

RESEARCH PROTOCOL

Mindfulness Based Cognitive Therapy for Bipolar Disorder

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| Coordinating investigator/project leader | Dr. Marloes J. Huijbers Radboudumc, department of psychiatry Reinier Postlaan 4 6525 GC Nijmegen |
| Principal investigator(s) (in Dutch: hoofdonderzoeker/ uitvoerder) | Prof. Dr. Anne E.M. Speckens Radboudumc, department of psychiatry Reinier Postlaan 4 6525 GC Nijmegen |
| <Multicenter research: per site> | <p>Pro Persona Drs. Marc Lochmann – van Bennekom Tarweweg 6 6534 AM Nijmegen Netherlands</p> <p>Altrecht Dr. Eline Regeer Lange Nieuwstraat 119 3512 PG Utrecht Netherlands</p> <p>Dimence Drs. Anja Stevens Pikeursbaan 3 7411 GT Deventer Netherlands</p> |
| Sponsor (in Dutch: verrichter/opdrachtgever) | Radboudumc Nijmegen, Netherlands Tel. +31 (0)24 – 3668456 Email: mindfulness@radboudumc.nl |
| Subsidising party | ZonMW: The Netherlands Organisation for Health Research and Development Den Haag, Netherlands Tel. +31 (0)70 – 3495111 Email: info@zonmw.nl |
| Independent experts | <p>Radboudumc: Dr. Marleen van Beek, psychiater</p> <p>Pro Persona: Dr. Florian Hardeveld, psychiater</p> <p>Altrecht: Dr. Aart de Leeuw, psychiater</p> <p>Dimence: Drs. Just Wernand, psychiater</p> |

PROTOCOL SIGNATURE SHEET

| Name | Signature | Date |
|---|-----------|------|
| Head of Department: <i>Prof. Dr. Aart H. Schene</i> Department of Psychiatry Radboudumc, Nijmegen | | |
| Principal Investigator: <i>Prof. Dr. Anne E.M. Speckens</i> Department of Psychiatry, Radboud Center for Mindfulness Radboudumc, Nijmegen | | |

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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 |
| AR | Adverse Reaction |
| ASRM | Altman Self Rating Mania Scale |
| BD | Bipolar Disorder |
| CCMO | Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek |
| CHIME | Comprehensive Inventory of Mindfulness Experience |
| DSMB | Data Safety Monitoring Board |
| FAST | Functioning Assessment Short Test |
| IDS-C | Inventory of Depressive Symptomatology- clinician rated |
| MBCT | Mindfulness Based Cognitive Therapy |
| METC | Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC) |
| MHC-SF | Mental Health Continuum – short form |
| QIDS-SR | Quick Inventory of Depressive Symptomatology – Self report |
| RPA-NL | Responses to Positive Affect- Dutch version |
| RRS | Ruminative Response Scale |
| (S)AE | (Serious) Adverse Event |
| SCS-SF | Self-Compassion Scale – short form |
| SCID-I | Structured Clinical Interview for DSM-IV-TR Axis I Disorders |
| 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. |
| TAU | Treatment as usual |
| TiC-P | Trimbos/iMTA questionnaire for costs associated with psychiatric illness |
| STAI | State/Trait Anxiety Inventory |
| Wbp | Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgegevens) |
| WMO | Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen) |
| YMRS | Young Mania Rating Scale |

SUMMARY

Rationale: Persistent and residual depressive symptoms in bipolar disorder (BD) are common and have been associated with negative effects on the course of BD. However, limited data are available on how to reduce these depressive symptoms, or how to improve outcomes for patients who do not benefit sufficiently from available treatments. Mindfulness-Based Cognitive Therapy (MBCT) is an innovative intervention that already has been shown effective in reducing depressive symptoms in unipolar recurrent depression. Therefore, it is hypothesized that, compared to usual care, MBCT will reduce depressive symptoms in BD patients.

Objective: Outcomes of MBCT for BD patients are examined on a symptomatic level (e.g. depression, (hypo)mania, anxiety, risk of relapse/recurrence) and in terms of functioning and mental health/well-being, including possible working mechanisms such as improvements of mindfulness and self-compassion skills.

Study design: A randomized, multicenter, evaluator-blinded, prospective clinical trial with assessments at baseline, and 3, 6, 9, 12 and 15 months follow-up.

Study population: Adult BD type I or BD type II patients (N = 160) who suffered from at least two lifetime depressive episodes (either current or in (partial) remission), and having suffered from at least one affective episode within the year prior to baseline, without (hypo)manic symptoms within the last 3 months.

Intervention: Patients will be randomly assigned to one of two groups: (1) Treatments as usual (TAU): Patients continue to receive usual care, typically consisting of pharmacotherapy, psycho-education and self-management interventions. (2) TAU + MBCT: Patients will be invited to participate in a MBCT-program in addition to their usual care.

Main study parameters/endpoints: Primary outcome is the severity of depressive symptoms at 3 months follow-up (T1), assessed with the Inventory of Depressive Symptomatology – Clinician administered (IDS-C; Akkerhuis, 1997).

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The burden associated with participation in MBCT is relatively high: consisting of 8 weekly group sessions of 2,5 hours and one silent day (6 hours), and home practice of about 45 minutes a day. Participation includes 6 research assessments consisting of interviews and questionnaires about psychological symptoms, functioning, and quality of life. Before and after the intervention the assessment will include computer tasks to assess cognitive control. Although the effort requested from patients is high, we expect that practicing mindfulness will be associated with enduring changes in patients' coping strategies in daily life, and as a result, can increase participants' autonomy and self-efficacy. The risks associated with participation are expected to be low. Although the increased awareness of difficult emotions may be confronting or overwhelming for some, this is a major topic that will be discussed during MBCT. If participants show a clear increase in symptoms, this will be discussed with their responsible clinician and additional guidance will be offered. Participants are encouraged to respect their boundaries (both physical and psychological) and are always free to suspend or adapt the practice as needed.

1. INTRODUCTION AND RATIONALE

Bipolar Disorder (BD) is characterized by its severe and chronic course, with patients suffering from recurrent depressive, (hypo)manic, and/or mixed episodes, being symptomatic about half of the time (Judd et al., 2002). According to the World Health Organization (2008), BD belongs amongst the leading causes of years lost due to disability. BD patients typically experience debilitating psychological stressors, such as social rejection, internalized stigma, and subjective distress (Davis & Kurzban, 2012), and is therefore associated with tremendous economic, social, and occupational burden (Dilsaver, 2011; McCrone, Dhanasiri, Patel, Knapp, & Lawton-Smith, 2008; Pini et al., 2005). In the Netherlands, BD affects approximately 1.2% of men and 1.4% of women (De Graaf, Ten Have, & van Dorsselaer, 2010). Although hospital admissions are more common during manic episodes, it has been shown that depressive symptoms substantially predominate over manic symptoms, and that illness-related disability is more strongly influenced by depressive episodes (Judd & Akiskal, 2003; Judd et al., 2002). It has been estimated that approximately 33 – 50% of BD patients attempt suicide at least once in their lifetime, whilst 15 – 20% die due to suicide (Gonda et al., 2012). Since the middle of the last century, pharmacological interventions have been the first-line treatment for BD (Vieta & Colom, 2004). However, it has become evident that pharmacological interventions alone are insufficient, since 60% of patients relapse within two years (Miklowitz et al., 2009; Oud et al., 2016). Therefore, augmentation of psychological interventions is required in order to improve symptoms and reduce relapse rates (Oud et al., 2016; Vieta & Colom, 2004). Adjunct psychosocial interventions appear to improve outcomes as patients learn to adopt behavioural strategies to manage their mood instability. However, in spite of these interventions, persistent or residual depressive symptoms remain in more than 40% of patients (Samalin, de Chazeron, Vieta, Bellivier, & Llorca, 2016). These symptoms are strongly associated with impairments in interpersonal and occupational functioning (Dilsaver, 2011; Samalin et al., 2017), and affect the course of BD and quality of life negatively (Gutiérrez-Rojas et al., 2008). Furthermore, these adjunct psychological interventions seem to become less effective in those who suffered more than twelve previous episodes (Scott et al., 2006). Limited data are available on how to optimize treatment of persistent or residual depressive symptoms in BD, or how to improve outcomes for patients who do not benefit sufficiently from available treatments. Furthermore, there is a need for interventions that not only target symptom reduction but also help patients to cope with their illness from a wider perspective, i.e. in terms of their personal values, goals, and social roles (Farkas, 2007).

Mindfulness-Based Cognitive Therapy (MBCT), an innovative psychological intervention, has been shown effective in reducing depressive symptoms in unipolar recurrent depression (Kuyken et al., 2016; van Aalderen et al., 2012), and appears to be promising for coping with severe mental illness (Davis & Kurzban, 2012). Little is known about the effectiveness of MBCT for BD, with only a number of pilot studies showing reductions in depressive symptoms (Miklowitz et al., 2009; Williams et al., 2008), and one RCT showing a reduction of anxiety symptoms but not of depressive symptoms (Perich, Manicavasagar, Mitchell, Ball, & Hadzi-Pavlovic, 2013). The study of Perich et al. (2013), however, showed high drop-out rates, which may have compromised the power to detect changes in depressive symptoms, especially given the fact that this was an euthymic group at baseline. Thus, there is a lack of sufficiently powered RCTs examining the effect of MBCT on BD patients. In addition, most studies have included remitted BD patients only, which may have limited the possible range of symptom reduction and the clinical representativeness of the studies. The proposed study will be the first RCT of MBCT for BD in the Netherlands, providing high-level evidence about the effectiveness of MBCT versus TAU for patients with BD. It will be offered in a multi-centre setting and using several outcome measures, including cost-effectiveness. If (cost-)effective, MBCT might widen the array of psychosocial interventions for patients with BD.

Growing evidence conceptualizes BD as having difficulties in emotion regulation (Gruber, Eidelman, & Harvey, 2008; Gruber, Eidelman, Johnson, Smith, & Harvey, 2011). Rumination of both positive and negative affect has been associated with the onset and maintenance of BD (Johnson, 2005; Nolen-Hoeksema, 1991). Ruminative responses to negative affect appear to create a vicious cycle of ruminative thinking, decreased motivation and interest, and loss of positive mood, which intensifies symptoms of depression (Johnson, McKenzie, & McMurrich, 2008), whilst rumination of positive affect

is associated with goal-directed activity and decreased sleep, which intensifies symptoms of mood elevation (Gruber, 2011). According to Segal, Williams, and Teasdale (2002), training in mindfulness should decrease the tendency of depressed patients to enter a vicious cycle of negative ruminative thinking. Studies investigating reductions of negative rumination during MBCT are scarce (Michalak, Holz, & Teismann, 2010). In a sample of 55 treatment-resistant depressed patients, Eisendrath et al. (2008) found significant reductions of negative rumination following MBCT. The study of Deckersbach et al. (2012) found a significant decrease of negative rumination after MBCT in a sample of ten BD patients. Other studies found statistical trends towards reductions of negative ruminative thinking after MBCT in a sample of 19 patients with residual depressive symptoms (Kingston, Dooley, Bates, Lawlor, & Malone, 2007), and 95 BD patients (Perich et al., 2013). To our knowledge, no studies to date have investigated the effect of MBCT on ruminative responses to positive affect in BD patients. The present study will be the first to examine differences in ruminative responses to both positive and negative affect following MBCT in BD patients.

Furthermore, little is known about the potential moderators and working mechanisms of recovery in BD. One of the possible moderators of MBCT for patients with recurrent depression is a history of childhood traumatic events (CTEs; Williams et al. 2014). CTEs also play a major role in BD. For example, CTEs are associated with higher risk of developing bipolar disorder and critically with a more severe clinical presentation over time (Aas et al., 2016). To find whether CTEs also have an influence on the effect of MBCT on BD, another goal of this study is to investigate whether the subgroup of patients with CTEs show a differential response to MBCT compared to subjects without CTEs. Moreover, CTEs contribute to the development of negative cognitive schemas, a finding that has mainly been described in patients with depression (Beck & Haigh, 2014; Gotlib & Joormann, 2010; Mathews & MacLeod, 2005). These schemas conceptualized on a cognitive level as a coalescence of different cognitive-affective biases (e.g. in attention and memory) leading to a biased view towards the self, the future and the environment, sustaining clinical symptoms in depression such as emotion dysregulation (Beck, 2008; Beck & Haigh, 2014). Research on cognitive bias in BD is limited and results are equivocal (Peckham, Johnson, & Gotlib, 2016). Findings include no attentional bias in euthymic BD patients (e.g. Peckham et al., 2016), but critically diminished attention towards positive words in mildly depressed BD patients (Jabben, Arts, van Os, & Krabbendam, 2010) and depressive mood-related negative recall bias in BD patients (Adams, Shapero, Pendergast, Alloy, & Abramson, 2014). It seems warranted to investigate whether MBCT results in changes in different forms (e.g. attentional memory) of these cognitive-affective biases in BD patients. If so, we will be able to advance our insight in the potential cognitive-affective working mechanisms of MBCT in BD.

In sum, the current study will combine measures of clinical and cost-effectiveness with cognitive measures addressing cognitive-affective bias and other psychological processes including rumination, mindfulness and self-compassion to assess the potential mechanisms of change in MBCT for bipolar disorder.

2. OBJECTIVES

Primary Objective:

- Is MBCT as an adjunctive treatment to TAU more effective in reducing depressive symptoms in patients with bipolar disorder, compared to TAU alone?

Secondary Objective(s):

- Is MBCT more effective than TAU in reducing levels of (hypo)manic and anxiety symptoms, the risk of relapse in depression or (hypo)mania, and ruminative brooding?
- Is MBCT equally effective in patients with < 12 mood episodes compared to patients with ≥ 12 episodes?
- Is MBCT more effective than TAU in improving mindfulness, self-compassion, functioning, and mental health/well-being?
- From the viewpoint of the society, is adding MBCT to TAU preferable in terms of societal costs and QALYs, compared to TAU alone?

Our hypothesis is that participants allocated to MBCT will have fewer depressive, (hypo)manic, and anxiety symptoms and experience fewer (hypo)manic or depressive episodes than those allocated to TAU over the 15 months study period. In addition, we hypothesize that MBCT will be associated with improvement in several areas of functioning and well-being. Furthermore, we expect that positive outcomes will be (partially) mediated by a reduction of ruminative thinking, and improvement of mindfulness and self-compassion skills.

3. STUDY DESIGN

A randomized, multicenter, prospective, evaluator-blinded clinical trial of MBCT added to treatment as usual (TAU) versus TAU alone. Assessments will be conducted at baseline and at 3, 6, 9, 12, and 15 months follow-up. At the end of the study period (15 months), the participants in the TAU group will be offered MBCT as well. Three external, specialized outpatients clinics for treatment of BD, will be participating in the present study. See Figure 1 for a prospective flow chart of the study.

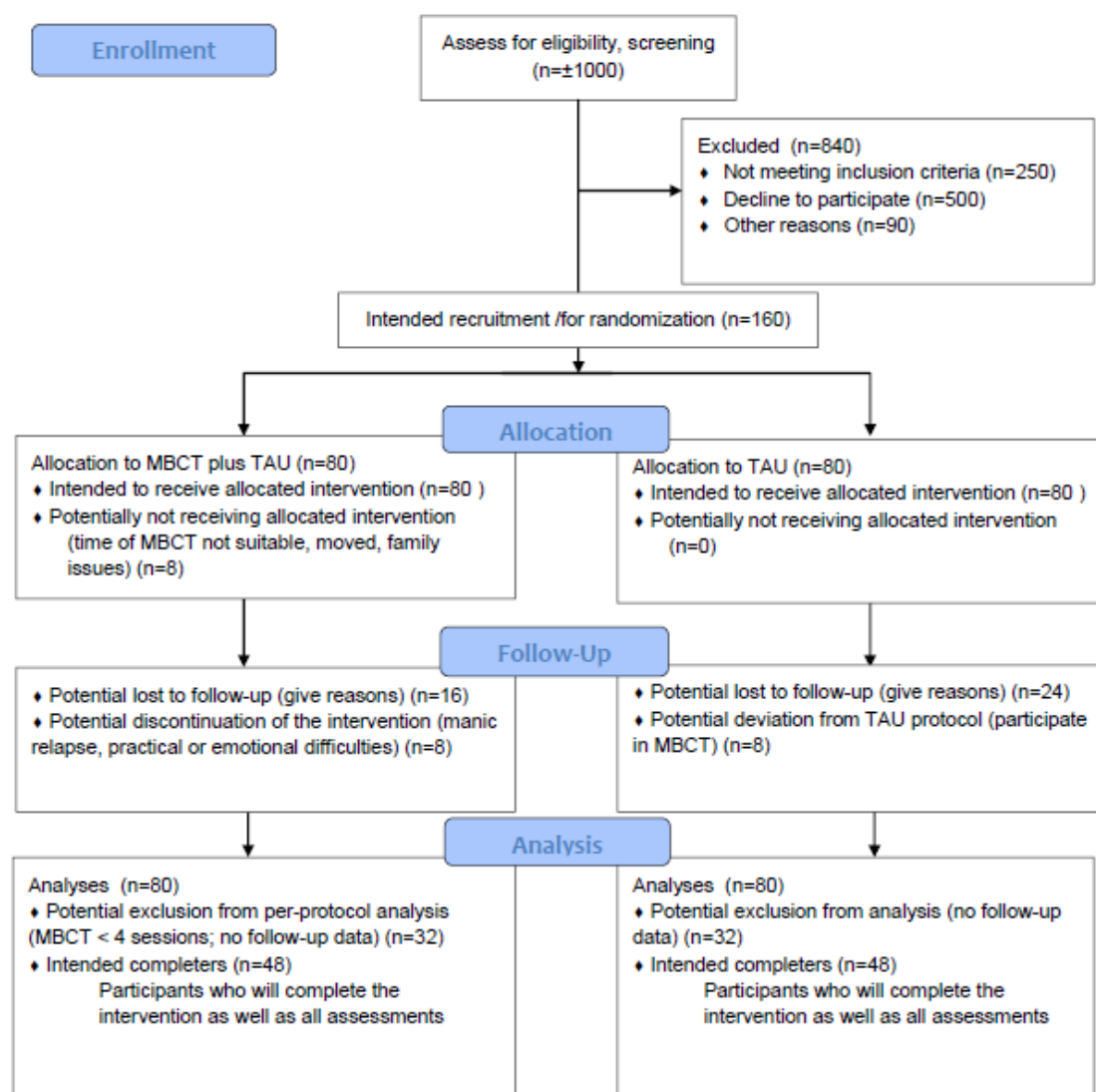


Figure 1. Prospective flow chart of the study

4. STUDY POPULATION

4.1 Population (base)

BD patients older than 18 years will be recruited from the specialized outpatient clinics of ProPersona, Dimence, and Altrecht, and through the Vereniging voor Manisch Depressieven en Betrokkenen (VMDB). The psychiatry department of the Canisius Wilhelmina Ziekenhuis (CWZ) will also support recruitment by referring potential participants to the Radboudumc.

4.2 Inclusion criteria

In order to be eligible to participate in this study, participants have to meet all of the following criteria:

- Confirmed diagnosis of bipolar I or II disorder.
- Having suffered at least two lifetime depressive episodes, either current or in (partial) remission at baseline (according to SCID-I assessment).
- Having suffered at least one affective episode (depressed or (hypo)manic) within the year prior to baseline.
- Young Mania Rating Scale score < 8.

4.3 Exclusion criteria

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

- A manic episode within three months before the start of the trial.
- Lifetime diagnosis of schizophrenia or schizoaffective disorder, current substance abuse disorder, organic brain syndrome, antisocial or borderline personality disorder.
- Risk of suicide or aggression.
- The presence of a concurrent significant medical condition impeding the ability to participate.

4.4 Sample size calculation

Sample size calculation is based on the estimated change in depressive symptoms from pre- to post-treatment. As we aim to include patients with all levels of depressive symptoms, we based our calculation on a previous study conducted at the Radboudumc Centre for Mindfulness (van Aalderen et al., 2012). In this study, levels of depression as assessed with the Inventory of depressive symptomatology – self-rated (IDS-SR) decreased in the MBCT+TAU group ($n = 102$) from $14.9 (\pm 9.2)$ to $10.3 (\pm 7.8)$ whereas the TAU group ($n = 103$) showed no change in depression levels (pretreatment: $M = 16.2 (\pm 9.4)$ and posttreatment: $M = 16.2 (\pm 9.8)$). This corresponded to an effect size of 0.5 for reduction of depressive symptoms in patients with recurrent (unipolar) depression (remitted $n = 124$, currently depressed $n = 58$). Based on a two-sided test with an alpha of 0.05 and a power of 80%, with an estimated effect size of 0.5, including a design factor of $1 - r^2$ (0.75), and taking account of a conservative estimate of 40% loss to follow-up, we intend to recruit $N = 160$ patients (80 per group).

We anticipate that about 25% of the population will have to be excluded due to (hypo)manic symptoms (when exceeding the maximum on the Young Mania Rating Scale) or other exclusion criteria. We further expect about 25% of the eligible patients to be interested in the study.

Approximately 690 BD patients are treated in ProPersona, with 518 (75%) meeting the inclusion criteria, of whom 130 (25%) would probably be interested to participate. The intended number of participants ($n = 60$) falls comfortably within this estimate. The number of BD patients treated in Dimence is about 900, with 675 (75%) meeting the inclusion criteria, of whom 169 (25%) would probably be interested to participate. Again, the intended number of participants ($n = 50$) falls well within this estimate. Approximately 650 BD patient are treated in Altrecht, with 100-150 new patients per year. About 487 (75%) of BD patients would be meeting the inclusion criteria, of whom 122 (25%) would probably be interested. The intended number of participants ($n = 50$) therefore seems feasible. Moreover, we will recruit patients through the patient association Vereniging voor Manisch Depressieven en Betrokkenen (VMDB) and the psychiatry department of the Canisius Wilhelmina

Ziekenhuis (CWZ). Patients whose attending physician is not affiliated with one of the participating centres will be asked permission to inform their attending physician about the patient's participation in the study.

5. TREATMENT OF SUBJECTS

5.1 Investigational treatment

Mindfulness Based Cognitive Therapy (MBCT) + TAU

This intervention will consist of usual care, with MBCT in adjunct. MBCT is a manualised group skills-training program (Segal, Williams, & Teasdale, 2012) designed as a relapse prevention programme for patients with recurrent depression. The training consists of eight weekly sessions of 2.5 hours, plus one day of silent practice. In addition, participants are instructed to practice 45 minutes a day. The program includes both formal and informal meditation exercises. Cognitive techniques that are part of the program include psychoeducation, monitoring and scheduling of activities, identification of negative automatic thoughts and devising a relapse prevention plan. The MBCT intervention offered in the current study will be based on the 8-week MBCT course developed by Segal et al. (2012), but will be adapted to address the needs of BD patients. A few examples of these adaptations are as follows: psychoeducation about manic symptoms in addition to psychoeducation about depression; introducing the 3-minute breathing space earlier in the programme and more often during sessions, especially when strong emotions are present; repeatedly bringing the focus to self-care; and making use of the mindful movement (yoga) exercises more frequently. All group sessions will be conducted at the respective mental health sites, with each group comprising 8 - 12 participants.

Mindfulness teachers

The mindfulness training will be taught by teachers qualifying the advanced criteria of the Association of Mindfulness Based Teachers in the Netherlands and Flanders, which include a) a minimum of 150 hours of education in MBSR/MBCT background and theory, training in teaching formal and informal meditation practices, psycho-education and inquiry, supervision and giving an MBSR or MBCT course including a reflection report; b) relevant professional training; c) minimum of three years of practicing meditation regularly and attending retreats; d) having attended MBSR / MBCT as a participant; e) continued training; and f) giving a minimum of two courses per two year. All teachers will receive additional training in the study protocol at the start of the project. We will organize peer supervision meetings every month during the intervention phase of the trial. Teacher competency will be assessed by the Mindfulness-based Interventions - Teacher Assessment Criteria (MBI: TAC, Crane et al., 2012). Videotapes of a random selection of sessions will be assessed by assessors who are familiar with this mindfulness-based program, are 'proficient' mindfulness teachers (level 5) and have received training in the use of these assessment criteria. An early study of the psychometric properties of the MBI:TAC suggests it has good reliability, face validity and promising evidence of validity (Crane et al., 2013).

Comparator: Treatment as usual (TAU)

Usual care of BD patients typically consists of pharmacotherapy, psycho-education and self-management interventions (usually with a psychiatric nurse). According to the guidelines (Trimbos Instituut, 2015), these interventions will be or will have been offered to patients prior to participation in the current study. It is expected that a large majority of participants receive some form of pharmacotherapy. Because of the clinical representativeness, we will not restrict TAU in any way. So switching, tapering or augmenting of medication might be part of TAU. We will keep a careful record of this in order to examine and control for possible differences between the two groups. However, frequent psychological treatments, i.e. fortnightly or more, such as (group-based) CBT, will be an exclusion criterion for the current RCT because of practical and methodological reasons. For a detailed description of the biological treatment options that are part of TAU, such as several pharmacotherapeutic options, electroconvulsive therapy, and heliotherapy, we refer to the clinical guidelines "Multidisciplinaire Richtlijn Bipolaire Stoornissen (derde, herziene versie)", pp 121-167 (Trimbos Instituut, 2015). Detailed information for each individual pharmacotherapeutic option can be

found on the pharmacotherapeutic compass: <https://www.farmacotherapeutischkompas.nl/> (Zorginstituut Nederland, 2017).

6. METHODS

6.1 Study parameters/endpoints

Outcome measures will be administered at 6 points in time: baseline (T0) and 3, 6, 9, 12 and 15-month follow-up (T1 – T5).

6.1.1 Main study parameter/endpoint

The primary endpoint of the study is severity of depressive symptoms at 3 months follow-up (T1), assessed with the *Inventory of Depressive Symptomatology – Clinician administered* (IDS-C; Akkerhuis, 1997). The IDS-C has good psychometric qualities (Rush, Gullion, Basco, Jarrett, & Trivedi, 1996; Trivedi et al., 2004) and will be administered by trained research assistants.

6.1.2 Secondary study parameters/endpoints

Clinician-administered measures

- *Structured Clinical Interview for DSM-IV-TR Axis I Disorders* (SCID-I; First, Spitzer, Gibbon, & Williams, 1996) or its successor for DSM 5 when available, to assess depressive and manic relapses. The SCID-I will be used to retrospectively assess possible relapses/recurrences in the past 3 months at each time point. The Dutch version of the SCID-I shows good to excellent inter-rater reliability (Lobbestael, Leurgans, & Arntz, 2011).
- *Young Mania Rating Scale* (YMRS; Young, Biggs, Ziegler, & Meyer, 1978), Dutch translation. The YMRS is an 11-item clinician-administered rating scale to assess the severity of (hypo)manic symptoms. It was found to be a reliable, valid, and sensitive rating scale to measure the severity of mania (Young et al., 1978).
- *Functioning Assessment Short Test* (FAST; Rosa et al., 2007), Dutch translation. The FAST is a brief instrument designed to assess the main functioning problems experienced by psychiatric patients, particularly bipolar patients. It comprises 24 items that assess impairment or disability in six specific areas of functioning: autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships, and leisure time. It has been shown to have strong psychometrics properties in terms of high internal consistency, test-retest reliability, and concurrent validity, and its ability to detect differences between euthymic and acute BD patients (Rosa et al., 2007).

Self-report measures

- *Quick Inventory of Depressive Symptomatology – Self Report* (QIDS-SR; Rush et al., 2003). The QIDS-SR is a 16-item self-report version of the IDS-C. The QIDS-SR has good psychometric qualities.
- *Altman self-rating mania scale* (ASRM; Altman, Hedeker, Peterson, & Davis, 1997). The ASRM is a 5-item self-report questionnaire, with each item representing one of the major symptoms of mania, rated in increasing severity from 0 (not present) to 4 (present in severe degree). The ASRM has good psychometric properties.
- *Prospective Life Chart, self-report*, Dutch translation (Kupka, Akkerhuis, Nolen, & Honig, 1997). The Prospective Life Chart documents the course and severity of recurrent affective episodes. The current study will use the Life Chart prospectively in order to gain more fine-grained information about the severity of (hypo)manic or depressive symptoms over time, across the entire study period (15 months). The Life Chart has been shown a valid and reliable instrument to document the severity of affective episodes (Kupka et al., 1997).
- *State/Trait Anxiety Inventory* (STAI; Spielberger, 1983). The STAI is a self-report measure which has been proven reliable and sensitive in the assessment of both state and trait

levels of anxiety. It is a standard international measure in anxiety research and its Dutch translation has been shown valid (Van der Ploeg, 2000).

- *Brooding subscale* of the extended version of the *Ruminative Response Scale* (RRS-EXT; Treynor, Gonzalez, & Nolen-Hoeksema 2003). The authors reported adequate internal consistency ($\alpha = .79$) and test-retest stability ($\alpha = .62$, with a one year time interval) for the brooding subscale, which consists of five items. We select the brooding subscale because over time, brooding, or rumination, has been more strongly related to levels of depression (Treynor et al., 2003).
- *The Comprehensive Inventory of Mindfulness Experience* (CHIME; Bergomi, Tschacher, & Kupper, 2014). The CHIME is a 37-item, self-report questionnaire, divided in eight subscales measuring eight mindfulness aspects, including inner awareness, outer awareness, acting with awareness, acceptance, decentering, openness, relativity, and understanding. The CHIME has shown satisfactory to good change sensitivity, internal consistency, and test-retest reliability (Bergomi et al., 2014; Nila, Holt, Ditzen, & Aguilar-Raab, 2016).
- *Self-Compassion Scale – short form* (SCS-SF; Raes, Pommier, Neff, & Van Gucht, 2011). The present study will use the 12-item Dutch short-form version of the SCS-SF to measure self-compassion. The scale consists of six components, including self-kindness, self-judgment, common humanity, isolation, mindfulness and over-identification. The SCS-SF has good reliability and validity (Raes et al., 2011).
- *Mental Health Continuum – short form* (MHC-SF; Lamers, Westerhof, Bohlmeijer, ten Klooster, & Keyes, 2011). Lamers, 2011). The MHC-SF is a 14-item self-report questionnaire that assesses emotional, psychological and social well-being. It has adequate psychometric qualities in terms of good internal consistency, (moderate) test-retest reliability, and good divergent and convergent validity.
- *Responses to Positive Affect- Dutch Version* (RPA-NL; Feldman, Joormann, & Johnson, 2008). The RPA is a 17-item questionnaire measuring self-reported levels of dampening and rumination in response to positive affect. The RPA-NL shows a satisfactory internal consistency (Raes, Daems, Feldman, Johnson, & van Gucht, 2009).
- *Childhood Trauma Questionnaire* (CTQ; Bernstein et al., 2003). This questionnaire with 28 items assesses five domains of abuse and traumatic experiences during childhood (physical abuse, emotional abuse, sexual abuse, physical neglect and emotional neglect). The CTQ shows good criterion-related validity (Bernstein et al., 2003).
- *Treatment Credibility Questionnaire* (TCQ; Borkovec and Nau, 1972, adapted version by Addis et al. (2004), with one additional item from the Credibility Expectancy Questionnaire (Deville and Borkovec, 2000). The TCQ that will be used in this study consists of 7 items that focus on credibility and expectancy of treatment. The TCQ shows good reliability (Borkovec & Nau, 1972).

Economic evaluation

- *EQ-5D-5L* (EuroQol Group, 2009). The EQ-5D-5L measures the quality of life by means of five dimensions, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. In addition it contains a visual analogue scale to determine Quality Adjusted Life Years (QALYs). The EQ-5D-5L shows to be a valid instrument (Janssen et al., 2013).
- *Trimbos/iMTA questionnaire for costs associated with psychiatric illness* (TiC-P; Hakkaart, Van Straten, Donker, & Tiemens, 2002). The TiC-P is a 38-item, self-report inventory measuring resource use, such as use of care, medication and illness related to work. It measures both direct costs, i.e. care consumption of people suffering from psychiatric illness, and indirect costs, i.e. costs associated with production loss. The TiC-P shows good reliability (Bouwman et al., 2013).

Cognitive measures

- *Stroop Task* (Stroop, 1935). Subjects are instructed to name the colour of the printed text on the card, not the colour of the word that is written. This task measures interference in attention.
- *Emotional Stroop Task* (Williams et al., 1996). This is an adapted version of the original colour Stroop task. Cards are filled with neutral stimuli (XXXX), negative words (e.g. 'sadness') and positive words (e.g. 'happy'), reaction time per card is measured.
- *Breathing Focus Task* (Hayes, Hirsch, Krebs, & Matthews, 2010). This task measures state rumination. Subjects are instructed to concentrate on their breathing for 5 minutes. The computer signals at random points in time, on which the subjects are instructed to tell the research assistant whether they focused on breathing or not. Furthermore, they are asked to tell whether their thoughts were positive, negative or neutral at the moment of the signal. After this, the subjective experience of the breathing task is assessed shortly (Hayes et al., 2010).
- *Self Referent Encoding Task* (Joormann et al., 2006). This task measures memory bias for emotional information. 24 words are presented on a computer screen (12 negative, 12 positive). Subjects are asked to rate whether or not the word describes them. After this, subjects are distracted for 3 minutes with a trail making task. The trail making task is followed by a free recall phase, in which they have to 3 minutes to write down as much words as they remember.
- *Pavlovian to instrumental transfer task* (Geurts et al., 2013; Huys et al., 2011). This task assesses positive and negative affective bias on goal-oriented, instrumental behaviour. At first, subjects are trained to react to instrumental stimuli with which they can earn small amounts of money (5 cents). Next, we show subjects neutral pictures that we then associate with monetary wins and losses. By this latter classical (or Pavlovian) conditioning procedure these neutral pictures acquire an affective valence and become conditioned stimuli (CS) with appetitive and aversive valence respectively. Finally we ask subjects to react to the instrumental stimuli again, but now also show them the CS on the background. The CS-dependent change in instrumental behaviour then is a measure of Pavlovian affective bias.

6.1.3 Other study parameters**Baseline parameters**

- Age
- Gender
- Ethnicity
- Level of education
- Marital status
- Employment status
- BD type (bipolar I or II)
- Age at onset
- Time since last episode of depression or (hypo)mania
- Number of previous episodes (manic and depressed, reported separately)
- Types and dose of medication being used
- Previous treatment with CBT and/or IP(SR)T (yes/no)
- Suicide attempt (lifetime; yes/no)
- Number of previous hospitalizations due to either manic or depressive episode
- Comorbid psychiatric diagnoses

Measures for adherence

Adherence to mindfulness practice and medication use will be assessed using prospective daily registration on the Life Chart.

6.2 Randomisation, blinding and treatment allocation

Randomisation will be performed within the datamanagement system Castor EDC. This will consist of stratified, variable block randomisation with the following stratification variables: Location (site); Gender; Depression (current versus remitted); BD type (I versus II); and number of previous episodes (<12 versus \geq 12). This system also allows for blinded (concealed) allocation such that research assistants on site can be kept blind to condition. MBCT teachers on site will be notified of the allocation to MBCT, allowing them to invite the patient to participate and coordinate further arrangements. As only assessors will be blind to treatment allocation due to the nature of the intervention, no indications for breaking the randomization code are pre-specified. In case of adverse reactions, patients are encouraged to discuss this with their MBCT teacher and responsible clinician.

6.3 Study procedures

Figure 2 provides a flowchart of the study procedures from referral to the final assessment. Patients will be recruited from several specialized, outpatient clinics in the Netherlands; ProPersona, Dimence, and Altrecht, and through the patient association; Vereniging voor Manisch Depressieven en Betrokkenen (VMDB). They will receive a letter from their attending clinicians, informing them about the study with an included information leaflet. This way, patients are free to choose whether to participate in the study, without feeling obligated to their clinicians when asked face-to-face. Interested patients are, after verbal consent is obtained, invited for a screening by telephone to assess global eligibility. Eligible patients will receive more information and a detailed description of the study procedure. After one week, patients will be contacted by telephone to assess whether they are still interested in participation. Patients who are still interested to participate will be invited for intake with a research assistant, where informed consent is obtained. They are thoroughly screened for in- and exclusion criteria with use of the SCID-I and YMRS. Altogether, this will take about 1.5 hours. When patients are still eligible and interested, they are invited for baseline assessment (T0), which consists of several clinician administered measures (IDS-C and FAST), which will take about 20 minutes. After a short pause, participants are asked to conduct five short computer tasks (Stroop, Emotional Stroop Task, Breathing Focus Task, Self Referent Encoding Task, and Attentional Control Scale). This will take about one hour. However, it is possible for participants to do only the first part of these measures, so they can skip the computer tasks if necessary. Furthermore, participants are asked to fill in several self-report questionnaires at home (STAI, brooding subscale of RRS, CHIME, SCS-SF, MHC-SF, RPA, CTQ, TiC-P, and EQ-5D-5L). After baseline assessment, patients are randomised to one of two groups: TAU or MBCT + TAU. Participants in the intervention group (MBCT + TAU) will receive an eight-week MBCT training, during which they daily have to document mood fluctuations, changes in medication, and major life events in the Life Chart. Furthermore, participants are asked to document adherence and adverse events in a personal diary. Participants in the comparator group (TAU) will receive their treatment as usual, while they daily document in the Life Chart as well. After three months (T1), participants are invited for follow-up assessment, during which the clinician administered questionnaires (YMRS, IDS-C, FAST, SCID-I) and computer tasks will be conducted again. Furthermore, patients are asked to fill out the online self-report questionnaires a second time. More follow-up assessments will take place after 6 months (T2), 9 months (T3), 12 months (T4), and 15 months (T5). During T2, T3, and T4 assessments patients are approached by telephone to assess depressive, manic, and anxiety symptoms, and global functioning over the past three months (IDS-C, YMRS, FAST, and SCID-I to assess manic and depressive symptoms retrospectively). Furthermore, during these assessments patients are asked to fill out the online questionnaires as well. The assessment at 15 months follow-up (T5), will consist of the clinician administered measurements (IDS-C, YMRS, FAST) and the online self-report measurements (STAI, brooding subscale of RRS, CHIME, SCS-SF, MHC-SF, RPA, TiC-P, EQ-5D-5L). Table 1 provides an overview of the assessments. After 15 months of follow-up the study will end, after which participants in the comparator group will be given the opportunity to participate in a MBCT-course as well.

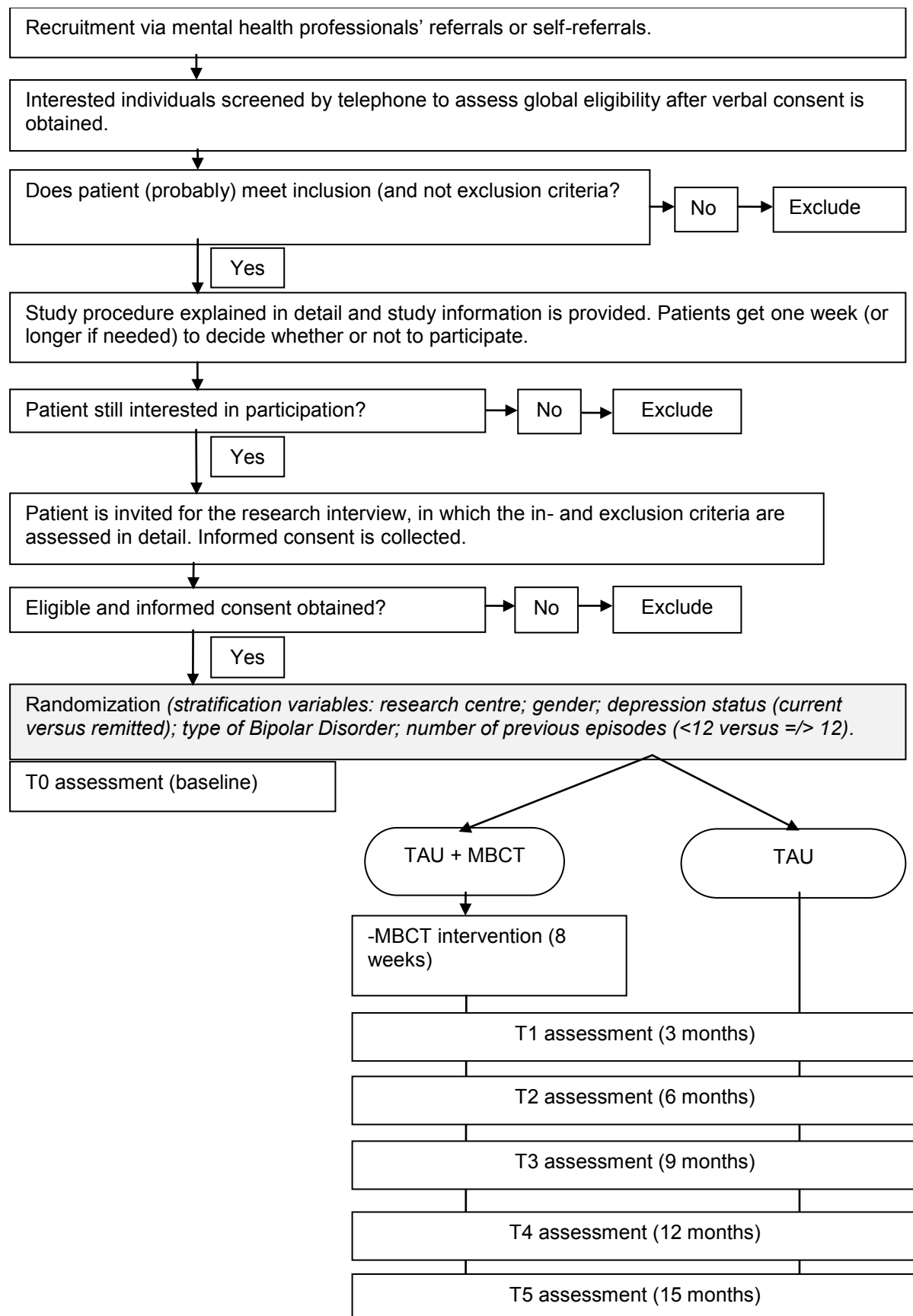


Figure 2. Flowchart of the study procedures

| Table 1. Overview assessments | | | | | | | |
|--|----|------|----|----|----|----|----|
| Interviews: | T0 | MBCT | T1 | T2 | T3 | T4 | T5 |
| SCID-1 (Full) | * | | | | | | |
| SCID-1 (depression / mania) | | | * | * | * | * | * |
| IDS-C | * | | * | * | * | * | * |
| YMRS | * | | * | * | * | * | * |
| FAST | * | | * | * | * | * | * |
| Self-report questionnaires: | T0 | MBCT | T1 | T2 | T3 | T4 | T5 |
| CTQ | * | | | | | | |
| TCQ | * | | | | | | |
| STAI | * | | * | * | * | * | * |
| MHC-SF | * | | * | * | * | * | * |
| RRS-Br | * | * | * | * | * | * | * |
| SCS-SF | * | * | * | * | * | * | * |
| Q-IDS - SR | | * | | | | | |
| ASRM | | * | | | | | |
| CHIME | * | * | * | * | * | * | * |
| RPA-NL | * | * | * | * | * | * | * |
| EQ-5D-5L | * | | * | * | * | * | * |
| TiC-P | * | | * | * | * | * | * |
| Life CHART (incl medication adherence) | * | | | | | | |
| Mfn adherence + Adverse events | * | | | | | | |
| Cognitive measures: | T0 | MBCT | T1 | T2 | T3 | T4 | T5 |
| <ul style="list-style-type: none"> self-referent encoding task and trail making task (distraction) breathing focus task emotional stroop task colour stroop task Pavlovian instrumental transfer Visual-analogue scale (mood rating; after breathing focus task) | * | | * | | | | |

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.

6.5 Replacement of individual subjects after withdrawal

After withdrawal, individual participants will not be replaced.

6.6 Follow-up of subjects withdrawn from treatment

Dropouts will be contacted by phone and asked to fill out the remaining questionnaires to supply the researchers with a post measurement and follow-up. Dropouts will be reminded that they are free to refuse.

6.7 Premature termination of the study

There are no criteria for premature termination of the study.

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 mindfulness training. 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;
- 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.

We expect the number of (S)AE's during the intervention to be minimal, as the intervention is non-invasive. Adverse events or reactions that may occur during the study will be examined at each assessment by explicitly asking if people may have noticed unpleasant effects that appear to be causally related to the MBCT training. Reported adverse events related to meditation could be relaxation-induced anxiety and panic, paradoxical increases in tension, impaired reality testing, confusion, disorientation, dissociation, feeling addicted to meditation and grandiosity (Dobkin, Irving, & Amar, 2012; Shapiro, 1992). Furthermore, we will be watchful for posttraumatic stress symptoms that might arise as a result of the MBCT training, such as re-experiencing. The principal investigators will check the questionnaires on signs of (S)AE's as well. All adverse events reported spontaneously by the participant or observed by the principal investigator or his/her staff will be recorded and reported 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.

The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events, except for the following SAEs:

- An elective hospital admission.
- Relapse into a (hypo)manic or depressive episode, which is an expected event in this specific population, since 60% of BD patients relapse within two years (Miklowitz et al., 2009; Oud et al., 2016). The study of Perich et al. (2013), who conducted a RCT of MBCT for BD, found that 59% of participants in the MBCT condition and 48% in the TAU condition reported a (hypo)manic episode, while 59% in the MBCT condition and 68% in TAU reported a depressive episode over a 12 month follow-up period. In that study, the median time to

(hypo)mania relapse was 130 days for MBCT and 143 for TAU. Median time to depressive relapse was 53 days for MBCT and 46 days for TAU.

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

It is estimated that the risk of harm is not increased when participating in this study. With regard to NFU-classification the risk is negligible. Therefore a DSMB is not needed for this study.

8. STATISTICAL ANALYSIS

Multilevel analysis will be used to account for the cluster-randomized design and therefore the hierarchical structure of the data, with outcome variables at the pre- and postmeasurements at the lowest level, nested within individuals, nested within treatment groups (for the intervention condition), and nested within condition (MBCT + TAU vs TAU). Any baseline parameters that may be inadvertently unequally distributed between the conditions are included as covariates. Multilevel logistic regression will be performed for dichotomous outcomes and multilevel regression analysis for normally distributed continuous outcomes. The clinical outcome data will be analysed and reported according to the CONSORT guidelines, i.e. on intention-to-treat basis. Given the anticipated drop-out, we will also analyze and report on the per-protocol group, and discuss possible differences between the two analysis sets.

Additional analyses will be performed within subgroups with and without a current depressive episode. To account for possible differences between therapy groups, we will add a random group effect. Sensitivity analyses will be conducted with different scenarios of imputed data sets, in case of missing data, to examine the influence of missing data on the pattern of outcomes.

8.1 Primary study parameter(s)

The primary analysis is aimed at comparing the effects of MBCT + TAU on depressive symptoms. The primary outcome parameter will be the total scores on the IDS-C. In order to investigate consolidation of treatment effect, we will follow-up participants for another 15 months. We will use a multilevel regression model for repeated measures to analyse differences between baseline, 3 months, 6 months, 9 months, 12 months, and 15 months follow-up measurements.

8.2 Secondary study parameter(s)

The secondary analysis is aimed at comparing the effects of MBCT + TAU on (hypo)manic and anxiety symptoms, quality of life, rumination, mindfulness and self-compassion skills. The secondary outcome parameters will be the total scores on the YMRS, FAST, STAI, RPA, MHC-SF, SCS-SF, CHIME, and the brooding subscale of the RRS. In order to investigate consolidation of treatment effect, we will follow-up participants for another 15 months. We will use a multilevel regression model for repeated measures to analyse differences between baseline, 3 months, 6 months, 9 months, 12 months, and 15 months follow-up measurements.

Furthermore, cost-effectiveness evaluation is carried out from a societal perspective considering direct as well as indirect costs. Data on resource use (health care uptake) and productivity losses will be collected with the Tic-P. Total costs for each patient will be obtained by multiplying these data with standard costs, based on the Dutch guideline for costing research (Hakkaart et al., 2002). Overall mean and median costs will be compared across the conditions and where relevant, differences will be calculated inclusive of 95% confidence intervals.

Cost-effectiveness and cost-utility analysis

For these analyses we will use SPSS statistical software and Excel (for the Bootstraps). Respondents for whom at least 75% of the data per measurement instrument are available will be included in the analysis. Missing cost and outcome data will be imputed using multiple imputation (MI) methods and last-observation carried forward (LOCF), for intention to treat (ITT) analysis following Dutch guidelines (Zorginstituut Nederland 2016).

A baseline analysis will be performed to examine the comparability of groups at baseline for both costs and outcomes. If necessary methods will be applied to control for differences in baseline (Manca, Hawkins, & Sculpher, 2005). To investigate whether data are normally distributed a Kolmogorov-Smirnov test will be performed. Despite the usual skewness in the distribution of costs, the arithmetic means will be generally considered the most appropriate measures to describe cost data (Barber & Thompson, 2000; Ramsey et al., 2005). Therefore arithmetic means (and standard deviations) will be presented. In case of skewness of the cost data, non-parametric bootstrapping will be used to test for statistical differences in costs between the intervention and control group. Non-parametric bootstrapping is a method based on random sampling with replacement based on individual data of the participants (A. H. Briggs, Wonderling, & Mooney, 1997). The bootstrap replications will be used to calculate 95% confidence intervals around the costs (95% CI), based on the 2.5th and 97.5th percentiles. If cost data are distributed normally, t-tests will be used.

The Incremental cost-effectiveness ratio (ICER) will be determined on the basis of incremental costs and effects of MBCT compared to TAU. The cost-effectiveness ratio will be stated in terms of costs per outcome rate (IDS-C), the cost-utility ratio will focus on the cost per QALY gained.

The ICER will be calculated as follows. $ICER = (C_i - C_c) / (E_i - E_c)$, where C_i is the total cost of the MCBT group, C_c is the total cost of the TAU group, E_i is the effect at 12 months follow-up for the MCBT group and E_c is the effect at 12 months follow-up for the TAU group.

Sensitivity analysis

Stochastic uncertainty of the ICER will be handled using 2,500 non-parametric bootstraps and by plotting the simulated ICERs on the ICER plane. Bootstrap simulations will be conducted in order to quantify the uncertainty around the ICER, yielding information about the joint distribution of cost and effect differences. The bootstrapped cost-effectiveness ratios will be subsequently plotted in a cost-effectiveness plane, in which the vertical line reflects the difference in costs and the horizontal line reflects the difference in effectiveness. The choice of treatment depends on the maximum amount of money that society is prepared to pay for a gain in effectiveness, which is called the willingness-to-pay (WTP) ceiling ratio. For decision-making purposes, the ICER acceptability curve will be plotted for various WTP ceilings for making judgments whether discontinuation offers good value for money relative to routine medical care. Deterministic one-way sensitivity analyses directed at uncertainty in the main effects and main cost drivers will be performed to assess the robustness of our findings. Additionally, a multi-way sensitivity (scenario-) analyses will be performed. In the sensitivity analysis uncertain factors of assumptions in the base case analysis will be recalculated in order to assess whether the assumptions have influenced the incremental cost-effectiveness ratio (ICER), for example by varying cost-prices and volumes between minimum and maximum (A. H. Briggs et al., 1997).

Budget-impact analysis

The budget impact analysis (BIA) will be conducted as outlined by the ISPOR Task Group (i.e. Mauskopf et al., 2007; Sullivan et al., 2014) to assess how health care budgets change when MCBT is offered over a range of implementation levels. The BIA will be conducted from various perspectives: (1) the societal perspective, i.e. including productivity losses; (2) the perspective of the public purse (in Dutch: netto Budgettaire Kader Zorg); and (3) the perspective of the health care insurer. In each perspective the following scenarios will be assessed: a scenario in which the intervention is offered to 40%, 60% and 80% of the target group and an extreme scenario in which 100% of the target group will be receiving the MCBT intervention. These scenarios will be compared with a base-case scenario

where 0% of the target group is offered MCBT (reflecting treatment as usual (TAU)). The BIA will be based on a health-economic simulation excel model, based on modelling techniques outlined in Briggs, Claxton, & Sculpher (2006) and following ISPOR modeling guidelines (Caro, Briggs, Siebert, & Kuntz, 2012). The BIA will be conducted according Dutch guidelines (Zorginstituut Nederland, 2016), taking into account the complexity and dynamics of clinical practice and specific characteristics of the Dutch health care system. Cost data will be extracted from the trial and are based on the Dutch manual of costing (Tan, Bouwmans-Frijters, & Hakkaart-van Roijen, 2012). Costs will be modelled out over the short term (12 months) and longer-term (36 months) as required by the Dutch guideline for health-economic evaluation (Zorginstituut Nederland, 2016). Long-term costs will be discounted according to the Dutch guidelines. The impact of MBCT on budgets is furthermore depending on (changes in) the prevalence of BD. Sensitivity analyses on the main input parameters will be conducted to assess the robustness of the outcomes.

8.3 Other study parameters

The potential effects of CTEs on MBCT treatment effect will be assessed by moderation analysis. Furthermore, we will assess whether MBCT induces change in the acquired cognitive-affective bias measures. In addition, mediation analysis will be used to study the effect of MBCT on cognitive control measures (cognitive-affective bias, rumination) in the MBCT + TAU versus the TAU group. Mediation and moderation analyses will be carried out using the PROCESS tool (Hayes, 2012). With PROCESS, estimates of mediation/moderation effects were computed using bootstrapping methods.

9. ETHICAL CONSIDERATIONS

9.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (6th edition, 2008) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

9.2 Recruitment and consent

A description of recruitment and informed consent procedures are appointed in the study procedures on page 15 of this study protocol.

9.3 Benefits and risks assessment, group relatedness

This study involves capacitated adults and examines a therapeutic intervention that already is adopted as a treatment option in the 'Multidisciplinaire Richtlijn Bipolaire Stoornissen' (Trimbos, 2015). Participation is free of charge. We believe that the risks of participation are negligible. However, because of this vulnerable patient group, we will be extra watchful for adverse reactions to the MBCT training, such as slight feelings of disorientation, confusion, dissociation, impaired reality testing, and grandiosity. If patients show a clear increase in symptoms, additional guidance will be offered. Participants are encouraged to respect their boundaries (both physical and psychological) and are always free to suspend or adapt the practice as needed. The burden associated with participation in MBCT is relatively high: consisting of 8 weekly group sessions of 2,5 hours and one silent day (6 hours), and home practice of about 45 minutes a day. Participation includes 6 research assessments consisting of interviews and questionnaires about psychological symptoms, functioning, and quality of life. Although the effort requested from patients is high, we expect that practicing mindfulness will be associated with enduring changes in patients' coping strategies in daily life, and as a result, can increase participants' autonomy and self-efficacy.

9.4 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.

9.5 Incentives (only applicable to the PIT task)

The Pavlovian instrumental transfer task (see section 6.1.2.) relies on reinforcement learning and previous studies with these tasks have used monetary incentives as reinforcement (Geurts et al. 2014, Huys et al 2011, Huys et al 2016). We will tell participants they will receive monetary reinforcement calculated based on their performance after the second time they participate in the task. We will inform them that the amount of money earned generally will amount to 5-6 euro. All participants involved will receive a gift-card of 5 euro with (depending on their performance) another 10-90 cents of money.

10. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

10.1 Handling and storage of data and documents

All data will securely be stored for 15 years after the study, until November 2036. All data will be kept and stored according to the Personal Data Protection Act (in Dutch: De Wet Bescherming Persoonsgegevens). After signing up and randomisation, participants will be linked to a unique number. Data which leads to the contact details (such as name, telephone number, and e-mail address) of the participant will be stored in a separate dataset from the dataset in which all other research data will be stored during the study. Only via the unique number, contact details can be linked to research data. Access to the code that couples the study data to the participants contact details is limited to the principal investigators and research assistant(s).

10.2 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. Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

10.3 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.

10.4 Temporary halt and (prematurely) end of study report

The investigator 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 participant's follow-up T5 questionnaires are finished. In case the study is ended prematurely, the investigator 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.

10.5 Public disclosure and publication policy

This study follows the basic principles of the CCMO's position on the disclosure/publication of research results obtained from studies involving human participants. Results of scientific research involving human participants will be disclosed unreservedly.

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