (T0, T1, T2, T3 and T4) is used as within between subject variables and scores of the same instruments and general functioning and coping and hopelessness (ALS-18, IFE-RIFT, BHS) are used as dependent variables.

To assess if (3) number of relapse into mania or depression decline more in the ImCT intervention compared to psychoeducation treatment Chi-square analyses are applied with as dependent variable number of relapses into mania or depression, using cut-of scores on the ASRM and QIDS-SR during the follow-up period and treatment condition (ImCT, psychoeducation treatment) as between groups variable.

To assess if (4) problematic imagery decreases and imagery characteristics changes more by using the ImCT intervention compared to psychoeducation treatment, comparable to 2a and 2b, two types of multivariate repeated measures analyses are applied, both with treatment condition (ImCT, psychoeducation treatment) as between groups variable. In the first type of analyses, the dependent variables are the scores of the weekly measures of imagery (VAS). In the second type of analyses, time (T0, T1, T2, T3 and T4) is used as within between subject variables and scores of imagery (MICQ-BD and DIS) are used as dependent variables.

Where possible multivariate analyses are used to analyse differences between groups, and repeated-measures ANOVA to analyse difference within groups. These will be used to minimise the correlations and dependencies between variables. In order to allow for reliable multivariate analysis, assumptions of sphericity are tested. Multivariate analyses between groups (ImCT, psychoeducation treatment) and repeated-measures ANOVA within groups (T0, T1, T2, T3, T4) are used to determine an omnibus effect. If differences are significant, post hoc analyses (mostly independent T-test) will be used to determine individual differences between groups and between points in time. Bonferoni corrections are used to correct for multiple testing.

Intention-to-treat analyses will constitute the central analyses and completers analyses will be done as supplementary analyses.

9   ETHICAL CONSIDERATIONS

9.1 Regulation statement

This study will be conducted according to the principles of the declaration of Helsinki (Brasil, 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

9.2 Recruitment and consent

Patients are recruited from a specialised centre for bipolar disorders in psychiatric hospital (Centrum Bipolair GGzE). The lead clinician (regie behandelaar) identifies eligible patients and subsequently give these patients the information letter as well as oral information about the study and asks permission to hand over their contact information to the researcher should they consider participating. Once patients have indicated to their nurse, psychiatrist or psychologist they would like to participate in this study, the researcher makes an appointment with the patient. During this appointment the researcher answers any remaining questions and if patients still agree with participation in the study they are given the informed consent letter. After one week in which patients can consider their participation in this study, the researcher makes another appointment with the participant during which both the researcher and participant sign the informed consent letter. At all times can patients withdraw from the study without explanation. Moreover, they have the opportunity to consult an independent expert (dr. S. Valentijn). Note that during the whole time that patients participate in this study they are allowed to continue or start with advice on mood stabilising medication from their psychiatrist.

Once the researcher has obtained informed consent, baseline measures are administered. Patients start with four weeks daily mood measurements. At the end of these four weeks, they are randomly allocated to either ImCt or psychoeducation treatment condition and fill in the pre-intervention measurements online after which they start with either of both treatments. At the end of the treatments they fill in the post-intervention measurements online. At 8 and 16 weeks follow-up measurements the patients fill in measurements online. All patients continue their daily mood monitoring until follow-up at 16 weeks. Screening for eligibility ceases after 96 patients are included, 48 in each condition.

9.3 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.
The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

9.4 Incentives (if applicable)

There is no special incentive, compensation or treatment that subjects will receive through participating in this study. However, participants will be reimbursed for their extra travel costs.

10 ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

10.1 Handling and storage of data and documents

All data are coded by means of number codes. Only the lead researcher has a key of names and participant numbers; the researchers of the research group of the project only get coded data, i.e., data with participant number, not with names. Codes are in chronological order, each subsequent participant is allocated the subsequent number. The participant data will be stored for up to 15 years after the last measurement of the last participant of this study. On the questionnaires used in this study is only the participant number visible, data is stored on a secure server, using Research Manager (which complies with the Dutch AVG, General Data Protection Regulation). Apart from the researchers of this team, inspectors of the national inspection of health (Inspectie Volksgezondheid) have access to the data.

10.2 Monitoring and Quality Assurance

Research manager will be able to provide an audit of all activities in this study, and changes made in the CRF. A delegation log, is made and kept up to date. The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments. There is no need to provide a monitor plan in paragraph 7.4 is mentioned that in this study a DSMB is not needed, as the interventions consists of either care as usual, or a variation on care as usual.

10.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

All substantial amendments will be notified to the METC and to the competent authority.

10.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

10.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

10.6 Public disclosure and publication policy

This trial is in the process of being pre-registered at ClinicalTrials.gov. The sponsor and investigator have agreed to full public disclosure of the research data and aim to publish the research data in a relevant journal, conform guidelines of the CCMO.

11. Ethical considerations

11. 1 Benefits and risk assessment:

Risks for patients participating in this study are minimal. This intervention has been successfully tested in a pilot study (Holmes et al., 2016), suggesting this intervention is able to decline mood variability in patients suffering from bipolar disorder, and also is well tolerated and well received by patients. The ImCT is offered without discontinuing care as usual (visits to the psychiatrist monitoring mood stabilizing medication). The same is the case for psychoeducation treatment. Psychoeducation treatment, although applied using a treatment protocol, is in line with psychological interventions offered routinely to BP patients. The extra burden for participants is the weekly questionnaires (20 minutes), and the questionnaires at T0-T4 (45 minutes), as daily monitoring is advised in current guidelines.

Should patients relapse into mania or depression, they will receive standard care as usual. The benefits of participating in this study are also minimal. For participant in the ImCT condition, there might be the added benefit of having an intervention aimed at changing imagery, expected to form a central part of emotion amplification, but these effects above psychoeducation are not yet demonstrated. For participants in the psychoeducation condition the effects are not different from treatment as usual. It is important to note, they have the the possibility to receive ImCT after their participation to this study has ended. In the same line, the patients in the ImCT condition have the possibility to receive psychoeduation after this study has ended.

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