Research protocol

B-Positive: Enhancing well-being in patients with bipolar disorder

Effectiveness of a positive psychology intervention for the treatment of euthymic patients with bipolar disorder to improve well-being: a randomized controlled trial

Jannis Kraiss, M.Sc.[1]
Dr. Peter ten Klooster[1]
Dr. Melissa Chrispijn[2]
Drs. Anja Stevens[2]
Erica Neutel[3]
Prof. dr. Ralph Kupka[4]
Prof. dr. Ernst T. Bohlmeijer[1]

[1]University of Twente, Faculty of Behavioural Sciences, Department of Psychology, Health and Technology, Enschede, the Netherlands

[2]Dimence Group, Specialized Center for Bipolar Disorders, Deventer, the Netherlands

[3]Dutch patient federation for manic depression, Amersfoort, the Netherlands

[4]VU University Medical Center, Amsterdam, the Netherlands

PROTOCOL TITLE B-Positive: Enhancing full recovery in patients with bipolar disorder

Protocol ID	NL62997.044.17
Short title	B-Positive
EudraCT number	-
Version	7.0
Date	23-09-2019
Coordinating investigator/project leader	Prof. dr. Ernst Bohlmeijer University of Twente Psychology, Health and Technology POBox 217 7500AE Enschede
Principal investigator(s) (in Dutch: hoofdonderzoeker/ uitvoerder)	Jannis Kraiss, M.Sc. University of Twente Psychology, Health and Technology POBox 217 7500AE Enschede
Sponsor (in Dutch: verrichter/opdrachtgever)	Prof. dr. Ernst Bohlmeijer University of Twente Psychology, Health and Technology POBox 217 7500AE Enschede
Subsidising party	ZonMW, Doelmatigheidsonderzoek Project number 843001803
Independent expert (s)	Prof. Anne E.M. Speckens Professor of psychiatry Radboud University Medical Center Radboud University Nijmegen Postbus 9010 6500 GL NIJMEGEN
Pharmacy	Not applicapble

PROTOCOL SIGNATURE SHEET

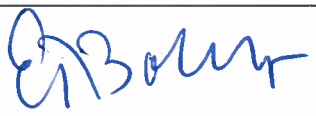
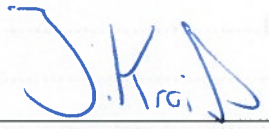
Name	Signature	Date
Sponsor or legal representative: *Prof. dr. Ernst Bohlmeijer* *Professor Mental Health Promotion*		23-09-2019
Principal Investigator: *Jannis Kraiss, M.Sc.* *Ph.D. Candidate*		23-09-2019

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AE	**Adverse Event**
AR	**Adverse Reaction**
ASRM	**Altman Self-Rating Mania Scale**
BD	**Bipolar Disorder**
BSI	**Brief Symptom Inventory**
CAU	**Care as usual**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
DSMB	**Data Safety Monitoring Board**
IC	**Informed Consent**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
MHC-SF	**Mental Health Continuum – Short Form**
NTR	**Netherlands Trial Register**
PANAS	**Positive and Negative Affect Schedule**
QIDS-SR	**Quick Inventory of Depressive Symptomatology – Self-Report**
QPR	**Questionnaire about the Process of Recovery**
RPA	**Responses to Positive Affect Questionnaire**
(S)AE	**(Serious) Adverse Event**
SCS-SF	**Self-compassion Scale – Short Form**
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.**
SRPQ	**Social Role Participation Questionnaire**
STAI	**State-Trait Anxiety Inventory**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
UT	**University of Twente**
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 (BD) is characterized by recurrent manic or (hypo)manic phases, alternating with (euthymic) states in which patients are relatively symptom free. The prevalence of BD is estimated at 1,3% in the Netherlands. Current treatment for BD in the euthymic phase often focuses on symptomatic and functional recovery, but residual subthreshold depressive symptoms often remain between episodes and form an important risk factor for recurrence. In order to reach full personal recovery, it is important to strive for complete mental health, which encompasses both the absence of mental illness and the presence of well-being. One prominent field focussing on the improvement of well-being, is positive psychology. *This is your life* is a generic self-help positive psychology intervention developed at the University of Twente, which aims to increase well-being. The current study aims to assess the effectiveness of *This is your life* adjusted for people with bipolar disorder in the euthymic phase.

Objective: The primary objective of the study is to assess whether a well-being intervention ('This is your life') offered to bipolar disorder (BD) patients in remission in addition to usual care (CAU) is more (cost-)effective than CAU only.

Study design: This study concerns a pragmatic randomized multicenter trial. Measurements take place at baseline, post-intervention and follow-up 6 and 12 months from baseline.

Study population: Patients with Bipolar I or II in the euthymic phase. Inclusion criteria are 1) 4 or more supportive sessions in the last year, and 2) residual depressive symptoms. Patients are excluded when they 3) suffer from an acute episode or 4) have current addiction problems, and/ or 5) have optimal levels of well-being.

Intervention (if applicable): We aim to adapt the multi-component positive psychology intervention *This is your life* as a group intervention for BD. The 8-week intervention focuses on six components, including personal strengths, resilience, post-traumatic growth, and positive relationships. The intervention consists of 8 meetings of 2 hours and home exercises.

Main study parameters/endpoints: *Well-being* (primary outcome) is measured with the Mental Health Continuum – Short Form. Secondary outcomes include *personal recovery* (measured with the Questionnaire about the Process of Recovery), *relapse* (semi-structured telephone interviews), *social role participation* (Social Role participation Questionnaire), *depressive symptoms* (Quick - Inventory of Depressive Symptomatology), manic symptoms (Altman Self-Rating Mania Scale), *anxiety symptoms* (Hospital Anxiety and Depression Scale), *dampening* (Responses to Positive Affect Questionnaire), *positive emotions* (Positive and Negative Affect Schedule), *self-compassion* (Self-compassion Scale – Short Form) and

positive relations (Psychological Well-being Scale). Economic evaluations are performed using the EuroQol Questionnaire and the Trimobs and iMTA questionnaire on costs associated with psychiatric illness.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The study is not expected to carry substantial risk or burden to the participants. The Living to the Full intervention has been studied several times in non-clinical populations and no negative effects have been reported. Participants in both conditions fill in four questionnaires, which will take approximately 45 minutes. Possible benefits for participants include improvement in well-being and psychological symptoms.

1. INTRODUCTION AND RATIONALE

Bipolar disorder (BD) is a severe mood disorder and is characterized by recurrent manic or (hypo)manic phases and intertwining episodes of depression, alternating with (euthymic) states in which patients are relatively symptom free (Grande, Berk, Birmaher, & Vieta, 2015; Kupka, Knoppert, & Nolen, 2008). Generally, it can be distinguished between bipolar I and bipolar II disorder. The difference is that patients with bipolar II disorder never experienced a full manic episode, only less severe hypomanic episodes (Berk & Dodd, 2005). Prevalence estimates from the Netherlands reveal a lifetime prevalence of 1.3% and 12-month prevalence of 0.8% for BD (de Graaf, ten Have, & van Dorsselaer, 2010). The economic burden in 2009 was estimated at 151 billion dollars per year in the United States (Dilsaver, 2011). Suffering from BD is associated with decreased quality of life, functional impairments among several domains, including work, social life, household, and other activities and high caregiver burden (Miller, Dell'Osso, & Ketter, 2014; Pompili et al., 2014).

According to the Dutch guidelines for BD (Multidisciplinaire Richtlijn Bipolaire Stoornissen, MDR-BS; Kupka et al., 2015) treatment is often long-lasting and can shift in terms of intensity, depending on the phase of illness. The course of illness differs individually in terms of duration as well as frequency and pattern of episodes. Another important factor is the extent to which patients recover in the euthymic phase.

Current treatment for BD in the euthymic phase generally focuses on symptomatic and functional recovery. However, often residual subthreshold depressive symptoms remain in phases between episodes (Fagiolini et al., 2005; Judd, Schettler, Akiskal, & et al., 2008; Kaya, Aydemir, & Selcuki, 2007), forming an important risk factor for recurrence (Fava, Ruini, & Belaise, 2007). Therefore, promoting complete mental health recovery in the euthymic phase has important potential for preventing recurrence of depressive or (hypo)manic episodes.

Besides symptomatic and functional recovery, another important component of recovery is personal recovery (Fava et al., 2007; Jones, Mulligan, Higginson, Dunn, & Morrison, 2013; Slade, 2010), which can be defined as the ability to live a meaningful, hopeful and contributing life, even in the presence of mental illness (Anthony, 1993). Leamy, Bird, Le Boutillier, Williams, and Slade (2011) created a conceptual framework for personal recovery in mental health, containing five processes of personal recovery: connectedness, hope and optimism about the future, identity, meaning in life and empowerment (giving the acronym CHIME) as important factors for personal recovery (Leamy et al., 2011). According to Keyes (2002) complete mental health recovery also encompasses the presence of well-being. Well-being, in turn, includes subjective well-being (i.e. positive affect and life-satisfaction),

psychological well-being (i.e. meaning, goals in life, mastery, positive relationships) and social well-being (i.e. contributing to society).

One prominent field of psychology focussing on the improvement of well-being is positive psychology (Seligman & Csikszentmihalyi, 2014). The effect of positive psychology interventions has been shown in several meta-analyses for both general and clinical populations (Bolier et al., 2013; Sin & Lyubomirsky, 2009) and also specifically for psychiatric and somatic disorders other than BD (Chakhssi, Kraiss, Spijkerman, & Bohlmeijer, 2017, in review). The meta-analyses revealed small to moderate but significant effects of positive psychology interventions on outcomes of well-being, depressive symptoms and anxiety. Follow-up effects show similar effect sizes, indicating stability of the effects. Positive psychology interventions target the aspects included in the CHIME framework of personal recovery in mental health (Leamy et al., 2011). Additionally, in a recent review on positive psychology and recovery, Slade (2010) underlines the importance of positive psychology to achieve personal recovery exactly for this reason.

For several reasons it is thus important to shift the focus away from functional and symptomatic recovery and towards improvement of well-being and personal recovery. First of all, research indicates that improvement of mental health and well-being buffers against the recurrence of mental illness (Keyes, Dhingra, & Simoes, 2010; Lamers, Westerhof, Glas, & Bohlmeijer, 2015; Trompetter, de Kleine, & Bohlmeijer, 2017). Secondly, current approaches often neglect the desire of patients with BD to improve personal recovery and well-being (Jones et al., 2013) and patients with serious mental illness, such as BD, express dissatisfaction with primary targets of treatment and instead argue for the importance of personal recovery outcomes (Jones, Higginson, Murray, & Morrison, 2010; Mead & Copeland, 2000). Thirdly, focussing on personal recovery and well-being can offer alternative routes to reduce subthreshold depressive symptoms.

To our knowledge, only a few small studies have researched the effect of interventions focussing on well-being or personal recovery for patients with BD in the euthymic phase. Deckersbach et al. (2012) report on a small uncontrolled clinical trial with 12 euthymic participants diagnosed with BD using Mindfulness-Based Cognitive Therapy. Analyses from pre- to follow-up indicated significant improvements in outcomes of depressive symptoms (Cohen's *d* ES = .75), positive affect (ES = .41) and aspects of psychological well-being (ES range from .62 for self-acceptance to .98 for environmental mastery). Eisner et al. (2017) conducted a proof-of-concept pilot study without control group with 37 participants with BD who did not have a current major depressive, manic or mixed episode. Significant improvements were obtained from baseline to post-treatment in psychological well-being (ES = 1.02), emotion regulation (ES = 1.34) and emotion reactivity (ES = .97). Finally, Jones et al. (2015) investigated the effectiveness of recovery-focused Cognitive Behavioral Therapy in a

randomized controlled pilot trial (*n* = 67) with care as usual as control. Personal recovery significantly improved from baseline to 6 and 12 months follow-up (ES = .62). Although no significant effects were obtained in average mood symptoms, patients in the recovery-focused CBT group showed significant longer time to relapse into depression or mania over a 15-month period compared to patients only receiving CAU. Specifically, 20 CAU patients versus 12 recovery-focused CBT patients relapsed and median survival times were longer for CBT (56 weeks) compared to CAU (18 weeks).

In summary, existing intervention studies for well-being or personal recovery of patients with BD are scarce and have used underpowered and/or weak methodological designs. Although the general outcomes for psychological well-being and personal recovery were promising in all three studies, and moderate to large effect sizes were reported for well-being or personal recovery (Cohen's *d* ranging from .62 – 1.02), the effectiveness of positive psychology interventions in BD still needs to be established in an adequately powered, randomized controlled trial.

With the aim to improve well-being among BD patients in the euthymic phase and to enhance personal recovery, we intend to adapt the multi-component positive psychology intervention *This is your life* as group intervention (Schotanus-Dijkstra, Drossaert, Pieterse, Walburg, & Bohlmeijer, 2015). *This is your life* was developed at the University of Twente and is based on empirically validated theories within positive psychology, including Seligman's well-being theory (PERMA model) (Seligman, 2011) and Ryff's Theory of psychological well-being (Ryff, 1989). *This is your life* focuses on six components in positive psychology: (1) positive emotions, (2) discovering and using personal strengths, (3) optimism and hope, (4) self-compassion, (5) resilience and post-traumatic growth and (6) positive relationships. In a recent randomized controlled trial the intervention as guided self-help with email support was highly effective in improving well-being and reducing psychopathology in people with suboptimal levels of mental health (Schotanus-Dijkstra et al., 2015).

The present study aims to contribute to the existing literature by investigating the effectiveness of a positive psychology intervention focussing on the improvement of well-being and enhancement of personal recovery. This study is the first to adapt, evaluate and implement an intervention for personal recovery for patients with bipolar disorder in the Netherlands and uses a more adequately designed and powered than studies before. Moreover, it is the first study ever that specifically evaluates a positive psychology intervention for patients with BD in the euthymic phase.

2. OBJECTIVES

Primary objective

The primary objective of this study is to evaluate whether the eight-week multicomponent well-being intervention *This is your life* as an adjunct to usual care (CAU) offered to BD patients in the euthymic phase, is effective in the short and long term in improving well-being.

Secondary objective(s)

Further, the study has the following secondary objectives:

1. To study whether the intervention *This is your life* in addition to CAU is more effective in the short and long term in improving outcomes of personal recovery, social role participation, and symptoms of depression, anxiety and mania than CAU only.
2. To find out whether *This is your life* is more effective in reducing relapses into depressive, (hypo)manic or mixed episodes in euthymic patients with BD in the long term than CAU only.
3. To explore possible working mechanisms for intervention effects of *This is your Life*, including positive emotions, positive emotion regulation, self-compassion and positive relations.
4. To evaluate the cost-effectiveness of the intervention *This is your life* in addition to CAU for the treatment of euthymic patients with BD compared to CAU only.

3. STUDY DESIGN

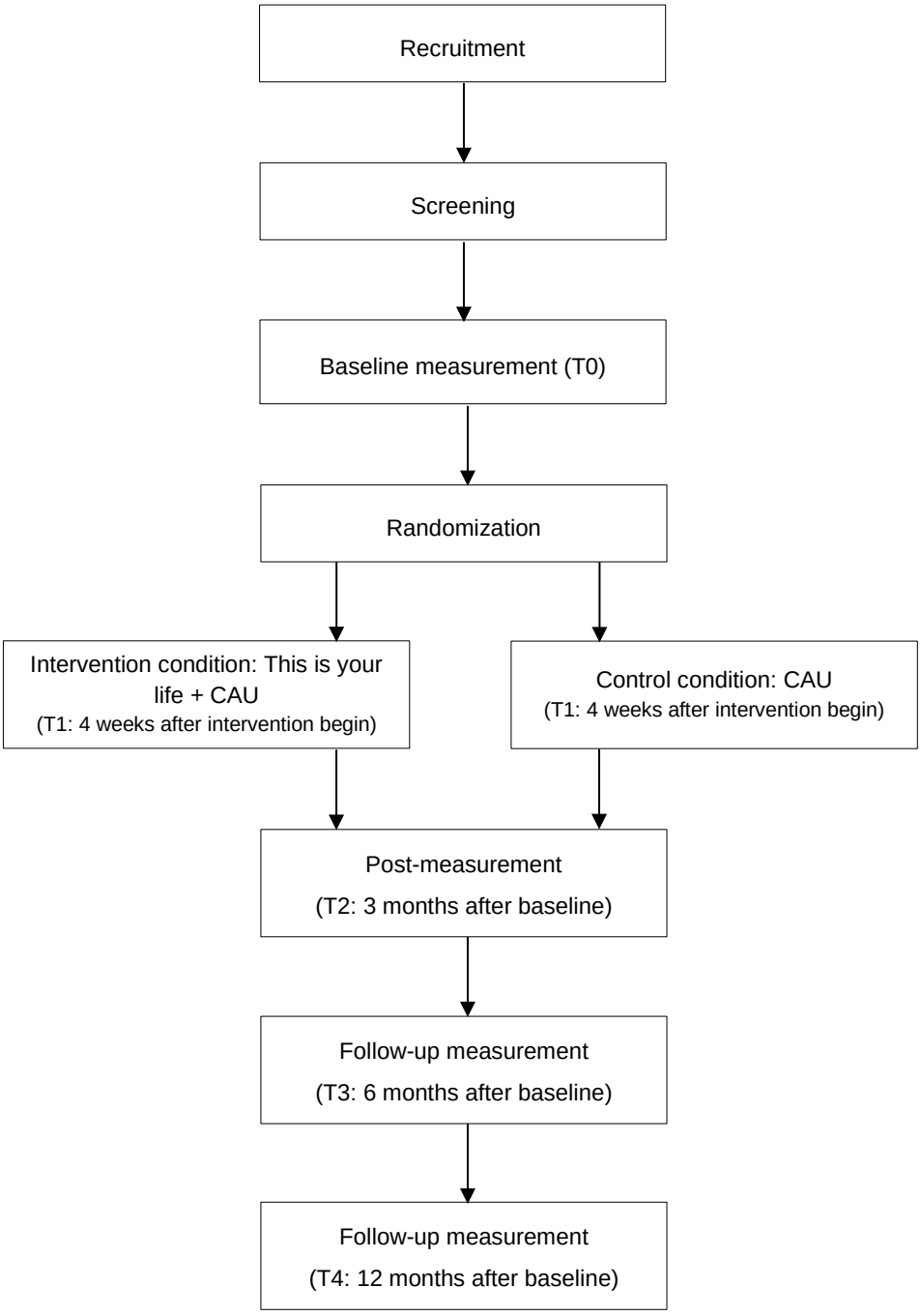
3.1. Design, duration and setting

This study uses a pragmatic, parallel-groups randomized non-blinded multicentre trial. Patients from nine different treatment centres will be randomly assigned to either a control or experimental condition. Since the prevalence of the diagnoses is different (Merikangas, Akiskal, Angst, & et al., 2007), the sample will be stratified on their diagnosis (BD I and BD II). Participants in the control condition receive CAU only and individuals in the intervention condition receive *This is your life* in addition to CAU. Both participants in the control and experimental condition receive CAU according to the MDR-BS, consisting mainly of psychopharmacotherapy, self-monitoring of mood and supportive group sessions focusing on functional issues.

The study takes place in the nine specialized treatment centres and are carried out by professional therapists. Before the randomization, screening and inclusion will be conducted by the principal investigator in the treatment centres. This process will be supported by therapists working in the treatment centers by referring possibly eligible participants to the principal investigator. The two participating treatment centres are *GGz in Geest* located in Amsterdam, the centre for bipolar disorders of the *Dimence Groep* in Deventer, Mediant located in Enschede, GGNet located in Doetinchem, GGZ Drenthe, the University Medical Centre Groningen and GGZ Noord-Holland Noord.

Figure 1 shows the flow of participants. The study takes 12 months for each individual to complete and includes five measurement points. Directly prior to the start of the intervention a baseline measurement is completed (T0) and four weeks after start of the intervention a mid-treatment measurement is conducted (T1). Directly following the intervention a post measurement will be conducted (T2): approximately three months after baseline. Additionally, two follow-up measurements are conducted, six months (T3) and twelve months after baseline (T4). Participants in both the experimental and control condition are estimated to spend approximately 36 minutes on average at each measurement point to complete one set of questionnaires (for a specific description of estimated durations for completing the questionnaire sets, *see 7.3. Study Procedures*). Additionally, participants in the experimental group spend two hours per week on the group intervention and approximately three hours per week (15 – 30 minutes per day) for a period of eight weeks exercising at home.

Figure 1: Flow of participants



4. STUDY POPULATION

4.1 Population (base)

Description of the population base

In the Netherlands, it is estimated that in 2009 approximately 1,3% of the Dutch population aged between 18-64 suffered from bipolar disorder with a slightly higher prevalence of 1,4 among women (de Graaf et al., 2010). This sums up to a total number of 136.300 persons diagnosed with BD. Even though it is difficult to estimate how high the proportion of persons in a euthymic phase in this population is, research has shown that between 20% and 35% of BD patients do not fully recover from a depressive or manic episode and remain with subthreshold symptoms (Fagiolini et al., 2013). This leaves a solid population base to gather sufficient participants and also underlines the need for more efficient treatment in the euthymic phase.

Study population

People participating are adult BD I and II patients in the euthymic phase currently under treatment for BD. The patients that are most suitable are patients with BD who suffer from residual or subsyndromal depressive symptoms but do not meet the criteria for a depressive mood episode.

The inclusion will be conducted by specialized treatment centers. Considering that the treatment centers have a case load of about 500 patients during a year which are in the euthymic phase we think the inclusion of sufficient participants is highly feasible. All the more because there is a high need for personal recovery outcomes among patients. Another reason why we think inclusion is feasible, is that the centers are academically oriented and have ample experience with participating in randomized controlled trials.

4.2 Inclusion criteria

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

(1) Current diagnosis of BD I or BD II (assessed using the MINI-international neuropsychiatric interview).
(2) Between the ages of 18-65.
(3) Four or more supportive sessions in the last year with a psychiatric nurse.
(4) Presence of subsyndromal depressive or (hypo)manic symptoms (assessed using the 7-point Clinical Global Impression Scale – Bipolar Disorder). Participants are included if they score between 2 (*minimal symptoms*) and 4 (*moderate symptoms*) for depressive symptoms *or* between 1 (no *symptoms*) and 3 (*light symptoms*) for manic symptoms.

4.3 Exclusion criteria

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

(1) Optimal level of positive mental health (assessed using the Mental Health Continuum-Short Form) (Lamers, Westerhof, Bohlmeijer, ten Klooster, & Keyes, 2011). Participants are excluded if they flourish (i.e. showing a high score of positive mental health), indicated by a score of 4 or 5 on at least one item of the emotional well-being subscale together with a score of 4 or 5 on at least 6 of the 11 remaining items of the Mental Health Continuum-Short Form.
(2) Currently in treatment for addiction problems.

4.4 Sample size calculation

The sample size calculation is conservatively based on the ability to detect at least a moderate effect of Cohen's *d* = 0.60 in the post-hoc tests on the primary outcome (well-being) at post-intervention (T1). For a two-sided independent t-test with 80% power and α = 0.05, this requires 45 patients for both treatment groups. Taking a drop-out rate of 20% into account, a total of 112 patients will need to be included for the per-protocol analysis.

Although meta-analyses on the effectiveness of positive psychology interventions report smaller average effect sizes for well-being and psychopathology (Bolier et al., 2013; Chakhssi et al., 2017, in review; Sin & Lyubomirsky, 2009), we think that an effect size of *d* = 0.60 is realistic for several reasons. Since most studies included in the meta-analyses used unguided and simple or stand-alone exercises only and not comprehensive intervention programs such as *This is your life*, higher effects can be expected from this multicomponent and group-based guided version of the intervention program. Furthermore, a recent trial (Schotanus-Dijkstra et al., 2017) evaluating the effectiveness of *This is your life* in individuals with low to moderate symptoms of depressions or anxiety, found large effect sizes for well-being at post-intervention (*d* = 0.89) and at a 12-month follow-up (*d* = 0.92). Additionally, pilot trials on the effect of personal recovery approaches for individuals with BD found strong effects in outcomes of depressive symptoms (*d* = .75), self-acceptance (*d* = 0.62), environmental mastery (*d* = 0.98) (Deckersbach et al., 2012), psychological well-being (*d* = 1.02), emotion regulation (*d* = 1.34) and emotion reactivity (*d* = .97) (Eisner et al., 2017).

5. TREATMENT OF SUBJECTS

Intervention: This is your life

We will re-design *This is your life* (Schotanus-Dijkstra et al., 2015) into a group-based (8-week, 2 hour sessions) intervention for BD, led by a psychologist with 8-10 participants. The intervention targets well-being and aims to enhance personal recovery.

The current version of *This is your life* is offered as an individual self-help book with e-mail support to participants with subclinical symptoms. The intervention is based on hallmark theories within positive psychology, including Seligman's comprehensive well-being theory (PERMA model; Seligman, 2011) and Ryff's theory of psychological well-being (Ryff, 1989). The intervention focuses on six key components in positive psychology: (1) Positive emotions, (2) Discovering and using personal strengths, (3) Optimism and hope, (4) Self-compassion, (5) Resilience and post-traumatic growth, (6) Positive relationships.

The adapted group intervention will consist of 8 meetings of 2 hours and homework assignments. Each group meeting will contain psycho-education on one of the six key components derived from positive psychological theory. Also, positive psychology exercises will be introduced, practiced, and discussed. For each of the six key components, 3-10 positive psychological – mostly evidence-based - exercises are available. An example of an exercise to increase the frequency of healthy positive emotions is the 'three good things exercise'. In this exercise, participants are instructed to think on a daily basis of three things that went well that day, such as having a nice conversation with a good friend, receiving a small gift from a significant other, or having a joyful dinner with family. Participants are also instructed to take some time to savor those positive moments (i.e. re-experience the positive feelings one had). Other examples of exercises include keeping a diary of pleasant experiences, creating an overview of personal strengths, visualizing your best possible self, wishing yourself something good and developing a compassionate inner voice, practicing active-constructive responding to stories of significant others and gratitude, and performing small and unexpected acts of kindness for others.

In a pilot study in spring 2017, the existing intervention was offered within one of the collaborating treatment centers to selected patients (N = 5) with BD who are currently in the euthymic phase. Aim of this pragmatic pilot was to evaluate the relevance and usability of the exercises for the target group of the bipolar patients and not to evaluate effects of the intervention. Participants rated the exercises on a scale from 1 (not at all) to 5 (extremely), representing the degree in which they found the exercise beneficial and useful. Results from these participants will be used to adapt the intervention to the BD patient group and group format. For example, it might be the case that a meeting on 'positive emotions' needs to include a discussion on the difference between healthy positive emotions and unhealthy positive emotions patients may experience in the context of a manic episode. Also, it might be helpful to address fear or recurrence into new mood episodes, as this is a general worry that many patients share that might impede the potential for personal recovery when left unaddressed (Goossens, Knoppert van der Klein, Kroon, & van Achterberg, 2007).

The evaluation of exercises showed that positive relationship exercises were rated the highest (M=4.27), followed by resilience (M=4.19), personal strength (M=4.1), positive

emotion (M=3.9), optimism and hope (M=3.58) and finally self-compassion (M=3.38) exercises. The results reveal that the exercises were well accepted and no exercise was rated particularly low. Furthermore, participants experienced the course as pleasant and enjoyable. From the results we conclude that the intervention is suitable for people with BD and all the exercises included in the pilot can also be included in the final intervention. However, since the pilot only contained 5 participants, the rating of the exercises should not be overestimated and we will base the exact selection of exercises not just on the results from this pilot. In spring 2018, a one-day workshop with patients will be conducted to further develop the intervention.

Usual care / comparison

Participants in the comparison group will receive CAU for BD in euthymic phases as described in the MDR-BS (2015), which comprises of supportive sessions with a psychiatric nurse and maintenance pharmacological treatment by a psychiatrist. Most patients receive 2-12 supportive sessions per year. CAU includes mainly psychoeducational elements that have the following aims: to give patients information about the illness in the context of the patients' life-history, to learn to identify early warning signals and prodromal symptoms, to develop and implement strategies to cope with prodromal symptoms, and to develop plans for acute crisis and stabilizing one's mood.

6. INVESTIGATIONAL PRODUCT

Not applicable

7. METHODS

7.1 Study parameters/endpoints

All data being gathered during the trial for the primary and secondary endpoints are self-reported data that will be retrieved from participants at five measurement moments via an online survey program, for which participants receive an invitation via e-mail. In addition, one telephone interview will be conducted with the participants at the end of the study (*see* 7.1.2.). To maximize response rates, participants will receive a reminder after three days each time the questionnaire has been sent.

At baseline, participants will be asked to state demographical data including gender, age, marital and employment status, ethnicity and education. Furthermore, participants will be asked to specify whether they followed psychoeducational group lessons in the past to adjust for the potentially confounding role of patient contact in the group lessons.

7.1.1. Main study parameter/endpoint

Well-being is measured with the Mental Health Continuum – Short Form (MHC-SF), a comprehensive well-validated measure of positive wellbeing (Lamers et al., 2011). The MHC-SF measures three dimensions of positive well-being: 1) emotional well-being (*three items*), defined in terms of the presence of positive feelings, the absence of negative feelings and satisfaction with life; 2) psychological well-being (*six items*), defined in terms of positive functioning in individual life in terms of e.g. self-acceptance, personal goals, positive relationships, and environmental mastery; 3) social well-being (*five items*), defined in terms of positive functioning in social life in terms of e.g. social integration and social contribution. Participants rate the frequency of feelings in the last month. A total score can be created by summing all 14 items, with higher scores indicating better positive well-being. The Dutch version of the MHC-SF showed high internal consistency for total scores ($\alpha = 0.89$) and for the subscales *emotional* ($\alpha = 0.83$) and *psychological well-being* ($\alpha = 0.83$) and adequate reliability for the subscale *social well-being* ($\alpha = 0.83$) and correlates well with corresponding aspects of well-being and functioning, showing convergent validity (Lamers et al., 2011).

7.1.2. Secondary study parameters/endpoints

To comprehensively assess personal recovery, the 15-item version of the Questionnaire about the Process of Recovery is used (QPR; Law, Neil, Dunn, & Morrison, 2014; Neil et al., 2009).The scale aims to assess personal recovery (e.g. “I feel better about myself” or “I can actively engage with life”), with items being scored on a 5-point Likert scale, ranging from 0

to (*disagree strongly*) to 4 (*agree strongly*) and higher scores being indicative of recovery. The internal consistency of the 15-item version has been found to be high (α = 0.89) in a sample of psychotic patients (Williams et al., 2015) and in a group of individuals with a schizophrenia spectrum diagnosis (α = 0.93) (Law et al., 2014). For this study, the QPR will be translated into Dutch via forward and backward translation.

Relapse will be assessed by performing semi-structured telephone interviews by trained student assistants with patients of both the intervention and control group. The student assistants conducting the interviews will be blind to treatment condition of the participants. The interview aims to retrospectively determine the mood development of the past nine months. Goal of the interviews is to illustrate the mood development in the time after the intervention and to capture depressive or manic mood swings. The interviews allow to graphically score severity of mood swings, the time they appeared (i.e. in which month) and which type of mood swings appeared (e.g. rapid cycling). The interview has been applied successfully in a previous study to measure relapse (van der Voort et al., 2011).

The Social Role Participation Questionnaire (SRPQ; Davis et al., 2011) assesses social role participation. We decided to assess this construct, since social role participation has been shown to be an important factor to build and maintain self-esteem and autonomy and can contribute to long-term mental health (Oude Voshaar et al., 2016). Social role participation can thus be seen as important part of recovery. For this study, the short version of the questionnaire (s-SRPQ; Oude Voshaar et al., 2016) will be used, which consists of 12 items, measuring the influence of (psychological) health on six social roles (e.g. intimate relationship or employment) along two dimensions: (1) satisfaction with role performance and (2) experienced physical / psychological difficulty. Items are scored on a 5-point Likert Scale, reaching from 0 (*not satisfied at all / no difficulties at all*) to 4 (*very much satisfied / not possible*), with higher scores indicating more satisfaction respectively more experienced difficulties with a social role. The psychometric qualities of the Dutch s-SRPQ were found to be good for the subscales *satisfaction* and *experienced difficulty (*α = 0.86) (Oude Voshaar et al., 2016).

Depressive symptoms are measured using the self-report version of the Quick Inventory of Depressive Symptomatology (QIDS-SR; Rush et al., 2003; Wardenaar et al., 2010). The QIDS-SR consists of 16 items that require individuals to rate different depression symptoms, such as sad mood, concentration, suicidal ideation, general interest, energy/fatigue, sleep, appetite and weight. Items are scored on a 4-point Likert Scale with different answering categories. A total score can be obtained by summing all items, with higher scores indicating more depressive symptomatology. The English version of the QIDS-SR has shown to be internally consistent (α = 0.86) (Rush et al., 2003). The QIDS-SR has been translated into

Dutch, validated in a sample of psychotic patients and shows good internal consistency (α = 0.87) (Lako et al., 2014).

Current manic symptoms are measured using the Altman Self-Rating Mania Scale (ASRM; Altman, Hedeker, Peterson, & Davis, 1997). The scale consists of five statements that represent different manic symptoms, including feeling more happy, self-confident and talkative than normal. All five items are rated on a 5-point Likert Scale with different answering categories. A total score can be obtained by summing all items, with higher scores indicating more manic symptomatology. The ASRM has high test-retest reliability (Altman et al., 1997), has been shown to be sensitive to changes of clinical states (Altman, Hedeker, Peterson, & Davis, 2001) and to predict related measures in non-clinical student samples (Meyer, Beevers, & Johnson, 2004). The ASRM has been translated into Dutch (Renes & Kupka, 2009) but not validated yet.

Symptoms of anxiety are assessed using the anxiety subscale of the Hospital Anxiety and Depression Scale (HADS-A; Zigmond & Snaith, 1983), which aims to measure anxiety symptoms with 7 items. Participants rate the frequency of symptoms (e.g. “Worrying thoughts go through my mind”) on scale ranging from 0 (“not at all”) to 3 (“very often”) and higher scores indicating indicate higher anxiety symptoms. The Dutch version of the HADS-A (Spinhoven et al., 1997) has been shown good internal consistency in a sample from the general population (α = 0.84) and in a sample of psychiatric outpatients (α = 0.81).

Positive emotion regulation is measured with the Responses to Positive Affect Questionnaire (RPA; Feldman, Joormann, & Johnson, 2008), which measures cognitive responses to positive affective states. For this study, only the subscale *dampening* is used (e.g. “I don’t deserve this”), which assesses the tendency to cognitively avoid or suppress positive emotions (eight items). Dampening of positive emotions has been associated with depressive symptoms, risk for mania and bipolar I disorder (Carl, Soskin, Kerns, & Barlow, 2013). Participants rate the items on a 4-point Likert scale, ranging from 1 (*almost never*) to 4 (*almost always*) and reflecting the frequency of certain cognitions. Higher scores indicate a greater tendency to cognitively suppress positive emotions. The dampening subscale of the Dutch version of the RPA (Raes, Daems, Feldman, Johnson, & Van Gucht, 2010) showed good internal consistency (α = 0.80).

Positive emotions are measured with the Positive and Negative Affect Schedule (PANAS; Watson, Clark, & Tellegen, 1988). The PANAS measures affect on two different dimensions: (1) positive and (2) negative affect and includes 20 items describing emotional states (e.g. “*active*” or “*anxious*”). Participants can score those states on a 5-point Likert Scale, representing the extent they experience an affect at this moment or have experienced in the past week, reaching from 1 (*very slightly or not at all*) to 5 (*extremely*). The scores can be summed up to gain and scores for positive and negative affect respectively, with higher

scores indicating higher affectivity. For this study, the Dutch version of the PANAS and only the positive affect subscale will be used, which showed acceptable reliability (α = .79) (Engelen, De Peuter, Victoir, Van Diest, & Van den Bergh, 2006).

Since people with bipolar disorder struggle to fruitfully regulate emotions (e.g. dampening) (Carl et al., 2013), we decided to assess the process of self-compassion, which has been associated with adaptive emotion regulation processes, including acceptance and positive reappraisal and negatively correlated with maladaptive strategies, such as thought suppression and rumination. Self-compassion is measured with the Self-Compassion Scale – Short Form (SCS-SF; Neff, 2003; Raes, Pommier, Neff, & Van Gucht, 2011). This shorter version of the original SCS (Neff, 2003) assesses the concept of self-compassion on six dimensions: (1) self-kindness, (2) self-judgment, (3) common humanity, (4) isolation, (5) mindfulness and (6) over-identification and contains twelve items (e.g. "*When I fail at something important to me I become consumed by feelings of inadequacy"*). Each dimension is assessed by two items, which are scored on a seven-point response scale ranging from 1 (*almost never*) to 7 (*almost always*), representing the extent an individual experiences certain aspects of self-compassion. Higher scores indicate an increased degree of self-compassion. The reliability of the total Dutch SCS-SF was shown to be good (α = .87), but psychometric properties of the subscales were questionable (Raes et al., 2011). For this reason, only total scores of the SCS-SF will be used.

The concept of positive relations is assessed using the Scales of Psychological Well-Being (SPWB; Ryff & Keyes, 1995), which assesses psychological well-being on six different dimensions (e.g. environmental mastery, self-acceptance). For this study, the subscale *positive relations* will be used measuring the extent to which an individual experiences meaningful intrapersonal relationships with other people (e.g. "*People would describe me as a giving person, willing to share my time with others*"). Items are scored on a scale ranging from 1 (strongly disagree) to 6 (strongly agree) with higher scores indicating more positive relations with others. Different versions of the SPWB exist within literature, differing in number of items per subscale (reaching from 3 items to 20 items per subscale). For economic reasons and since the short version of this subscale (3-items) showed bad to inacceptable internal consistency (α = .52 respectively .44), we decided to use the Dutch 9-item version of the *positive relations* subscale, which showed acceptable internal consistency in two previous studies (α = .77) in samples of psychology students and professionals from divers occupation background (Van Dierendonck, 2004).

Table 1: overview of study parameters

Concept	Instrument	Measurement point
Well-being	Mental Health Continuum – Short Form (MHC-SF; Lamers et al., 2011)	T0, T2, T3, T4
Personal recovery	Questionnaire about the Process of Recovery (QPR; Law et al., 2014)	T0, T2, T3, T4
Relapse	Semi-structured telephone interviews (van der Voort et al., 2011)	T4
Social role participation	Short Social Role Participation Questionnaire (s-SRPQ; Oude Voshaar et al., 2016)	T0, T2, T3, T4
Depressive symptoms	Quick - Inventory of Depressive Symptomatology (QIDS-SR; Rush et al., 2003)	T0, T2, T3, T4
Manic symptoms	Altman Self-Rating Mania Scale (ASRM; Altman et al., 1997)	T0, T2, T3, T4
Anxiety symptoms	Subscale *anxiety* of the Hospital Anxiety and Depression Scale (HADS-A; Spinhoven et al., 1997)	T0, T2, T3, T4
Positive emotion regulation	Subscale *dampening* of the Responses to Positive Affect Scale (RPA; Feldman et al., 2008; Raes et al., 2010)	T0, T1, T2
Positive emotions	Subscale *positive emotions* of the Positive and Negative Affect Schedule (PANAS; Watson et al., 1998; Engelen et al., 2006)	T0, T1, T2
Self-compassion	Self-Compassion Scale – Short Form (SCS-SF; Neff, 2003; Raes et al., 2011)	T0, T1, T2
Positive relations	Subscale *positive relations* (9-item version) of the Scales of Psychological Well-being (Ryff & Keyes, 1995; Van Dierendonck, 2004)	T0, T1, T2
Quality of Life	EuroQol Questionnaire (EQ-5D-5L; Herdman et al., 2011)	T0, T3, T4
Costs associated with psychiatric illness	Trimbos and iMTA questionnaire (Bouwmans et al., 2013)	T0, T3, T4

7.1.3. Other study parameters

Economic evaluations are performed using the five item version of the EuroQol questionnaire (EQ-5D-5L; Herdman et al., 2011) and the Trimbos and iMTA questionnaire on costs associated with psychiatric illness (TiC-P; Bouwmans et al., 2013). The EQ-5D-5L is a quality of life measure consisting of five items representing five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/ depression). For each dimension/item, individuals rate the extent of problems ranging from 'no problems' to 'extreme problems'. The TiC-P is a measure of health care utilization and production loss in patients with a psychiatric disorder. Items are generic and not related to a specific psychiatric disease. A first part of the TiC-P includes 9 structured no/yes items on medical consumption (e.g. contact with specific mental health care providers). A second part (13 items) consists of the Short Form-Health and Labour Questionnaire, a generic instrument to collect data on productivity losses due to health problems (e.g. absence from work).

7.2. Randomisation, blinding and treatment allocation

This study concerns a non-blinded study. After a participant is included in the study, signed the informed consent, and the baseline measurement has taken place, randomisation will be centrally conducted by the principal investigator via stratified (per centrum) block randomisation. For this purpose, lists with random numbers will be generated beforehand (one list for each center) with an online tool (https://sealedenvelope.com/). The lists contain a random sequence of treatment allocations (i.e. participants are either allocated to the intervention or control condition according to the corresponding record) and are divided in blocks of allocations (20 allocations per block). By using blocks of allocations, 20 participants can be allocated to either the intervention or control condition and afterwards the following block is used. This ensures that the group sessions can start before the inclusion of participants is complete. The first participant included in the study is allocated according to the first record on the list, the second participant according to the second record on the list and so forth.

7.3. Study procedures

The study contains five measurement points: one before the intervention (baseline), one intermediate measurement (four weeks after begin of the intervention) one after the intervention (approximately three months after baseline), and two follow-up measurements (respectively 6 and 12 months after baseline). In order to screen for eligibility criteria, in – and exclusion criteria will be checked by therapists working at the treatment centers, who then ask possibly eligible participants if they are interested to participate in the study. After possible participants signed the informed consent, the principal investigator contacts the

possible participant and agrees on a time and date to conduct the additional screening. In order to participate, patients must have had 4 or more supportive sessions during the last year, which is an important indicator of lack of recovery. Furthermore, the presence of subsyndromal depressive and manic symptoms but absence of several mood disorders is rated by the therapist using the CGI-BD. Patients scoring 1 – 3 on the evaluation of mania and 1 – 4 on the evaluation of depression will be included. These scores represent minimal, mild, and moderate illness but exclude those who are markedly or (very) severely ill (Spearing, Post, Leverich, Brandt, & Nolen, 1997). When still eligible, the principal investigator asks the patients to fill in the MHC-SF (Keyes et al., 2008; Lamers et al., 2011), which will take approximately five minutes. Patients who already flourish (i.e. patients with high mental-health as indicated by scores on the MHC-SF), will be excluded and only patients with low or moderate mental health will be included. Participants are excluded if they score 4 or 5 on at least one item of the emotional well-being subscale together with a score of 4 or 5 on at least 6 of the 11 remaining items of the MHC-SF.

Eligible participants are then asked to complete the whole test battery (see Table 1 for an overview) at baseline. Since the MHC-SF has already been completed for screening reasons before, participants are not asked to complete it again at baseline. We estimate that baseline measurements take 45 minutes to complete. Afterwards, allocation of participants to the intervention or control group takes place, using the pre-generated randomization list. After participants are allocated to the experimental condition, the intervention will be carried out by the trained therapists. The therapists executing the intervention will receive a training, in which both the background and components of *This is your life* will be illustrated. Participants in the intervention condition receive the intervention in addition to CAU. Participants in the control condition receive CAU only. It must be noted that not all intervention groups will be run at the same time. We aim to execute three sequential group interventions at each of the nine treatment centers, with the first group starting approximately in January 2019 and the last group finishing in fall 2019.

We assume that completing the test batteries takes approximately 45 minutes at baseline (T0), 15 minutes at mid-treatment (T1) and about 35 minutes at the post-measurement (T2). At the follow-up measurement 6 months after baseline (T3) it takes approximately 25 minutes to complete the questionnaires and at follow-up 12 months after baseline (T4) about 35 minutes. This sums up to approximately two hours and 30 minutes participants have to complete questionnaires. Additionally, participants of the intervention and control group will be approached 12 months after baseline for a semi-structured telephone interview with the goal to retrospectively assess relapse into mood episodes in the past nine months. To successfully perform the interviews, a guideline will be prepared and the interviews will be

conducted according to a fixed scheme. One interview takes approximately 30 minutes to complete.

7.4. 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.

7.4.1. Specific criteria for withdrawal (if applicable)

Not applicable.

7.5. Replacement of individual subjects after withdrawal

Participants will not be replaced after withdrawal. We have taken 20% drop-out into account.

7.6. Follow-up of subjects withdrawn from treatment

Withdrawn participants will be approached maximally once, in order to ascertain reasons for drop-out.

7.7. Premature termination of the study

There are no criteria for premature termination of the study. We expect that enough participants will be included and anticipate no other serious threats to the successful continuation of the study.

8. SAFETY REPORTING

8.1. Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the principal investigator 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.

8.2. AEs, SAEs and SUSARs

8.2.1. 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 experimental intervention. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

8.2.2. 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.

An elective hospital admission will not be considered as a serious adverse event.
The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events.
The principal investigator 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 principal investigator has first knowledge of the serious adverse events.

8.3. 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 will be reported till end of study within the Netherlands, as defined in the protocol.

9. STATISTICAL ANALYSIS

Analyses will be done on both intention to treat (ITT) and per protocol basis. The primary ITT analyses will be performed using linear mixed modelling (LMM) that adequately deals with missing at random data and the nested structure of repeated-measures data. LMMs with time, treatment and time-by-treatment interactions will be performed to test the effectiveness of the intervention in improving continuous outcomes of well-being, personal recovery, social participation, depressive symptoms, manic symptoms, anxiety symptoms, positive emotions, positive emotion regulation and self-compassion. Post-hoc independent t-tests with Holm-Bonferroni correction will be performed to test for significant between-group differences at all time-points. Based on estimated marginal means and corresponding standard errors from the LMM models, between-group standardized effect sizes will additionally be expressed as Cohen's d with 95% confidence intervals (CI). Binary relapse data from the interviews will be analyzed with Kaplan Meyer survival estimates to compare the time to relapse and relapse rates between the intervention and control group. Differences in the proportion of relapsed patients and predictors of relapse will be additionally examined using generalized (binary) LMMs with post-hoc chi-square tests and relative risks (RR) with 95% CI to examine the significance and magnitude of differences at each follow-up point.
To calculate the cost-effectiveness of the intervention, quality adjusted life years (QALYs) will be taken into account as primary utility measure. QALYs will be calculated from the EQ-5D-5L.The incremental cost-utility ratio (ICUR) will be calculated by dividing the difference in costs calculated from the TiC-P by the difference in the QALYs produced by the two groups. The ICUR is expressed as costs per QALY gained. Uncertainty surrounding incremental cost-effectiveness ratios will be addressed in two stages. First, both probabilistic (bootstrap analysis) and deterministic sensitivity analysis will be applied to the trial results, which will be reported using the appropriate cost effectiveness plane and cost-effectiveness acceptability curve. This will provide the one-year health-economic trial-based outcomes, while taking uncertainty explicitly into account. Second, probabilistic (Monte Carlo simulation) and deterministic sensitivity analysis will be applied to the model-based economic evaluation, such that the health-economic outcomes at longer time-horizons can be estimated, while explicitly taking into account uncertainty. As model-based results due to extrapolation become increasingly uncertain with increasing extrapolation, clinical expert opinion will be

used to make conservative estimates of how treatment effects sustain and after how many years it is reasonable to no longer expect any differences between the intervention and control condition.

10. ETHICAL CONSIDERATIONS

10.1. Regulation statement

The study will be carried out according to the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013) and the Medical Research Involving Human Subjects Act (WMO).

10.2. Recruitment and consent

The principal investigator is primarily responsible for recruitment of participants. Recruitment will take place in the participating treatment centres and will start in September 2018. We will closely work together with Dimence in Deventer, GGZ inGeest in Amsterdam, Mediant in Enschede, GGNet in Doetinchem, GGZ Drenthe, the University Medical Centre Groningen and GGZ Noord-Holland Noord, where gathering of participants is also supported by health-care professionals. In order to gather sufficient participants, professionals will play an active role, by informing patients about the study and handing out information folders. Furthermore, the principal investigator will ensure to regularly visit the treatment centres in the recruitment phase (approximately once a week) in order to inform and remind health-care professionals about (the progress of) the study and to stimulate the recruitment process on-site.

Possible participants are asked by their therapists whether they want to participate in the study. Since we want to recruit participants as extensive as possible, it is possible that participants are asked by a therapist who is involved in the study and part of the research group. In this case, a dependency relationship between the possible participant and the therapist exists. To guarantee interests of the participants, voluntariness and the fact that participation has no consequences for further treatment will be emphasized. This is also emphasized in the patient information letter and informed consent.

Participants possibly meeting the inclusion criteria receive the information package from their therapist (including the patient information letter and informed consent). A period of 2 weeks is granted to the participant to think about whether to participate in the study. If they decide to participate, they send the signed informed consent to the principal investigator. Alternatively, the principal investigator and participant will agree on a time and place to hand over the consent form personally. .Afterwards, the principal investigator contacts possible participants to agree on a date and time for the additional screening. . The information letter

also contains the explicit note that possible participants can always contact the principal investigator or independent expert in case of questions, concerns or doubts.

10.3. Objection by minors or incapacitated subjects (if applicable)

Not applicable.

10.4. Benefits and risks assessment, group relatedness

One possible benefit is a potential improvement in wellbeing and psychopathology for euthymic patients with bipolar disorder. As a consequence, relapse into mood episodes might be decreased as well. It is also expected that the intervention in combination with CAU demonstrates improved cost-effectiveness compared to CAU only. Hence, the economic burden is potentially decreased as well. If the intervention proves effective, the intervention is likely to be implemented as an additional intervention to the existing CAU.

This is your life has been carried out several times by the University of Twente and no negative events have occurred. However, since the effect of positive psychology interventions for individuals with BD is relatively unclear, the consequences for participants in the intervention group are not fully predictable. It cannot be ruled out that interventions enhancing positive behaviours, cognitions or emotions such as *This is your life* might heighten the risk for a manic phase. In case participants become manic in the course of the intervention, participants in the experimental condition are asked to stop immediately with the intervention, but participants in both conditions are requested to complete the remaining measurements if reasonably possible. Since the intervention is carried out in treatment centres specialized on bipolar disorder, possible participants dropping out due to severe symptoms of depression or mania, will find themselves in a protective environment where professionals are able to take care of them.

Also, certain parts of the intervention might be confronting for participants by reviving certain cognitions or behaviours they usually try to avoid (e.g. memories). However, since such experiences can have a healthy impact and possibly lead to improvement of the illness by paving the way towards recovery, we think that this is a reasonable risk which should be taken. No risk is expected from filling out the questionnaires or the semi-structured interview, which are all commonly used and well-validated. The interviews are solely carried out by trained personnel. Furthermore, participation in the study is full voluntary and can be stopped at any time and without explanation, if the patient wishes so.

10.5. Compensation for injury

The University of Twente has a liability insurance which is in accordance with article 7 of the WMO. Since no major risks are expected for participating in the study, the principal investigator asks for dispensation from the statutory obligation to provide insurance.

10.6. Incentives (if applicable)

Participants receive compensation for travelling.

11. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

11.1. Handling and storage of data and documents

Data will be handled confidentially in accordance with the Dutch Personal Data Protection Act. Personal data will be coded with an individual ID-code, which is not relatable to the participant. A list will be created, which contains the ID-codes, stored on a separate computer and maintained by the secretary of the Department of Psychology, Health and Technology of the University of Twente. The computer of the secretary is locked by a password and the file containing the ID-codes will be locked with a separate password. All collected data will be stored in a file containing only the identification code. So, the data of the same person can be matched across different measurement points. These data will be stored and collected by the researchers, who do not have access to the code list, whereas the secretary does not have access to the data.

The coded research data will be stored at the IGS Datalab of the University of Twente for a period of 15 years. In this time period, data is accessible to other researchers. After the period of 15 years, data will be stored in long time storage at Data Archiving and Networked Services (DANS) by the Royal Dutch Academy of Sciences (KNAW). .

Participants who want to be informed about their personal data or who want their data deleted can send a request to the principal investigator. For this, no reason is needed, since participants always have the right to be informed about their personal data. After the personal data is deleted, informing participants about their personal data is no longer possible.

11.2. Monitoring and Quality Assurance

The study process is continuously monitored by dr. E.T. Bohlmeijer (project leader), dr. R. Kupka (VU Medisch Centrum), dr. P.M. ten Klooster (UT; daily supervisor), dr. A. Stevens (Dimence) and dr. M. Chrispijn (Dimence). Additionally, to optimize the research process and the intervention, E. Neutel, who is active in the Dutch patient association for bipolar disorder, is part of the research group as project advisors. The principal investigator will have weekly meetings with the daily supervisor and once in two weeks with the project leader and daily supervisor. One time per month, dr. A. Stevens and dr. M. Chrispijn will join these meetings. The broader research group will meet at least four times per year.

11.3. 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.

11.4. Annual progress report

The principal 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.

11.5. Temporary halt and (prematurely) end of study report

The University of Twente 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 measurement. 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 University of Twente 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 University of Twente will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

11.6. Public disclosure and publication policy

We aim to publish seven articles about the study. One article will describe the research protocol. A second article will focus on the effectiveness of the intervention and the third article will focus on possible moderators and working mechanisms of the intervention. The fourth article will contain economic evaluations to determine whether the intervention in addition to CAU is more cost-effective than CAU only.. Fifthly, an article evaluating the psychometric properties of the QPR is planned and sixthly an article focusing on a psychometric validation of the SRPQ. All articles will be submitted to scientific peer- reviewed journals. The trial is registered in the Netherlands National Trial Register (NTR) (TrialRegister.nl) with the number NTR6729.

No specific arrangements are made between the sponsor and the investigator concerning the public disclosure and publication of the research data.

12. STRUCTURED RISK ANALYSIS

Not applicable.

13. REFERENCES

Altman, E., Hedeker, D., Peterson, J. L., & Davis, J. M. (2001). A comparative evaluation of three self-rating scales for acute mania. *Biological Psychiatry, 50*(6), 468-471. doi:10.1016/S0006-3223(01)01065-4

Altman, E. G., Hedeker, D., Peterson, J. L., & Davis, J. M. (1997). The Altman self-rating mania scale. *Biological Psychiatry, 42*(10), 948-955.

Anthony, W. A. (1993). Recovery from mental illness: The guiding vision of the mental health service system in the 1990s. *Psychosocial rehabilitation journal, 16*(4), 11.

Berk, M., & Dodd, S. (2005). Bipolar II disorder: a review. *Bipolar Disord, 7*(1), 11-21. doi:10.1111/j.1399-5618.2004.00152.x

Bolier, L., Haverman, M., Westerhof, G. J., Riper, H., Smit, F., & Bohlmeijer, E. (2013). Positive psychology interventions: a meta-analysis of randomized controlled studies. *BMC Public Health, 13*(1), 119.

Bouwmans, C., De Jong, K., Timman, R., Zijlstra-Vlasveld, M., Van der Feltz-Cornelis, C., Tan, S. S., & Hakkaart-van Roijen, L. (2013). Feasibility, reliability and validity of a questionnaire on healthcare consumption and productivity loss in patients with a psychiatric disorder (TiC-P). *BMC health services research, 13*(1), 217.

Carl, J. R., Soskin, D. P., Kerns, C., & Barlow, D. H. (2013). Positive emotion regulation in emotional disorders: A theoretical review. *Clinical psychology review, 33*(3), 343-360. doi:https://doi.org/10.1016/j.cpr.2013.01.003

Chakhssi, F., Kraiss, J. T., Spijkerman, M., & Bohlmeijer, E. T. (2017, in review). The Effect of Positive Psychology Interventions on Well-Being and Distress in Clinical samples with Psychiatric or Somatic Disorders: A Systematic Review and Meta-Analysis. *BMC Psychiatry*.

Davis, A. M., Palaganas, M. P., Badley, E. M., Gladman, D. D., Inman, R. D., & Gignac, M. A. (2011). Measuring participation in people with spondyloarthritis using the social role participation questionnaire. *Annals of the rheumatic diseases, 70*(10), 1765-1769.

de Graaf, R., ten Have, M., & van Dorsselaer, S. (2010). *De psychische gezondheid van de Nederlandse bevolking*. Retrieved from Utrecht:

Deckersbach, T., Hölzel, B. K., Eisner, L. R., Stange, J. P., Peckham, A. D., Dougherty, D. D., . . . Nierenberg, A. A. (2012). Mindfulness-Based Cognitive Therapy for Nonremitted Patients with Bipolar Disorder. *CNS Neuroscience & Therapeutics, 18*(2), 133-141. doi:10.1111/j.1755-5949.2011.00236.x

Dilsaver, S. C. (2011). An estimate of the minimum economic burden of bipolar I and II disorders in the United States: 2009. *Journal of Affective Disorders, 129*(1), 79-83. doi:http://dx.doi.org/10.1016/j.jad.2010.08.030

Eisner, L., Eddie, D., Harley, R., Jacobo, M., Nierenberg, A. A., & Deckersbach, T. (2017). Dialectical Behavior Therapy Group Skills Training for Bipolar Disorder. *Behav Ther, 48*(4), 557-566. doi:10.1016/j.beth.2016.12.006

Engelen, U., De Peuter, S., Victoir, A., Van Diest, I., & Van den Bergh, O. (2006). Verdere validering van de Positive and Negative Affect Schedule (PANAS) en vergelijking van twee Nederlandstalige versies. *gedrag en gezondheid, 34*(2), 61-70.

Fagiolini, A., Forgione, R., Maccari, M., Cuomo, A., Morana, B., Dell'Osso, M. C., . . . Rossi, A. (2013). Prevalence, chronicity, burden and borders of bipolar disorder. *J Affect Disord, 148*(2-3), 161-169. doi:10.1016/j.jad.2013.02.001

Fagiolini, A., Kupfer, D. J., Masalehdan, A., Scott, J. A., Houck, P. R., & Frank, E. (2005). Functional impairment in the remission phase of bipolar disorder. *Bipolar Disord, 7*(3), 281-285. doi:10.1111/j.1399-5618.2005.00207.x

Fava, G. A., Ruini, C., & Belaise, C. (2007). The concept of recovery in major depression. *Psychological medicine, 37*(3), 307-317.

Feldman, G., Joormann, J., & Johnson, S. L. (2008). Responses to Positive Affect: A Self-Report Measure of Rumination and Dampening. *Cognitive Therapy and Research, 32*(4), 507-525. doi:10.1007/s10608-006-9083-0

Goossens, P. J. J., Knoppert van der Klein, E. A. M., Kroon, H., & van Achterberg, T. (2007). Self-reported care needs of outpatients with a bipolar disorder in the Netherlands. *Journal of psychiatric and mental health nursing, 14*(6), 549-557.

Grande, I., Berk, M., Birmaher, B., & Vieta, E. (2015). Bipolar disorder. *The Lancet, 387*(10027), 1561-1572. doi:10.1016/S0140-6736(15)00241-X

Herdman, M., Gudex, C., Lloyd, A., Janssen, M., Kind, P., Parkin, D., . . . Badia, X. (2011). Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Quality of life research, 20*(10), 1727-1736.

Jones, S., Higginson, S., Murray, C., & Morrison, A. P. (2010). *Recovery experiences in bipolar disorder*. Paper presented at the Britisch Association for Behavioural and Cognitive Psychotherapy Annual Conference, Manchester, UK.

Jones, S., Mulligan, L. D., Higginson, S., Dunn, G., & Morrison, A. P. (2013). The bipolar recovery questionnaire: psychometric properties of a quantitative measure of recovery experiences in bipolar disorder. *Journal of Affective Disorders, 147*(1), 34-43.

Jones, S., Smith, G., Mulligan, L. D., Lobban, F., Law, H., Dunn, G., . . . Morrison, A. P. (2015). Recovery-focused cognitive–behavioural therapy for recent-onset bipolar disorder: randomised controlled pilot trial. *The British Journal of Psychiatry, 206*(1), 58-66. doi:10.1192/bjp.bp.113.141259

Judd, L. L., Schettler, P. J., Akiskal, H. S., & et al. (2008). Residual symptom recovery from major affective episodes in bipolar disorders and rapid episode relapse/recurrence. *Archives of General Psychiatry, 65*(4), 386-394. doi:10.1001/archpsyc.65.4.386

Kaya, E., Aydemir, Ö., & Selcuki, D. (2007). Residual symptoms in bipolar disorder: The effect of the last episode after remission. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 31*(7), 1387-1392. doi:http://dx.doi.org/10.1016/j.pnpbp.2007.06.003

Keyes, C. L. (2002). The mental health continuum: From languishing to flourishing in life. *Journal of health and social behavior*, 207-222.

Keyes, C. L., Dhingra, S. S., & Simoes, E. J. (2010). Change in Level of Positive Mental Health as a Predictor of Future Risk of Mental Illness. In *American Journal of Public Health* (Vol. 100, pp. 2366-2371): American Public Health Association.

Keyes, C. L., Wissing, M., Potgieter, J. P., Temane, M., Kruger, A., & Van Rooy, S. (2008). Evaluation of the mental health continuum–short form (MHC–SF) in setswana-speaking South Africans. *Clinical Psychology & Psychotherapy, 15*(3), 181-192.

Kupka, R., Knoppert, E., & Nolen, W. (2008). *Handboek bipolaire stoornissen*. Utrecht: De Tijdstroom.

Lako, I. M., Wigman, J. T. W., Klaassen, R. M. C., Slooff, C. J., Taxis, K., Bartels-Velthuis, A. A., & investigators, G. (2014). Psychometric properties of the self-report version of the Quick Inventory of Depressive Symptoms (QIDS-SR(16)) questionnaire in patients with schizophrenia. *BMC Psychiatry, 14*, 247. doi:10.1186/s12888-014-0247-2

Lamers, S. M. A., Westerhof, G. J., Bohlmeijer, E. T., ten Klooster, P. M., & Keyes, C. L. (2011). Evaluating the psychometric properties of the mental health continuum-short form (MHC-SF). *Journal of Clinical Psychology, 67*(1), 99-110.

Lamers, S. M. A., Westerhof, G. J., Glas, C. A. W., & Bohlmeijer, E. T. (2015). The bidirectional relation between positive mental health and psychopathology in a longitudinal representative panel study. *The Journal of Positive Psychology, 10*(6), 553-560. doi:10.1080/17439760.2015.1015156

Law, H., Neil, S. T., Dunn, G., & Morrison, A. P. (2014). Psychometric properties of the questionnaire about the process of recovery (QPR). *Schizophr Res, 156*(2-3), 184-189. doi:10.1016/j.schres.2014.04.011

Leamy, M., Bird, V., Le Boutillier, C., Williams, J., & Slade, M. (2011). Conceptual framework for personal recovery in mental health: systematic review and narrative synthesis. *The British Journal of Psychiatry, 199*(6), 445-452. doi:10.1192/bjp.bp.110.083733

Mead, S., & Copeland, M. E. (2000). What recovery means to us: consumers' perspectives. *Community Ment Health J, 36*(3), 315-328.

Merikangas, K. R., Akiskal, H. S., Angst, J., & et al. (2007). Lifetime and 12-month prevalence of bipolar spectrum disorder in the national comorbidity survey replication. *Archives of General Psychiatry, 64*(5), 543-552. doi:10.1001/archpsyc.64.5.543

Meyer, B., Beevers, C. G., & Johnson, S. L. (2004). Goal Appraisals and Vulnerability to Bipolar Disorder: A Personal Projects Analysis. *Cognitive Therapy and Research, 28*(2), 173-182. doi:10.1023/b:cotr.0000021538.34160.52

Miller, S., Dell'Osso, B., & Ketter, T. A. (2014). The prevalence and burden of bipolar depression. *Journal of Affective Disorders, 169*(Supplement 1), S3-S11. doi:https://doi.org/10.1016/S0165-0327(14)70003-5

Neff, K. D. (2003). The development and validation of a scale to measure self-compassion. *Self and identity, 2*(3), 223-250.

Neil, S. T., Kilbride, M., Pitt, L., Nothard, S., Welford, M., Sellwood, W., & Morrison, A. P. (2009). The questionnaire about the process of recovery (QPR): A measurement tool developed in collaboration with service users. *Psychosis, 1*(2), 145-155. doi:10.1080/17522430902913450

Oude Voshaar, M., van Onna, M., van Genderen, S., van de Laar, M., van der Heijde, D., Heuft, L., . . . Boonen, A. (2016). Development and Validation of a Short Form of the Social Role Participation Questionnaire in Patients with Ankylosing Spondylitis. *J Rheumatol, 43*(7), 1386-1392. doi:10.3899/jrheum.151013

Pompili, M., Harnic, D., Gonda, X., Forte, A., Dominici, G., Innamorati, M., . . . Girardi, P. (2014). Impact of living with bipolar patients: Making sense of caregivers' burden. *World Journal of Psychiatry, 4*(1), 1-12. doi:10.5498/wjp.v4.i1.1

Raes, F., Daems, K., Feldman, G., Johnson, S., & Van Gucht, D. (2010). A psychometric evaluation of the Dutch version of the responses to positive affect questionnaire. *Psychologica Belgica, 49*(4).

Raes, F., Pommier, E., Neff, K. D., & Van Gucht, D. (2011). Construction and factorial validation of a short form of the self-compassion scale. *Clinical Psychology & Psychotherapy, 18*(3), 250-255.

Renes, J. W., & Kupka, R. W. (2009). Altman Self-Rating Mania Scale (ASRM) - Nederlands vertaling (ASRM-NL)

Rush, A. J., Trivedi, M. H., Ibrahim, H. M., Carmody, T. J., Arnow, B., Klein, D. N., . . . Keller, M. B. (2003). The 16-Item quick inventory of depressive symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biological Psychiatry, 54*(5), 573-583. doi:http://dx.doi.org/10.1016/S0006-3223(02)01866-8

Ryff, C. D. (1989). Happiness is everything, or is it? Explorations on the meaning of psychological well-being. *Journal of personality and social psychology, 57*(6), 1069.

Ryff, C. D., & Keyes, C. L. M. (1995). The structure of psychological well-being revisited. *Journal of personality and social psychology, 69*(4), 719.

Schotanus-Dijkstra, M., Drossaert, C. H., Pieterse, M. E., Walburg, J. A., & Bohlmeijer, E. T. (2015). Efficacy of a Multicomponent Positive Psychology Self-Help Intervention: Study Protocol of a Randomized Controlled Trial. *JMIR Res Protoc, 4*(3), e105. doi:10.2196/resprot.4162

Schotanus-Dijkstra, M., Drossaert, C. H. C., Pieterse, M. E., Boon, B., Walburg, J. A., & Bohlmeijer, E. T. (2017). An early intervention to promote well-being and flourishing and reduce anxiety and depression: A randomized controlled trial. *Internet Interventions, 9*(Supplement C), 15-24. doi:https://doi.org/10.1016/j.invent.2017.04.002

Seligman. (2011). Flourishing. *A new understanding of happiness and well-being–and how to achieve them. Boston: Nicholas Brealey*.

Seligman, & Csikszentmihalyi, M. (2014). Positive Psychology: An Introduction. In M. Csikszentmihalyi (Ed.), *Flow and the Foundations of Positive Psychology: The Collected Works of Mihaly Csikszentmihalyi* (pp. 279-298). Dordrecht: Springer Netherlands.

Sin, N. L., & Lyubomirsky, S. (2009). Enhancing well-being and alleviating depressive symptoms with positive psychology interventions: a practice-friendly meta-analysis. *Journal of Clinical Psychology, 65*(5), 467-487. doi:10.1002/jclp.20593

Slade, M. (2010). Mental illness and well-being: the central importance of positive psychology and recovery approaches. *BMC health services research, 10*(1), 26.

Spearing, M. K., Post, R. M., Leverich, G. S., Brandt, D., & Nolen, W. (1997). Modification of the Clinical Global Impressions (CGI) Scale for use in bipolar illness (BP): the CGI-BP. *Psychiatry Res, 73*(3), 159-171.

Spinhoven, P., Ormel, J., Sloekers, P., Kempen, G., Speckens, A., & Van Hemert, A. (1997). A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. *Psychological medicine, 27*(2), 363-370.

Trompetter, H. R., de Kleine, E., & Bohlmeijer, E. T. (2017). Why Does Positive Mental Health Buffer Against Psychopathology? An Exploratory Study on Self-Compassion as a Resilience Mechanism and Adaptive Emotion Regulation Strategy. *Cognitive Therapy and Research, 41*(3), 459-468. doi:10.1007/s10608-016-9774-0

van der Voort, T. Y., van Meijel, B., Goossens, P. J., Renes, J., Beekman, A. T., & Kupka, R. W. (2011). Collaborative care for patients with bipolar disorder: a randomised controlled trial. *BMC Psychiatry, 11*(1), 133.

Van Dierendonck, D. (2004). The construct validity of Ryff's Scales of Psychological Well-being and its extension with spiritual well-being. *Personality and individual differences, 36*(3), 629-643.

Wardenaar, K. J., van Veen, T., Giltay, E. J., den Hollander-Gijsman, M., Penninx, B. W. J. H., & Zitman, F. G. (2010). The structure and dimensionality of the Inventory of Depressive Symptomatology Self Report (IDS-SR) in patients with depressive disorders and healthy controls. *Journal of Affective Disorders, 125*(1), 146-154. doi:http://dx.doi.org/10.1016/j.jad.2009.12.020

Watson, D., Clark, L. A., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: the PANAS scales. *Journal of personality and social psychology, 54*(6), 1063.

Williams, J., Leamy, M., Pesola, F., Bird, V., Le Boutillier, C., & Slade, M. (2015). Psychometric evaluation of the Questionnaire about the Process of Recovery (QPR). *The British Journal of Psychiatry, 207*(6), 551.

Zigmond, A. S., & Snaith, R. P. (1983). The hospital anxiety and depression scale. *Acta psychiatrica scandinavica, 67*(6), 361-370.