Cognitive Behavioral Analysis System of Psychotherapy (CBASP) vs. Behavioral Activation (BA) in persistently depressed treatment-resistant inpatients: Efficacy, moderators, and mediators of change

Acronym: ChangePDD

NCT Number: NCT04996433

Document Date: 22.10.2024

University Greifswald
Clinical Psychology and Psychotherapy
Franz-Mehring Str. 47
17487 Greifswald

Study Protocol

Cognitive Behavioral Analysis System of Psychotherapy (CBASP) vs. Behavioral Activation (BA) in persistently depressed treatment-resistant inpatients: Efficacy, moderators, and mediators of change

Acronym: ChangePDD

Cognitive Behavioral Analysis System of Psychotherapy (CBASP) vs. Behavioral Activation (BA) bei stationären Patienten mit persistierend depressiven und therapieresistenten Störungen: Wirksamkeit, Moderatoren und Mediatoren der Veränderung

Version 4.0

Coordinating Investigator

Prof. Dr. Eva-Lotta Brakemeier
University Greifswald
Clinical Psychology and Psychotherapy
Franz-Mehring-Str. 47
17487 Greifswald
Email: eva-lotta.brakemeier@uni-greifswald.de
Phone.: +49 3834 420 3786 Fax: +49 3834 420 3736

Table of Contents

List of Abbreviations

Abbreviation	Definition
AE	Adverse Event
ATHF-SF	Antidepressant Treatment History Form - Short Form
ATR	Adverse Treatment Reaction
BA	Behavioral Activation
BADS	Behavioral Activation Depression Scale
BDI-II	Beck's Depression Inventory
BDNF	Brain-Derived Neurotrophic Factor
BRS	Brief Resilience Scale
BSI	Brief Symptom Inventory
CBASP	Cognitive Behavioral Analysis System of Psychotherapy
CBASP-CAR / BA-CAR	Observer based Competence and Adherence Rating of CBASP / BA
CBT	Cognitive Behavioral Therapy
CRF	Case Report Form
C-SSRS	Columbia – Suicide Severity Rating Scale
CTQ	Childhood Trauma Questionnaire
DAS	Dysfunctional Attitude Scale
DIPS	Diagnostic Interview for Mental Disorders
DMC	Data Monitoring Committee
DSM	Diagnostic and Statistical Manual of Mental Disorders
EC	Ethics Committee
ECR-RD8	Experience in Close Relationships – Revised 8-item version
eCRF	Electronic Case Report Form
ECT	Electroconvulsive Therapy
EDC	Electronic Data Capture
ES	Euthymia Scale
FPFV	First Patient First Visit
GAF	Global Assessment of Functioning
GSE	General Self-Efficacy Scale
HDRS-24	Hamilton Depression Rating Scale, 24-item version
IAD	Interpersonal Activation Diary
ICH-GCP	International Conference on Harmonization - Good Clinical Practice

Abbreviation	Definition
IDS-SR	Inventory of Depressive Symptoms, Self-Report
IIP-32-R	Inventory of Interpersonal Problems, 32-item version, revised
IMI-R	Impact Message Inventory – Revised
ISF	Investigator Site File
ITT	Intention to Treat
KKS	Coordinating Center for Clinical Trials
LGCM	Latent Growth Curve Model
LQPT	Lübecker Questionnaire of Preoperational Thinking
LPLV	Last Patient Last Visit
MINI-ICF	Measure of disorders of capacity as defined by the International Classification of Function
MPQ	Mental Pain Questionnaire
PDD	Persistent Depressive Disorder
PI	Principal Investigator (Coordinating Investigator)
PID5BF + M	Personality Inventory for DSM-5 Brief Form Plus Modified
RCT	Randomized Controlled Trial
R-GPTS	Revised-Green Paranoid Thoughts Scale
RSQ	Rejection Sensitivity Questionnaire
SAB	Scientific Advisory Board
SAE	Severe Adverse Event
SATR	Severe Adverse Treatment Reaction
SCID-PD	Structured Clinical Interview for DSM-5 – Personality Disorders
SEPIPS	Side Effects of Psychological Interventions Process Scale
SNI	Social Network Index
TR	Treatment-Resistance
UCLA	UCLA Loneliness Scale
WAI	Working Alliance Inventory
WHO-5	Well-Being Index
WHOQoL	World Health Organization Quality of Life

1. Study Synopsis

Title of the Study	Cognitive Behavioral Analysis System of Psychotherapy (CBASP) vs. Behavioral Activation (BA) in persistently depressed treatment-resistant inpatients: Efficacy, moderators, and mediators of change
Study Acronym	ChangePDD
Coordinating Investigator	Prof. Dr. Eva-Lotta Brakemeier
Indication	Persistent depressive disorder (PDD) with treatment-resistance (TR)
Objectives	To compare CBASP conducted over 16 weeks (acute and continuation treatment) with BA (same dose and duration) in PDD inpatients with TR regarding efficacy, moderators and mediators of change
Study Design	Prospective, multicenter, evaluator-blinded, parallel-group, randomized controlled intervention trial with an active control condition
Number of Patients	To be assessed for eligibility: n = 1000 to be screened at sites To be allocated to study: n = 396 To be analyzed: n = 396; Intention to Treat (ITT) Sample, 14% expected dropout included
Randomization	Randomization with stratification for severity of depression and study site with an allocation ratio of 1:1
Eligibility Criteria - Inclusion	– Age 18 - 75 years – Primary DSM-5 diagnosis of PDD (300.4, 296.2x, 296.3x) – Total Hamilton Depression Rating Scale (HDRS-24) Score ≥ 20 – Treatment-resistance (TR) (defined by the ATHF-SF or medication intolerance or one psychotherapy at least 25 sessions by a certified therapist in the current episode) – Sufficient knowledge of the German language – Written informed consent
Eligibility Criteria - Exclusion	– Bipolar I or II disorder – Active substance use disorders (abstinence shorter than 6 months) – Schizophrenia spectrum and other psychotic disorders – Antisocial personality disorder – Acute suicidality (HRSD item 3 > 2 or agreement with C-SSRS item 4 and/or item 5) – Previous CBASP or BA treatment within the last year – Inability to tolerate CBASP or BA (e.g., organic brain disorders, severe cognitive deficits) – Inability to participate in dayclinic or outpatient continuation treatment – Participation in another (psycho)therapeutic study of an interventional nature
Test and Reference Treatment	Experimental intervention: CBASP Control intervention: BA
Time schedule	– Study treatment per patient: 112 days (16 weeks) – Study duration per patient: 448 days (64 weeks, incl. follow-up) – First patient first visit (FPFV) to last patient last visit (LPLV): 34 months (without follow-up), 46 months (incl. follow-up; both estimated) – Estimated duration of the entire study: 58 months

	– Estimated recruitment period: 30 months
Primary endpoint	– Change in depression severity (HDRS-24 score) after 16 weeks
Secondary and further endpoints	Secondary endpoints: – Depressive and anxiety symptomatology (HDRS-24 and IDS-SR) assessed every second week during treatment and at week 64; IDS-SR also measured every second month during follow-up – Specific other important psychological variables (BSI, GAF, WHOQoL) assessed at week pre, 1, 5, 10, 16, and 64 – Response, remission, dropout and relapse rates (according to HRSD-24 and hospitalization rates) assessed at week 5, 10, 16 and 64 (relapse rate only at week 16 and 64) – costs and benefits (cost interview) assessed at week pre, 16, 64 Further endpoints: – Other interesting psychological variables (BDI-II, BRS, DAS, ECR-D, ES, IMI-R, LQPT, Mini-ICF, MPQ, PID5BF+M, R-GPTS, RSQ, SES, SNI, UCLA, WBI, WHOQOL, WHO-5) assessed at week pre, 1, 5, 10, 16, and 64 Main moderators (assessed at baseline): – Child maltreatment (CTQ) – Epigenetic (BDNF methylation) Main mediators (assessed at baseline and week 1, 2, 4, 6, 8, 10, 12, 14, 16, and 64): – Interpersonal problems (IIP-32-R) – Activities (BADS, actimeter-measured step-counts) Mediators only included in the two add-on studies: – Interpersonal Activation Diary (IAD; assessed daily for one week before treatment, at weeks 1 to 16 and for one week after treatment) – Social context, valence, arousal (assessed daily for one week before and after treatment respectively) – Effort Task (assessed at week 1, 5, 16) Safety: – (Severe) Adverse events, negative effects including side effects (SEPIPS) and medication will be monitored – C-SSRS
Statistical analysis	Description of the primary efficacy analysis and population: Latent Growth Curve Model (LCGM) capturing non-linear trajectories of change in HDRS-24 scores from pre to 16 weeks as a function of treatment group in the Intention to Treat (ITT) sample Secondary endpoints LCGMs for continuous secondary endpoints; Logistic regression analyses of dichotomous secondary outcomes Sensitivity analyses: - LCGMs including covariates - LCGMs based on the per protocol sample Moderator analyses: - Two-group LCGMs including covariates Mediator analyses: - Dynamic Panel Models, Dynamic SEM, Latent Growth Mediation Models

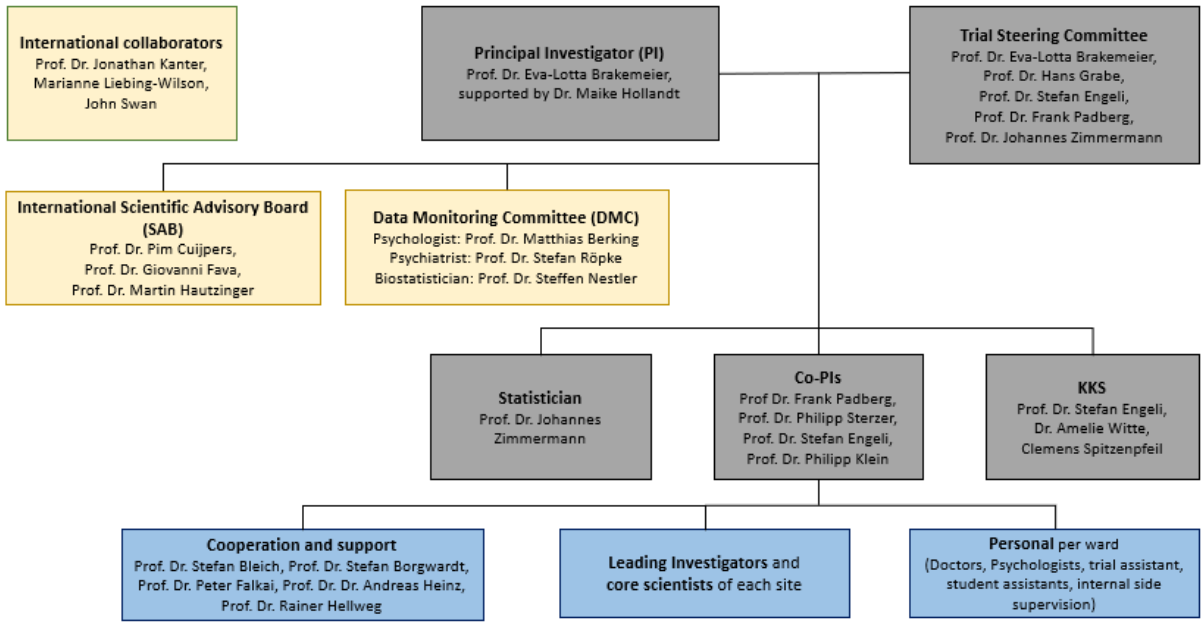
Participating sites	sites to be involved: 1) Berlin, Charité, University Medicine Berlin 2) Hanover, Hanover Medical School 3) Lübeck, University Hospital of Lübeck 4) Marburg, University Hospital of Marburg 5) Munich, University Hospital of Munich 6) Tübingen, University Hospital of Tübingen 7) Bonn, University Hospital of Bonn 8) Jena, University Hospital of Jena

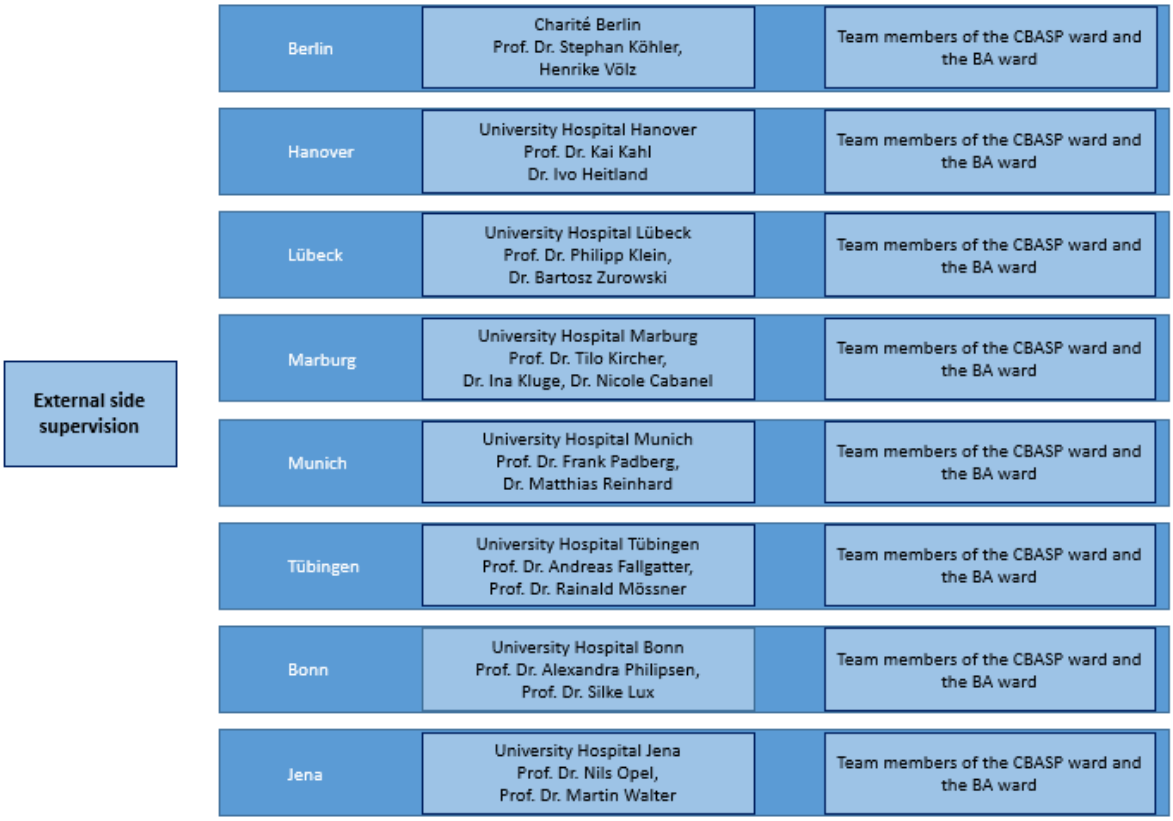
2. Responsibilities and Cooperation

2.1. Responsibilities

The following Figure 1 gives an overview of all persons, committees, boards and sites involved in the study ChangePDD.

Figure 1: Persons, committees, boards and sites involved in the study ChangePDD





2.1.1. Investigator's responsibilities

The **Principal Investigator (PI) / Coordinating Investigator (CI)** Prof. Dr. Eva-Lotta Brakemeier is a highly experienced scientist and psychotherapist and has sufficient experience in conducting clinical studies. She is responsible for the project coordination and project management, especially for conducting the clinical study in accordance with this study protocol, the ethical principles that have their origin in the Declaration of Helsinki (current version) as well as with ICH Guideline for Good Clinical Practice (ICH-E6 (R2)) and the relevant national laws and applicable regulatory requirements.
In particular, during the whole trial, she will keep the regular contact to all study parties for clinical and organizational questions. For the initiation, she has to review and design the study protocol, study manuals, patient information, and informed consent form; in addition, she will revise the eCRF and coordinate the training of the participating sites and therapists as well as provide working instructions. During the recruitment phase, she is responsible to revise the study documents, schedule the investigator meetings and presentations, participate in the meetings with project management at KKS, coordinate the training and supervision, communicate with and participate on meetings with DMC, progress reporting, generation and review of amendments, as well as supervise and evaluate SAE reports. During the follow up phase, she will coordinate the CBASP- and BA-CAR ratings as quality assurance and start preparation of the final reports. Concerning the analysis, she will prepare the final reports, presentations, and publications.
She is supported in all these tasks by Dr. Maike Hollandt, the **Clinical Project Management**, located at the University of Greifswald.

2.1.2. Further responsibilities

To successfully manage the trial, the KKS Greifswald, the Trial Steering Committee and the participating sites will cooperate intensively while being supported by the DMC and the SAB (see Fig. 1).

The **KKS Greifswald** will support the Clinical Project Management with the coordination of the study. In Detail, the KKS Greifswald is responsible for support concerning preparing and review of the clinical trial protocol and the informed consent form as well as the application to the ethics committees. Furthermore, the eCRF system will be managed by the KKS Greifswald. Monitoring will also be provided. In the recruitment and follow-up phase, the KKS prepares safety analyses and reports these to the DMC.

The **Statistician** Prof. Dr. Johannes Zimmermann is responsible for biometrics. In the initiation phase, he draws up the statistical analysis plan as well as standards for the data management and conceptualizes the eCRF and specific data formats. The main task is the blinded analysis of the data and the provision of the final statistical analysis. In all these tasks, he is supported by a coworker at pre- or post-doc level.

The **Leading Investigators** of each site are responsible for recruiting and conducting study treatments while the **Core Scientists** support recruitment and conduction of study treatments as well as trainings and supervision.

Further responsibilities will be specified in separate contracts between the participating parties.

2.2. Coordinating and Participating Sites

Table 1 lists all participating sites including the respective leading investigators and core scientists (main contact persons) as well as the addresses.

Table 1: participating clinical sites including the respective leading investigators and core scientists (main contact persons)

Charité, Universitätsmedizin Berlin Klinik für Psychiatrie und Psychotherapie (CCM) Charité – Universitätsmedizin Berlin Charitéplatz 1 10117 Berlin	Prof. Dr. Stephan Köhler stephan.koehler@charite.de Tel.: +49-30-450-617405 / Fax: +49-30-450-517903 M.Sc.-Psych. Henrike Völz henrike.voelz@charite.de Tel.: +49-30-450-617408
Medizinische Hochschule Hannover Klinik für Psychiatrie, Sozialpsychiatrie und Psychotherapie Medizinische Hochschule Hannover Carl-Neuberg-Straße 1 30625 Hannover	Prof. Dr. Kai Kahl kahl.kai@mh-hannover.de Tel.: +49-511-532-2495 / Fax.: +49-511-532-2415 Dr. Ivo Heitland heitland.ivo-aleksander@mh-hannover.de Tel.: +49-511-532-7367/ Fax.: +49-511-532-7375
Universität zu Lübeck Klinik für Psychiatrie und Psychotherapie Universität zu Lübeck Ratzeburger Allee 160 23562 Lübeck	PD Dr. Philipp Klein philipp.klein@uksh.de Tel.: +49-451-500-98871 Dr. med. Bartosz Zurowski bartosz.zurowski@uksh.de Tel: +49-451-500-98831
Universitätsklinikum Marburg Klinik für Psychiatrie und Psychotherapie	Prof. Dr. Tilo Kircher tilo.kircher@staff.uni-marburg.de

Rudolf-Bultmann-Straße 8 35039 Marburg	Tel.: +49-6421-58-65200 / Fax: +49-6421-58-65197 Dr. Ina Kluge ina.kluge@staff.uni-marburg.de Tel.: +49-6421-58-6219
Klinikum der Universität München Klinik für Psychiatrie und Psychotherapie Nußbaumstr. 7 80336 München	Prof. Dr. Frank Padberg frank.padberg@med.uni-muenchen.de Tel.: +49-89 4400-53358 / Fax: +49 89 4400-53930 Dr. Matthias Reinhard matthias.reinhard@med.uni-muenchen.de Tel.: +49-89 4400-55512
Universitätsklinikum Tübingen Allgemeine Psychiatrie und Psychotherapie mit Poliklinik Calwerstraße 14 72076 Tübingen	Prof. Dr. Andreas J. Fallgatter andreas.fallgatter@med.uni-tuebingen.de Tel.: +49-7071-29-84858 / Fax: +49-7071-29-5379 Prof. Dr. Rainald Mössner rainald.moessner@med.uni-tuebingen.de Tel.: +49-7071-29-4141
Universitätsklinikum Bonn Klinik und Poliklinik für Psychiatrie und Psychotherapie Venusberg-Campus 1, Gebäude 80/82 53127 Bonn	Prof. Dr. Alexandra Philipsen alexandra.philipsen@ukbonn.de Tel.: +49-228-287-15723 / Fax: +49 228-287-16097 Prof. Dr. Silke Lux silke.lux@ukbonn.de Tel.: +49-228-287-16368
Universitätsklinikum Jena Klinik und Poliklinik für Psychiatrie und Psychotherapie Philosophenweg 3 07743 Jena	Prof. Dr. Nils Opel nils.opel@med.uni-jena.de Tel.: +49 – 3641-9-390101/ Fax: +49-3641-9-390102 Prof. Dr. Martin Walter martin.walter@med.uni-jena.de Tel.: +49-3641-9390102

2.3. Financial support

The study is supported by the **German Research Foundation** within the Program **Clinical Trials**.

2.4. Signature and Consent statement

I have read this protocol and agree to conduct the study in accordance with the study protocol, the current version of the Declaration of Helsinki, ICH-GCP Guideline (International Conference on Harmonization - Good Clinical Practice) and applicable national laws and regulatory requirements. I also agree to handle all information concerning this study confidentially.

I will ensure that all personnel involved in the study under my direction will be informed about the contents of this study protocol and will receive all necessary instructions for performing the study according to the study protocol.

Principal Investigator (PI):

Prof. Dr. Eva-Lotta Brakemeier

21.10.2024

Date	Signature

I have read this protocol and agree to conduct the study in accordance with the study protocol, the current version of the Declaration of Helsinki, ICH-GCP Guideline (International Conference on Harmonization - Good Clinical Practice) and, applicable national laws and regulatory requirements. I also agree to handle all information concerning this study confidentially.
I will ensure that all personnel involved in the study under my direction will be informed about the contents of this study protocol and will receive all necessary instructions for performing the study according to the study protocol.

Charité – Universitätsmedizin Berlin

Prof. Dr. Stephan Köhler

16.10.2024 

Date Signature

M.Sc.-Psych. Henrike Völz

21.10.2024 

Date Signature

I have read this protocol and agree to conduct the study in accordance with the study protocol, the current version of the Declaration of Helsinki, ICH-GCP Guideline (International Conference on Harmonization - Good Clinical Practice) and, applicable national laws and regulatory requirements. I also agree to handle all information concerning this study confidentially.
I will ensure that all personnel involved in the study under my direction will be informed about the contents of this study protocol and will receive all necessary instructions for performing the study according to the study protocol.

Medizinische Hochschule Hannover

Prof. Dr. Kai Kahl

22.10.2024

Date Signature

Dr. Ivo Heitland

22.10.2024

Date Signature

I have read this protocol and agree to conduct the study in accordance with the study protocol, the current version of the Declaration of Helsinki, ICH-GCP Guideline (International Conference on Harmonization - Good Clinical Practice) and, applicable national laws and regulatory requirements. I also agree to handle all information concerning this study confidentially.
I will ensure that all personnel involved in the study under my direction will be informed about the contents of this study protocol and will receive all necessary instructions for performing the study according to the study protocol.

Universität zu Lübeck

PD Dr. Philipp Klein

17/10/2024 _____
Date Signature

Dr. Bartosz Zurowski

17.10.2024 _____
Date Signature

I have read this protocol and agree to conduct the study in accordance with the study protocol, the current version of the Declaration of Helsinki, ICH-GCP Guideline (International Conference on Harmonization – Good Clinical Practice) and, applicable national laws and regulatory requirements. I also agree to handle all information concerning this study confidentially.
I will ensure that all personnel involved in the study under my direction will be informed about the contents of this study protocol and will receive all necessary instructions for performing the study according to the study protocol.

Universitätsklinikum Marburg

Prof. Dr. Tilo Kircher

21.10.24 x

Date Signature Hr. Prof. Tilo Kircher

Dr. Ina Kluge

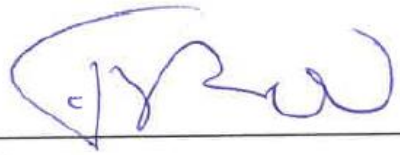
17.10.24

Date Signature Fr. Dr. Ina Kluge

I have read this protocol and agree to conduct the study in accordance with the study protocol, the current version of the Declaration of Helsinki, ICH-GCP Guideline (International Conference on Harmonization – Good Clinical Practice) and, applicable national laws and regulatory requirements. I also agree to handle all information concerning this study confidentially.
I will ensure that all personnel involved in the study under my direction will be informed about the contents of this study protocol and will receive all necessary instructions for performing the study according to the study protocol.

Klinikum der Universität München

Prof. Dr. Frank Padberg

2024-10-21 | 

Date | Signature

Dr. Matthias Reinhard

2024-10-21

Date | Signature

I have read this protocol and agree to conduct the study in accordance with the study protocol, the current version of the Declaration of Helsinki, ICH-GCP Guideline (International Conference on Harmonization – Good Clinical Practice) and, applicable national laws and regulatory requirements. I also agree to handle all information concerning this study confidentially.
I will ensure that all personnel involved in the study under my direction will be informed about the contents of this study protocol and will receive all necessary instructions for performing the study according to the study protocol.

Universitätsklinikum Tübingen

Prof. Dr. Andreas J. Fallgatter

16.10.2024 _____ _____

Date Signature

Prof. Dr. Rainald Mössner

17.10.2024 _____ _____

Date Signature

I have read this protocol and agree to conduct the study in accordance with the study protocol, the current version of the Declaration of Helsinki, ICH-GCP Guideline (International Conference on Harmonization – Good Clinical Practice) and, applicable national laws and regulatory requirements. I also agree to handle all information concerning this study confidentially.
I will ensure that all personnel involved in the study under my direction will be informed about the contents of this study protocol and will receive all necessary instructions for performing the study according to the study protocol.

Universitätsklinikum Bonn

Prof. Dr. Alexandra Philipsen

18.OKT.2024 _____

Date Signature

Prof. Dr. Silke Lux

22.10.24 _____

Date Signature

I have read this protocol and agree to conduct the study in accordance with the study protocol, the current version of the Declaration of Helsinki, ICH-GCP Guideline (International Conference on Harmonization – Good Clinical Practice) and, applicable national laws and regulatory requirements. I also agree to handle all information concerning this study confidentially.
I will ensure that all personnel involved in the study under my direction will be informed about the contents of this study protocol and will receive all necessary instructions for performing the study according to the study protocol.

Universitätsklinikum Jena

Prof. Dr. Nils Opel

21.10.2024

Date | Signature

Prof. Dr. Martin Walter

21.10.2024

Date | Signature

3. Scientific Background

Up to one third of depressed patients develop persistent depressive disorder (PDD) with an estimated lifetime prevalence between 3% and 6% (Angst et al., 2009; Murphy & Byrne, 2012). Given the high degree of suicidality, comorbidity, and non-response to outpatient treatments (Murphy & Byrne, 2012; Bschor et al., 2014; Murphy et al., 2017; Köhler et al., 2019), many PDD patients require hospitalization as guidelines recommend; accordingly, about half of all psychiatric inpatients with depression suffer from PDD (Härter et al., 2004; Hölzel et al., 2010; Bschor et al., 2014; DGPPN et al., 2015; Köhler et al., 2016). In Germany, about 70.000 PDD patients are currently treated as inpatients per year, causing an enormous economic burden of an estimated 1 billion € annually. Thus, they constitute one of the main cost drivers for depression care (Luppa et al., 2007). However, for these inpatients no evidence-based treatment exists (Köhler et al., 2016; Schefft et al., 2019). Despite an overall reduction in depression with long psychotherapeutic inpatient treatment (Keller et al., 2001), PDD inpatients reach lower response rates, report higher treatment dissatisfaction, and are more likely to relapse after discharge than acutely depressed inpatients (Härter et al., 2004; Keller et al., 2001). Since most inpatients are non-responders to standard treatments, new treatment-phase programs combining acute and continuation treatments are urgently needed to overcome treatment-resistance (TR) (Köhler et al., 2016; Schefft et al., 2019).

CBASP is the only psychotherapy specifically tailored for PDD (McCullough et al., 2014) demonstrating efficacy as outpatient treatment through a growing number of RCTs (Keller et al., 2000; Schramm et al., 2011; Wiersma et al., 2014; Michalak et al., 2015; Schramm et al., 2017; see Jobst et al., 2016 and Negt et al., 2016 for a review and meta-analysis). Thus, we modified CBASP as a manualized multimodal inpatient program for the severely ill PDD inpatients with TR (Brakemeier & Normann, 2012; Brakemeier, Guhn & Normann, 2021). Our pilot studies indicate very good feasibility and promising outcome (Brakemeier et al., 2011; Brakemeier et al., 2015; Sabaß et al., 2018; Guhn et al., 2019). Therefore, a randomized controlled trial is now mandatory for testing the superiority of the inpatient CBASP program vs. an evidence-based psychotherapy such as cognitive behavioral therapy (CBT), the 'gold standard' in depression treatment. We chose a specific version of CBT – behavioral activation (BA) (Kanter, 2009; Martell et al., 2015) – since BA is at least as effective as standard CBT in severely depressed patients (Cuijpers et al., 2007; Dimidjian et al., 2006; Spates et al., 2006; Shinohara et al., 2013; Richards et al., 2016) while being easier to train and to implement in inpatient settings (Snarski et al., 2011). In addition, we will address the important psychotherapy research question: what works for whom and why? (e.g., Norcross & Wampold, 2011).

Moderator analyses will examine whether child maltreatment (Bernstein & Fink, 1998; Nemeroff et al., 2003; Brakemeier et al., 2018) and methylation of exon IV of the BDNF gene (Frieling & Tadić, 2013; Tadić et al., 2014) have an impact on the differential efficacy of the treatments. DNA methylation of the BDNF exon IV promoter region as an epigenetic mechanism will be assessed at the beginning of treatment to predict changes of depressive symptoms and their treatment response. Epigenetic mechanisms are modulated by environmental stimuli and are adaptive to different disease stages (Menke und Binder, 2014). First evidence for epigenetic markers like BDNF as outcome predictor (in a pharmacotherapy depression trial) has been gathered (e.g., Frieling & Tadić, 2013; Lieb et al., 2018). DNA methylation of one specific CpG located in the promoter region of BDNF exon IV has repeatedly been shown to accurately predict non-response to monoaminergic antidepressant drugs. As BDNF has been implicated in neurobiological processes fundamental to successful psychotherapy (i.e., learning, memory, neural plasticity) it is reasonable to believe that

epigenetic (dys-)regulation of the BDNF gene might also play a role in response to psychotherapy and might therefore be useful as a prognostic marker. Apart from the BDNF system, (dys-)regulation of several genes have been proposed to be involved in neurobiological pathways underlying psychotherapeutic processes (e.g. Vinkers et al., 2021). Epigenome wide association studies as well as candidate gene studies are possible to detect new genetic loci involved (Vinkers et al., 2021). Machine learning algorithms integrating epigenome wide methylation data have been shown to be potent predictive tools for e.g. age acceleration ("epigenetic clocks") (e.g. Chaix et al., 2017). In a similar way, it is likely that algorithms can be trained to learn based on the epigenome which therapy will suit best the individual patient's needs. Thus, in our study, blood samples for epigenetic analyses will be drawn to assess potential biomarkers for CBASP/BA response.
Regarding mediator analyses, we will examine whether the differential efficacy of the treatments can be explained by treatment-specific changes in interpersonal problems (Horowitz et al., 2000; Jacobs & Scholl, 2005; Constantino et al., 2008; Klein et al., 2018) or activity levels (Kanter et al., 2007; Rosenbaum et al., 2015; Forbes, 2020). A follow-up survey 48 weeks after the end of the interventions is intended to provide valuable results regarding the long-term outcome of the treatments. Finally, we will conduct cost-benefit analyses to assess the economic implications of both interventions.
Thus, the novel aspects of this trial are 1) comparing the multimodal CBASP inpatient program with a strong active comparator within treatment-resistant PDD patients by 2) applying a treatment-phase program while investigating 3) moderators and 4) mediators of treatment effects to assist clinicians in guiding the choice between CBASP and BA for inpatients with PDD. Notably, 5) a cost-effectiveness perspective further addresses health-economic issues and will enhance the relevance and potential benefit of CBASP (and BA) for public health (Drummond, 2007). Therefore, this trial will provide valuable information concerning allocation of resources (inpatient, dayclinic, and outpatient treatment) and may be of interest to decision makers in healthcare policy. Many hospitals in German-speaking (like Switzerland and Austria) and other countries (like USA, Denmark and Canada) already have implemented CBASP concepts. Due to the relatively short interventions, dose, and duration of the treatment-phase program, it is comparable to clinical practice, being at the same time affordable (for example by the German Health Care System). Notably, even in other countries the short inpatient intervention followed by dayclinic and outpatient treatment could be implemented. However, additional evidence needs to be provided before the CBASP inpatient program for treatment-resistant PDD is established on a broader scale influencing clinical practice. Thus, the results of this study have the potential to relieve the burden of this very serious and cost-intensive disease while improving human health.

4. Rationale and Hypothesis

4.1. Rationale

About half of all psychiatric inpatients with depression suffer from persistent depressive disorder (PDD). Given their high degree of treatment-resistance, comorbidity, suicidality, and hospitalization rates, this patient group appears to be particularly difficult to treat and, from a health economic perspective, constitutes a major challenge. The Cognitive Behavioral Analysis System of Psychotherapy (CBASP) is the only psychotherapy specifically tailored for PDD. Originally developed as an outpatient treatment, we have modified CBASP for the severely ill PDD patients with TR as a multimodal inpatient concept. Our pilot studies indicate

very good feasibility and promising outcome. Therefore, a randomized controlled trial is now mandatory for testing the superiority of the inpatient CBASP program vs. the evidence-based Cognitive Behavioral Therapy (CBT), the 'gold standard' in depression treatment. Behavioral Activation (BA) was chosen as the control intervention because BA, as a specific variant of CBT, is at least as effective as standard CBT in severely depressed patients while being easier to train and implement in inpatient settings. Both therapies will be applied as a treatment-phase program (10-week inpatient/ dayclinic acute treatment followed by 6-week outpatient continuation group-treatment) in combination with standardized and guideline-based pharmacotherapy. The proposed prospective, multi-center, randomized study with 396 PDD patients with TR will therefore address the primary research question: Is the CBASP program more effective than the BA program in this patient group? Our hypothesis is that after 16 weeks of treatment, CBASP will show a significant superiority over BA in reducing depressive symptoms. In addition, we will address the important psychotherapy research question: what works for whom and why? Moderator analyses will examine whether child maltreatment and methylation of exon IV of the BDNF gene have an impact on the differential efficacy of the treatments. Regarding mediator analyses, we will examine whether the differential efficacy of the treatments can be explained by treatment-specific changes in interpersonal problems or activity levels. A follow-up survey 48 weeks after the end of the interventions will provide valuable results regarding the long-term outcome of the treatments.
Finally, the health economic potential of the interventions will be investigated through cost-benefit analyses in order to provide important information on the cost-effectiveness of implementation in routine care for health policy. Thus, the results of this study will have the potential to relieve the burden of this very serious and cost-intensive disorder while improving human health. In addition, moderator and mediator analyses may guide personalized treatment and enable therapists to more specifically address psychotherapeutic needs of individual PDD patients in the future.

4.2. Hypothesis

It is hypothesized that CBASP (being tailored for the burdened subgroup of TR PDD inpatients) is significantly more effective than BA (being tailored for depression in general) after 16 weeks of treatment-phase programs (overall 20 individual and 26 group therapy sessions).

5. Study Design

This prospective, multi-center, randomized study with 396 TR PDD patients will compare the two manual-based inpatient programs CBASP (Brakemeier & Normann, 2012; Brakemeier, Guhn & Normann, 2021) (as experimental intervention) and BA (Martell et al., 2015) (as control intervention).
To control group effects, we provide the treatment teams with precise study manuals for the CBASP- and BA-programs that describe all study treatments in detail. Since the risk of systematic errors is higher in inpatient psychotherapy studies than in outpatient studies due to more uncontrollable factors, we have done everything possible to minimize these uncontrollable factors, mainly by parallelization. Thus, the study manuals guarantee that both groups receive the same type, dose, and duration of study treatments, the same additional treatments, the same algorithm concerning medication, and the same dose of team training and supervision, etc. (see chapter 9). In addition, the study manuals clearly specify which additional treatments are allowed for study patients. Furthermore, important conditions

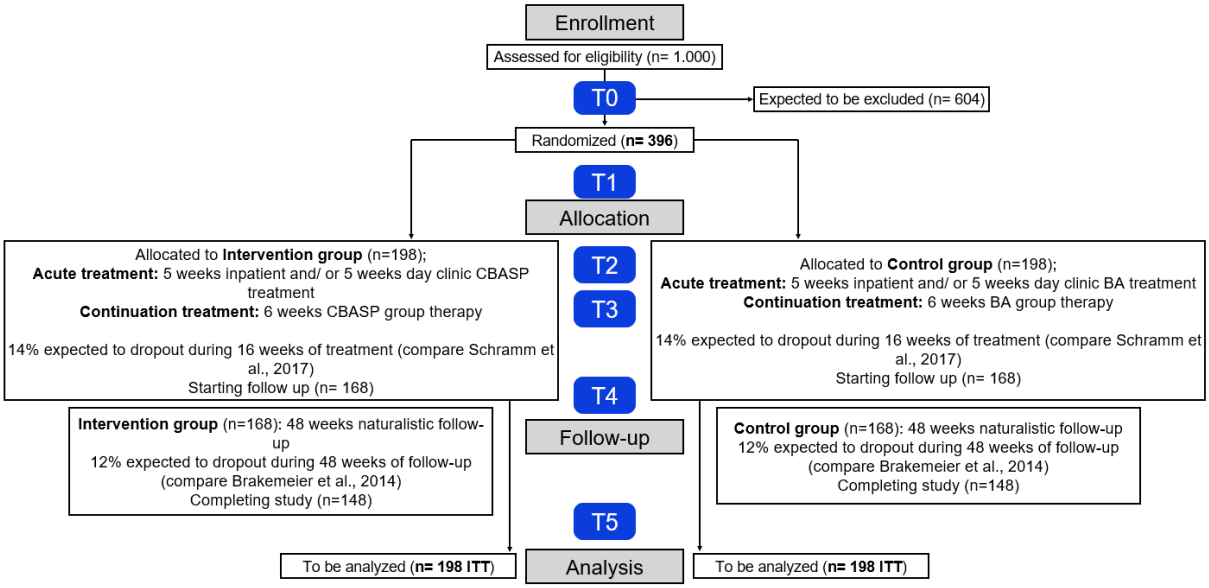
immanent in the inpatient setting also minimize confounding variables (such as same location and environment, same weather, same diet, same daily routine, same general hospital rules, same hospital climate, same chief physician, no or sparse interaction with family and friends, no work practice). In order to enable comparability of the participating sites and reduce a site effect, or a possible allegiance bias discriminating BA, the two interventions are carried out in each participating site on two separate specialized wards.
The sufficient sample size (N=396) and the recruitment sites in different regions of Germany will assure generalizability of results and representativeness of the sample. Furthermore, we kept exclusion criteria to a minimum (expecting a high rate of comorbidity) to even enhance generalizability of our findings. Inclusion/exclusion criteria are specified to yield a population of PDD patients with a high degree of TR (see 8.2 and 8.3).

Power calculation for the proposed sample size of N=396 is based on a simulation study as recommended for linear-mixed effects models (Gelman & Hill, 2007). Please note that this estimate already takes into account that we expect about 14% missing data at the primary endpoint (i.e., after 16 weeks), because the simulation study already included assumptions about missing data. Concerning expected dropout rates, based on the RCT trial by Schramm et al. (2017), where 3% of patients dropped out immediately after randomization, we expect that about 5% of patients to drop out of the study immediately after randomization (no treatment and follow-up), although all efforts will be made during the informed consent procedure to include only patients who are willing to accept both arms and to continue study visits until W64/T5 (even if they drop out of treatment). In addition, in our one-arm pilot study (Brakemeier et al., 2015), 92.9% of the patients (65 out of 70) were fully compliant with the CBASP inpatient regime. Since in BA the same dose and duration of psychotherapy is scheduled we expect about 90% compliance in the multicenter trial in both groups. Therefore, we expect 95% x 90% = 85.5% of randomized patients to have HDRS-24 non-missing in week 16. Moreover, in our CBASP pilot study (Brakemeier et al., 2015), we observed only 12.9% losses to 6-months follow-up and 14.3% to 12-months follow-up. Therefore, we expect 15% of those who start treatment to have HDRS-24 missing in week 64, leaving 95% x 85% = 80.8% of those randomized with non-missing HDRS-24 in week 64.
We anticipate that about 1.000 patients have to be screened in order to randomize 396 patients (40% informed consent). In comparable studies slightly higher rates are found: in our own inpatient RCT study with depressed patients having received Electroconvulsive Therapy (ECT; Brakemeier et al., 2014) 61% informed consent and the RCT of Keller et al. (2000) 85% informed consent. The reason for why we are more conservative is that in the Brakemeier et al. (2014) trial the depressive patients while having been randomized had already successfully responded to inpatient treatment and were randomized to maintenance therapy. In the Keller et al. (2000) study all treatments were outpatient. PDD patients with TR who report for inpatient admission may be more difficult to motivate to participate in this inpatient RCT due to the severity and chronicity of the disease.
Regarding internal validity, group effects, the comparability of the sites, a site effect, or a possible allegiance bias discriminating BA, we have taken many precautions, as described in the following. Randomization with stratification for severity of depression (HDRS-24; Hamilton, 1960) and study site will be performed with an allocation ratio of 1:1. Due to the nature of interventions, blinding of patients/therapists concerning the treatment program is impossible, but all assessments as well as data analysis will be blinded to treatment allocation. Notably, patients are blinded to the study hypothesis by the Informed Consent process, as patients are told in the patient information and educational discussions about the study that they will in any case receive one of two different scientifically based psychotherapy programs,

although it is unclear which of the two programs is more effective; one program focuses on coping with interpersonal problems, the other on building up activities that seem important for personal life (see Informed Consent Form). Similarly, the members of the treatment teams of each study ward are not informed about the study hypothesis; however, they are informed that it has not yet been scientifically clarified which therapy is more effective.
Measures to ensure blinding will include locating the raters separately from the study wards, instructing patients not to mention information that could reveal their allocation, and providing back-up raters in case of unintentional unblinding. All blinded raters (student assistants at each participating site) will be trained in all instruments. Concerning the main outcome variable, HDRS-24, raters will be certified by a central rating of three videotaped HDRS-24 interviews. Additionally, all raters will be trained and certified in the Diagnostic Interview for Mental Disorders (DIPS for DSM-5, German version; Margraf, Cwik, Pflug & Schneider, 2021) to ensure that a valid primary categorical diagnosis of PDD (300.4, 296.2x, 296.3x) is used as an inclusion criterion. Additionally, the adherence and competence of the psychotherapists with regard to the specific CBASP or BA techniques will be evaluated (measured with the observer-rated video-based CAR instruments). Since the patients will evaluate their subjective acceptance, satisfaction with and effectiveness of received treatments and the atmosphere of the ward etc. with the standardized questionnaire RevieW (Koy, 2019) every week of treatment, we will also consider these subjective evaluations in our analyses (see 6.2).

Study Flow Chart

Figure 2: Study Flow Chart



6. Outcome Measures

6.1. Primary Endpoint

The primary endpoint will be

- the change in HDRS-24 item score (Hamilton, 1960; Williams, 1988) from baseline to 16 weeks after randomization

The HDRS is considered being the "gold standard" as the most frequently used and well-validated clinician rated measure of depression severity (Carrozzino et al., 2020). As recommended by Carrozzino et al. (2020) we will use a semi-structured version of the 24 item version, including item definitions, anchor points and semi-structured interview questions. Each item is evaluated on a 3 to 5 level scale for each of which a short description is given. The time frame of the asked symptomatology applies to the last week before the interview. On average, the processing time is 15 minutes. The range of the HDRS-24 is from 0 to 75. It is not recommended to make a diagnosis of depression based on cut-off value because the HDRS is primarily designed to be sensitive to changes and is therefore more suitable for measuring changes in the course. Most of the relevant trials we refer to use HDRS-24 change as primary outcome. The endpoint was set at week 16 after admission on the respective psychotherapy wards, as CBASP is expected to show superiority over BA with a long duration and high dosage (see Cuijpers et al., 2010; Wiersma et al., 2014; Brakemeier et al., 2015; Schramm et al., 2017). HDRS-24 will be administered at each study visit, primary efficacy is computed from HDRS-24 interviews at screening (T0), week 1 (T1), 5 (T2), 10 (T3), 16 (T4), 64 (T5) by blinded observers being not otherwise involved.

6.2. Secondary Endpoints, Moderators and Mediators

Secondary endpoints will be the following questionnaires and interviews:

- HDRS-24 (see above), assessed every second week and at week 64
- IDS-SR (Rush et al., 2000), assessed every second week and every second month during follow-up
- Brief Symptom Inventory (BSI; Derogatis & Spencer, 1993), assessed at week pre, 1, 5, 10, 16, and 64
- Global Assessment of Functioning (GAF; Hall, 1995), assessed at week pre, 1, 5, 10, 16, and 64
- World Health Organization Quality of Life (WHOQoL; Angermeyer et al., 2000), assessed at week pre, 1, 5, 10, 16, and 64
- Response (50% decrease on HDRS-24 score in comparison to baseline), remission (HDRS-24 of 10 or less on the HDRS-24), relapse rates (defined as rehospitalization for symptomatic worsening and/or a combination of an increase in HAMD 24 from discharge of equal or greater than 10 points and a current HAMD 24 score of equal or greater than 18 points), and dropout, assessed at week 5, 10, 16, and 64 (relapse-rate only at week 16 and 64)
- Cost interview (Wagner et al., 2014) assessed at week pre, 16, and 64; through the cost interview, the direct medical costs (inpatient stays, doctor's visits, emergency treatment, etc.), the direct non-medical costs (informal help, delinquent behavior, etc. and the indirect costs (days of incapacity to work, disability, unemployment) are recorded. In addition, a distinction is made as to whether the costs are due to mental disorders versus physical illnesses.

In addition, the following other important psychological variables will be assessed as further endpoints at week pre, 1, 5, 10, 16, and 64:

- Beck's Depression Inventory (BDI-II; Hautzinger et al., 2006)
- Brief Resilience Scale (BRS; Smith et al., 2008)
- Dysfunctional Attitude Scale (DAS; Hautzinger et al., 2005)
- Euthymia Scale (ES; Carrozzino et al., 2019)

- Experience in Close Relationships Scale – Revised 8-item version (ECR-RD8; Ehrenthal et al., 2021)
- General Self-Efficacy Scale (GSE; Schwarzer & Jerusalem, 1995)
- Impact Message Inventory revised (IMI-R; Casper et al., 2000)
- Lübecker Questionnaire of Preoperational Thinking (LQPT; Kühnen et al., 2011)
- Measure of disorders of capacity as defined by the International Classification of Function (Mini-ICF; Linden & Baron, 2005)
- Mental Pain Questionnaire (MPQ; Fava et al., 2019)
- Personality Inventory for DSM-5 Brief Form Plus - Modified (PID5BF+ M; Kerber et al., 2022; Bach et al., 2020)
- Rejection Sensitivity Questionnaire (RSQ; Downey & Feldman, 1996; Staebler et al., 2011)
- Revised-Green Paranoid Thoughts Scale (R-GPTS; Freeman et al., 2019)
- Social Network Index (SNI; Cohen, 1997)
- UCLA Loneliness Scale (UCLA; Döring et al., 1993; Russell, 1996)
- Well-being Index (WHO-5; Krieger et al., 2014)

The main moderators (measured at baseline) are:

- Child maltreatment measured by Childhood Trauma Questionnaire (CTQ; Bernstein et al., 2003; Wingenfeld et al., 2010)
- Epigenetic (Brain-derived neurotrophic factor (BDNF) methylation)

The main mediators (measured at baseline and week 1, 2, 4, 6, 8, 10, 12, 14, 16, and 64) are:

- Interpersonal problems (Inventory of Interpersonal Problems-revised, IIP-32-R, 32-item version; Horowitz et al., 2000)
- Activities (Behavioral Activation Depression Scale, BADS; actimeter-measured step-counts)

Finally, the following instruments are also applied to measure other important constructs

- Therapeutic relationship (Working Alliance Inventory, WAI; Wilmers et al., 2008) measured at week 1, 2, 4, 5, 6, 8, 10, 12, 14, and 16)
- Subjective evaluation of important specific and unspecific working mechanisms of treatment (Review of last Week, RevieW; Koy, 2019; measured every week during the 16 weeks of treatment)

6.3. Further Endpoints

Safety will be assessed by monitoring adverse events, side effects and medication. (Severe) Adverse events (SAEs) and medication will be continuously monitored via a standardized questionnaire; negative effects including side effects of psychotherapy will be measured at wk. 5, 10, 16, and 64 with the SEPIPS (Side Effects of Psychological Interventions Process Scale; Herzog et al., in prep.). Additionally, the interview C-SSRS (Columbia-Suicide Severity Rating Scale, Posner et al., 2011), measured at baseline, and at weeks 5, 10, 16, and 64, will be used to record the severity of potential suicidal thoughts and actions. In addition to the main

measurement time points, the C-SSRS may be used voluntarily in any other study visit if the therapist deems it necessary for patient safety reasons.

7. Methods of Data collection

The investigators are responsible for the performance of the trial in accordance with GCP guidelines and the study protocol as well as the correct data entry to the corresponding electronic case report form (eCRF). The self-reported questionnaires are completed by the patient herself/himself using tablets or computers electronically from the clinic and are thus directly integrated into the eCRFs. The study staff also enters the results of the clinical interviews directly into the eCRFs. The blood sample (approximately 7 ml) will be taken at admission (no later than two workdays after admission). Blood samples will be stored at the study centers and then transported regularly to the central sample storage in the Hannover Unified Biobank (HUB). The blood will be evaluated in a study laboratory (Molecular Neuroscience laboratory at Hannover Medical School) regarding methylation of exon IV of the BDNF gene. Blood respectively DNA samples will be stored for further exploratory genomic and epigenomic studies examining BDNF as a moderator for the response of depressed patients to methods of psychotherapy.
All patients will receive an actimeter to measure the number of steps during the study.
The data of the patients are documented with the eCRF. It should be noted that patients are invited to the clinic for all study visits so that they always use the certified equipment and study staff are always available to help with any questions but could also receive a link to eCRF questionnaires via email if required. Personal presence to the study visits is preferred and will also contribute to a maximum good data quality. The data is entered directly into the eCRF via the web browser. As the system is a web application, a stable internet connection and an input device is required. Standardized input devices will be available to patients. Study assistants are trained in how to use the eCRF system and tutorial videos for all study personnel are available.
Furthermore, the study therapists should, if possible, record all individual sessions via video, but at least 6 sessions (including sound) by standard video cameras for 1) supervision/certification purposes, 2) conducting the CAR ratings (assessment of adherence and competence) and 3) research purposes in the field of psychotherapy process research. Standardized evaluation methods are used to assess which processes take place in the therapy sessions and how these processes are related to the therapy outcome. In addition, all HRSD Interviews will be video-recorded to enable standardized and blinded IMI ratings of patients, conducted by study assistants in each participating study site.

Selection of patients

The investigators will keep a record of all study candidates who were considered for enrollment including screening failures that were never enrolled. A screening log form will be filed in the ISF.

8. Study Population

8.1. Treatment groups

The study population consists of psychiatric inpatients with persistent depressive disorder who have been treatment-resistant. In total, the sufficiently large sample size (N=396)

recruited at participating sites in different regions of Germany (with a shared amount of patients) will assure generalizability and representativeness of results. Furthermore, we kept exclusion criteria to a minimum (expecting a high rate of comorbidity) to even enhance generalizability of our findings. Inclusion/exclusion criteria are specified to yield a population of PDD patients with a high degree of TR.

Patient recruitment

The screening of the patients will be performed in the participating study sites. The recruitment of patients is supported by advertising measures, which will be produced throughout the study period. For example, flyers will be sent and distributed to therapists in outpatient and inpatient practice and a study-website will provide information about the study and contact information for the individual study sites. If necessary, advertisements for the study will also be placed on other relevant external websites. It is expected that screening of 1.000 persons will result in 396 patients eligible for the study. The recruitment period is expected to last for 30 months.

8.2. Inclusion criteria

- Age range: 18-75 years
- Primary DSM-5 diagnosis of PDD (300.4, 296.2x, 296.3x)
- Total HDRS score (24-item version) ≥ 20 at screening visit
- TR: Treatment-resistance defined by the Antidepressant Treatment History Form – Short-Form (ATHF-SF; Sackeim et al., 2019) or medication intolerance or one psychotherapy (at least 25 sessions in the current episode conducted by a certified therapist)
- Sufficient knowledge of the German language
- Written informed consent

8.3. Exclusion criteria

- Bipolar I or II disorder, active substance use disorders (abstinence shorter than 6 months), schizophrenia spectrum and other psychotic disorders, or antisocial personality disorder (all according to DSM-5)
- Acute suicidality (HRSD item 3 > 2 or agreement with C-SSRS item 4 and/or item 5)
- Previous CBASP or BA treatment within the last year
- Inability to tolerate CBASP or BA (e.g., organic brain disorders, severe cognitive deficits)
- Inability to participate in dayclinic or continuation treatment
- Participation in another (psycho)therapeutic study of an interventional nature

8.4. Methods against bias

8.4.1. Randomization

Randomization with stratification for severity of depression and participating site with an allocation ratio of 1:1 will be performed by a blinded statistician. To ensure allocation concealment, only the leading investigator at each site will see the result of the allocation. This procedure is intended to minimize the bias due to allocation concealment. The randomization of an eligible patient can only take place if **all** inclusion criteria and **none** of the exclusion criteria are fulfilled.
The group assignment is based on random permuted blocks with random block sizes and stratification for severity of depression (binary) and participating site. Regarding the severity of depression, an HRSD-24 score of at least 27 points was chosen as the binary cut-off criterion, since in the study by Schramm et al. (2017) the mean value of the HRSD-24 scale at the beginning of the study was also 27 points. Stratified permuted blocks ensure balance between both treatment groups, the balance within each participating site, and balance of the major covariate (depression severity). The use of random block sizes ensures that the next randomization assignment cannot be guessed.

8.4.2. Blinding

Due to the nature of interventions, blinding of patients/therapists concerning the treatment is impossible. However, the patients/treatment team on the wards will be blinded regarding the primary study hypothesis (see 4.2) because the patients and the treatment teams will be told that it is not yet known which of the two psychotherapy programs is more effective in treating PDD patients with TR. In addition, the clinical raters (thus, all assessments) and the trial statistician (thus, the data analysis) will be blinded to treatment allocation during the analysis of the primary outcome. Ideally, the same clinical rater (student assistants at each participating site) will rate the patient at all measurement times. Procedures to ensure blinding will include locating the clinical raters separately from the study wards, instructing patients not to mention information that could reveal their allocation, and providing backup raters in case of unintentional unblinding. All blinded clinical raters will be trained in all instruments. Concerning HDRS-24, the raters are first trained through a three-hour (web-based) training session and then complete an evaluation of three standardized videotaped HDRS-24 interviews. Only if they have successfully completed these three ratings (which means that the difference is less than 3 points for each rating), they will be admitted as study raters. Strict concealment of randomization will be guaranteed to exclude selection bias (see 8.4.1). Since randomization of therapists is impossible, demographic and professional characteristics of therapists will be assessed (instrument: THAT; Klug et al., 2002).

8.4.3. Control of therapy allegiance

Therapy allegiance, i.e. treatment preference of the investigators or therapists, has been discussed as an important influencing factor for results in psychotherapy research (Luborsky et al., 1999; Munder et al., 2013; Robinson, Berman & Neimeyer, 1990). Thus, several procedures have been implemented to minimize the allegiance effect:

1. Several investigators have been involved in the design of this study who represent a “mix of therapy allegiances”.

2. The two interventions are carried out in all sites with the same lengths and duration.
3. The entire treatment team of each study ward will be trained and supervised either in BA or in CBASP by highly experienced CBASP/BA experts. Before study start, all wards of the participating sites will be trained (intensive training workshops, same amount for both arms) in one of the two concepts and fresh-up team trainings for both arms will be performed once a year. Furthermore, videotaped trainings are available for both arms, which can be used for fresh-up trainings if needed. The same amount of training and supervision for each study ward will be offered with the possibility that rather unexperienced BA wards receive more training/supervision inter alia by our BA experts. In addition, training on-site visits of the core team of less experienced sites on an experienced BA ward will be organized.

Experts in their respective fields are characterized by at least 5 years of experience. Experts are listed with contact details for every site.

8.4.4. Control of overlapping treatments

The following measures will be taken to prevent confounding of treatment conditions through the overlap of treatment methods:

- All study therapists are obligated to adhere to the therapeutic procedures and interventions described within the manuals. Additionally, we have implemented several measures to assess treatment adherence and competence: The study therapists should, if possible, record all individual sessions via video, but at least 6 sessions. We will randomly select one patient per study therapist, and for these cases, three therapy sessions – one from the initial, one from the middle, and one from the final treatment phase – will be rated. The ratings will be conducted by trained master's level students under the supervision of CBASP and BA experts. In addition, 5% of these videos will also be rated by BA and CBASP experts to assess inter-rater reliability. The competence and adherence ratings are based on scales used in previous studies for CBASP and BA, developed in line with the established Cognitive Therapy Scale (CTS; Weck et al., 2010), which measures psychotherapeutic competencies in cognitive therapy. Our adapted instruments, referred to as Competence and Adherence Ratings (CAR), are specific to BA (BA-CAR) and CBASP (CBASP-CAR). These scales evaluate psychotherapeutic skills, including the application of core techniques of BA and CBASP, the use of structural and stylistic strategies, the management of the therapeutical relationship, and the handling of session-specific problems. A minimum cut-off has been set to define sufficient therapist adherence, while competence is reflected by the overall score achieved (with higher scores reflecting greater competence). All videos will be rated using both the BA-CAR and CBASP-CAR rating scales, allowing us to compare the two therapeutic approaches in terms of core techniques and other psychotherapeutic competencies (as described above).
- The two interventions are carried out on two separate specialized wards. Each study therapist will be involved in only one of the two psychotherapy programs and will accordingly only perform one of the two psychotherapies.
- To evaluate therapist attitudes towards CBASP and BA, questionnaires will be applied.
- Possible influences through qualification differences of the therapists will be controlled as follows

- All therapists have completed professional training or are in their at least second training year (out of three) for certification as licensed psychotherapist or are in an advanced training stage as a medical specialist.
- All therapists have completed a comprehensive training (at least 12 UE) within the respective treatment approach. All therapists will conduct two pilot cases with at least 8 sessions, supervised for at least 3 sessions. Pilot cases could be study patients if previously approved by PI.
- Concerning their influence upon the efficacy of treatment, level of training and professional experience of the therapists will be collected and reviewed.

8.4.5. Control of confounding factors

- The influence of the trial site upon efficacy of the respective treatment approaches will be investigated as a separate factor.
- Patients will be asked not to engage in off-study psychosocial or psychiatric interventions during the 16 weeks of treatment period.

8.4.6. Control of measurement bias

- All clinical raters will have completed (web-based) training for rating HRSD and use of the DIPS interview.
- Guidelines for all rating scales are available.
- The interrater reliability will be determined on the basis of at least 3 recorded HRSD ratings.

9. Study Procedure

9.1. Study visit overview

The following Table 2 summarizes the proposed frequency and scope of trial visits including all instruments and the duration of post-trial follow-up, as well as the six main measurement time points (T), and 17 trial visits (V).
Deviations from the time structure of trial visits or the duration and implementation of the individual treatment phases must be approved by the principal investigator in advance (see also corresponding guidelines).

Table 2: Frequency and scope of trial visits

	pre-Screenir	Baseline	Inpatient				Dayclinic			Continuationphase			Naturalistic follow-up					
Main Measurement Timepoints (T)	Tpre	T0	T1			T2			T3			T4						T5
Trial Visits (V)	V1a	V1b-d	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11[1]	V12	V13	V14	V15	V16	V17[1]
Week	pre		1	2	4	5	6	8	10	12	14	16	24	32	40	48	56	64
Telephone screening for elegibility	x																	
Informed Consent		x																
Randomization[2]		x																
In-/Exclusion criteria		x																
Patients master data		x																
Patient preference		x																
ATHF / concomitant medication		x																
DIPS		x										x						x
SCID-5-PD		x										x						x
Primary Efficacy																		
HDRS-24[3]		x	X	x	x	X	x	x	X	x	x	X						x
Secondary endpoints																		
IDS-SR		x	x	x	x		x	x	x	x	x	x	x	x	x	x	x	x
BSI, GAF[3], WHOQoL		x	x			x			x			x						x
Cost Interview		x										x						x
Further endpoints																		
BDI-II, BRS, DAS, ECRRD8, ES, GSE, IMI-R[3], LQPT, MINI-ICF[3], MPQ, PID5BF+M, RSQ, R-GPTS, SNI, UCLA, WBI		x	x			x			x			x						x
Moderators of Change																		
CTQ		x																
BDNF methylation			x															
Mediators of Change																		
IIP-32-R, BADS, Step counts[8]		x	x	x	x		x	x	x	x	x	x						x
Side effects /(Serious) Adverse events																		
SAEs and medication			x	x	x	x	x	x	x	x	x	x						x
SEPIPS						x			x			x						x
CSSRS[3]		x	x			x			x			x						x
Therapeutical Relationship, Adherence- and Competence Rating, Subjective Evaluation of Important Domains, Therapist																		
WAI			x	x	x	x	x	x	x	x	x	x						
CBASP-CAR[3], BA-CAR[3]			x[6]															
ReviewW[3]			x	x x	x	x	x x	x x	x x	x x	x x	x						
THAT[7]			x															

Primary endpoint is marked red

1 Visit can be divided into smaller units and may take up to one week
2 Randomization will be performed between T0 and T1
3 blinded observer ratings, bold capital letters are primary efficacy
4 two crosses per cell because the questionnaire Review is done weekly
5 may be used voluntarily in any other visit if deemed necessary
6 one rating per patient randomly drawn out of a pool of at least 6 videos per patient
7 will be filled in by each active study therapist once certified
8 step counter will be given out to T0 and are collected at T4, for T5 step counter will be given out one week prior (week 63)

9.2. Visit 1

Visit 1 (T0) is divided into Visit 1a – 1d and takes place during the screening phase, before randomization. A screening guideline is provided for all study sites, which elaborates each Visit (1a – 1d). Individual adjustments (e.g. additional screening visits) could be made if needed, and the conditions are defined in the screening guideline.

9.3. Visit 2-5

- Visits 2-5 take place during the inpatient phase I
  - Visits 2 within the first two working days after admission (week 1)
  - Visits 3 and 4 at the end of weeks 2 and 4 of the inpatient treatment
  - Visit 5 at the last or penultimate day of the inpatient phase
- Conduction of the corresponding instruments (see Table 2)
- Visit 2 and 5 are main measuring points (T1 and T2)

9.4. Visit 6-8

- Visits 6-8 take place during the inpatient phase II / dayclinic phase

- Visits 6 and 7 at the end of weeks 6 and 8 of the inpatient phase II / dayclinic phase
- Visit 8 at the last or penultimate day of the inpatient phase II / dayclinic phase

– Conduction of the corresponding instruments (see Table 2)

– Visit 8 is a main measuring point (T3)

9.5. Visit 9-11

– Visits 9-11 take place during the continuation phase

- Visits 9 and 10 at the end of weeks 12 and 14 of the continuation treatment
- Visit 11 at the last or penultimate day of week 16 (last week of the continuation phase)

– Conduction of the corresponding instruments (see Table 2)

– Visit 16 is the main measuring point (T4, primary outcome)

9.6. Visit 12-17

– Visits 12-17 take place during the naturalistic follow-up.

- Visits 12-16 at the end of weeks 24, 32, 40, 48, and 56 of the naturalistic follow-up
- Visit 17 at the last or penultimate day of week 64 (last week of the naturalistic follow-up)

– Conduction of the corresponding instruments (see Table 2)

– Visit 17 is a main and the last measuring point (T5)

9.7. Conduction of the Interventional Arm (CBASP)

The CBASP program will follow a strict standardized treatment manual being based on (Brakemeier & Normann, 2012; Brakemeier, Guhn & Normann, 2021).
During the 5-week inpatient phase I and the 5-week inpatient phase II / dayclinic treatment the patient will receive the following CBASP treatments per week:

– 2 individual therapy sessions (duration: approx. 50 min per session)

– 2 group therapy sessions (duration: approx. 100 min per session)

– 1 nurse contact (therapeutic exchange with a nurse) (duration: approx. 25 min per contact)

– 1 exercise therapy (duration: approx. 75 min per therapy)

During the 6-week outpatient treatment the patient will receive the following CBASP treatment per week:

– 1 group therapy session (duration: approx. 100 min per session)

Six individual sessions per patient will be videotaped (including sound) for supervision purposes, for conducting the CAR ratings (assessment of adherence and competence) and for research purposes in the field of psychotherapy process research. Standardized evaluation methods are used to assess which processes take place in the therapy sessions and how these processes are related to the therapy outcome.

In addition, the following workshops and supervisions are conducted for the CBASP treatment team:

- one start-up site workshop before study start conducted for the entire treatment team by one of the CBASP experts
- one start-up expert workshop before study start (after the start-up site training workshop) by an international expert; duration 9 hours (12 UEs)
- fresh up training once a year conducted by one of the CBASP experts; duration 9 hours (12 UEs). Videotaped trainings are available and can be used for fresh up trainings if needed or for when team members are unable to attend training.
- weekly CBASP supervisions or intervisions by a site supervisor for individual therapists; duration approx. 60 minutes
- every second month CBASP team supervisions by external experts; duration approx. 120 minutes

If required, fresh up training workshop and CBASP team supervisions/intervisions can be combined.

9.8. Conduction of the Control Arm (BA)

The BA program will follow a strict standardized treatment manual being based on (Martell et al., 2015).
During the 5-week inpatient phase I and the 5-week inpatient phase II / dayclinic treatment the patient will receive the following BA treatments per week:

- 2 individual therapy sessions (duration: approx. 50 min per session)
- 2 group therapy sessions (duration: approx. 100 min per session)
- 1 nurse contact (therapeutic exchange with a nurse) (duration: approx. 25 min per contact)
- 1 exercise therapy (duration: approx. 75 min per therapy)

During the 6-week outpatient treatment the patient will receive the following BA treatment per week:

- 1 group therapy session (duration: approx. 100 min per session)

Six individual sessions per patient will be videotaped for supervision purposes, for conducting the CAR ratings (assessment of adherence and competence) and for research purposes in the field of psychotherapy process research. Standardized evaluation methods are used to assess which processes take place in the therapy sessions and how these processes are related to the therapy outcome.

In addition, the following workshops and supervisions are conducted for the BA treatment team:

- one start-up site workshop before study start conducted for the entire treatment team by one of the BA experts
- one start-up expert workshop before study start (after the start-up site training workshop) by an international expert; duration 9 hours (12 UEs)
- fresh up training once a year conducted by one of the BA experts; duration 9 hours (12 UEs). Videotaped trainings are available and can be used for fresh up trainings if needed or for when team members are unable to attend training.

- weekly BA supervisions or intervisions by a site supervisor for individual therapists; duration approx. 60 minutes
- every second month BA team supervisions by external experts; duration approx. 120 minutes

If required, fresh up training workshop and BA team supervisions/intervisions can be combined.

9.9. Concomitant Therapy

To control group effects, it is clearly defined which additional treatments/services are permitted and which are prohibited for study patients (see Table 3 and additional guidelines for concomitant therapy). With the permitted treatments/services, strict attention must be paid to ensuring that study patients in both treatment groups participate equally (parallelization).

Table 3: Permitted and prohibited treatments/services

	Permitted (if performed in parallel for both study groups)	**Prohibited**
Inpatient treatment phase I (5 weeks) **And** **Inpatient treatment phase II or dayclinic treatment (5 weeks)**	standardized physiotherapy group (up to 3/week)	Mindfulness-based groups offered by therapists
	standardized occupational therapy group (up to 3/week)	All further psychotherapeutic or non-psychotherapeutic group offers or individual sessions
	algorithm-based study medication*	
	Crisis talk	
	Only if absolutely necessary for daily structure and performed in parallel for both study groups	
	relaxation-group	
	mindfulness-based group	
	patient café	
	excursion	
	morning exercise	
	patient group	
	Social Counseling	
Outpatient treatment 6 weeks	algorithm-based study medication*	All further treatments by the clinic/ward
	If possible in these 6 weeks, outpatient psychotherapy should pause	

***Medication add-on treatment**

Most patients will be on medication at study entry due to the severity of illness. All patients will receive an optimized, algorithm-based antidepressant medication following the current S3-Guidelines on Unipolar Depression (DGPPN et al., 2015; Middleton et al., 2005). In case of nonresponse:

- 1st line dose escalation (if appropriate)
- 2nd line lithium augmentation
- 3rd line augmentation with 2nd generation antipsychotics or evidence-based combinations of antidepressants
- 4th line change of antidepressant.

Only the following psychopharmacological rescue medication may be prescribed during the course of the study:

- Zopiclone (on demand up to 7.5 mg/day orally) or Quetiapine (on demand up to a dose of 50 mg/day orally) for sleep disturbances.
- Promethazine (on demand up to 75 mg/day orally) or Quetiapine (on demand up to 50 mg/day orally) for agitation.

After discharge from inpatient setting or dayclinic, all patients will continue on their last medication, which may be further optimized according to the S3-Guideline (DGPPN et al., 2015) if needed during continuation treatment. Deviations from aforementioned medication specifications must be approved by the principal investigator in advance. Medication is documented in the eCRFs and will be treated as covariates in the final efficacy analysis.

9.10. Study Sites

The participating sites that were selected by the Coordinating Investigator have adequate staff and experience in treating overall 400 patients and in conducting clinical studies with the same or similar indications. The participating sites include experienced psychotherapists and physicians and supportive staff with adequate time, the targeted patient population and technical expertise to complete the protocol.

9.11. Treatment after end of study

After the end of the study treatment (i.e. after 16 weeks) a naturalistic follow-up takes place for 48 further weeks (12 months). During this time, due to the naturalistic character patients may receive any therapy, but CBASP patients should not receive BA therapy and BA patients should not receive CBASP therapy. After the end of the study (i.e. after the follow-up), patients can receive the other treatment if they are interested and indicated, whereby study staff will help to arrange appropriate CBASP or BA treatment places (inpatient or outpatient).

9.12. Study Schedule

Schedule

- Recruitment period (months): 30
- Study treatment per patient (days): 112 (16 weeks)
- Study duration per patient (days): 448 (64 weeks, incl. follow-up)
- First patient in to last patient out (months): 34 (without follow-up), 46 (incl. follow-up)
- Duration of the entire study (months): 58

End of the study is defined as “Last Patient Out” and database closure.

10. Add-on Studies

In the following, two add-on studies are described, which are used to investigate further mediators and mechanisms of change of the two treatment programs. After consenting to the main ChangePDD study, the patients are informed about these two add-on studies and can then decide whether they want to participate in one or both of the additional studies. Participation in these add-on studies is therefore not obligatory for the study patients but optional. Thus, the two studies are described separately. In order to get an overview of the design and the instruments when patients participate in both add-on studies in addition to ChangePDD, we have adapted Table 2 accordingly (see 10.3).

10.1. ChangePDD-EMA

In this add-on study, in addition to the questionnaire-based measurement of symptoms described above (see chapter 6), data on affect, interpersonal behavior, social context, and loneliness are collected using an EMA (Ecological Momentary Assessment) approach. Responsible for this add-on study are Prof. Dr. Stephan Köhler, Dr. Johannes Wolf and Prof. Dr. Eva-Lotta Brakemeier (PIs of this add-on study) as well as Dr. Anne Guhn, Prof. Dr. Johannes Zimmermann, Dr. Tim Kaiser, Prof. Dr. Philipp Sterzer. As already mentioned, participation in this supplementary study is optional and does not influence inclusion in the main ChangePDD study. The add-ons to the regular study design and data analysis are described below.

10.1.1. Theoretical motivation

Compared to healthy controls and patients with episodic depression, PDD patients report more hostile-submissive interpersonal styles (Bird et al., 2018). However, there has been less research on the “in-the moment assessment” of social experiences in patients in PDD with regard to dynamic interplay of affect, interpersonal behavior and social context. Ecological Momentary Assessment (EMA) provides an ecologically valid tool to monitor daily experiences and its influence on social interaction. Recent research indicates a close relationship between negative affective experiences during social interactions and the perceived effectiveness and enjoyment of those experiences at the end of the day (Geyer et al., 2018). In addition, a recent non-controlled CBASP study reports less loneliness after 10 weeks of inpatient CBASP (Reinhard et al., accepted). To what extent this is specific to CBASP or will also be a concomitant effect in BA warrants investigation.

The ChangePDD trial is particularly suitable to target the assessment of social interactions and behavioral activation in PDD patients as well as treatment change through therapeutic strategies that target both social interactions (CBASP) and mobility (BA). By the use of a

smartphone application, participants are asked daily short questions about their current mood, interpersonal strength, behavioral activation/avoidance, social stress, and feelings of loneliness. This will be done over the course of the *ChangePDD* trial starting one week before admission to the ward and ending one week *after* the end of the outpatient treatment (see figure 5).

10.1.2. ChangePDD-EMA study design

In addition to data collection of the main mediators described above (see 6.2: IIP-32-R, BADS and actimeter-measured step count) collected during the treatment phase within ChangePDD (see Table 2), this add-on study will collect EMA data during three phases: 1) 1 week pre-treatment, 2) 16 weeks of ChangePDD treatment, 3) one week post-treatment (total 18 weeks of EMA data collection). During the pre- and post-treatment weeks, 5 assessments per day are conducted and during the main study phase only one assessment per day is conducted (see Figure 5).

Figure 5: Study Design ChangePDD-EMA

Patients will be informed about this add-on study ChangePDD-EMA during study visit 1, where they will sign the informed consent.

The assessment will be conducted via the app “Avicenna Research” (formerly: “Ethica”). The app is DSGVO-compliant. The encryption matches a standard in the industry according to the producers. There will be a strict anonymization of the data with a clear division between personal data (meta data; accessible only by personnel for technical purposes) and study data (anonymous; accessible only by scientists). Participants are able to withdraw their consent at any point. At no point in time will assessed data be passed on to third parties. The servers on which the data is stored are located in Canada. A detailed description of the data protection concept can be found on the provider’s website: https://avicennaresearch.com/legal#privacy-policy. Several scientific EMA-studies have been conducted via this program worldwide and in Europe.
Furthermore, the app is compatible with Android and Apple and will be installed on the patients’ smartphone after their informed consent. After completing the study, it will be deleted.

10.1.3. ChangePDD-EMA data assessment and analysis

The Interpersonal-Activation-Diary (IAD) was developed following Zimmermann et al. (2019) for this add-on study and consists of 23 items (see Table 4). These domains, which include

interpersonal strength, behavioural activation/avoidance, social stress, and loneliness are hypothesized to be mechanisms of change especially of CBASP (interpersonal strength, social stress, loneliness) and of BA (behavioural activation/avoidance).

During the pre- and post-treatment weeks there will be 5 times daily request for data entry between 10 a.m. and 8 p.m.

- First to fourth survey

a) 1 item on valence: My mood is… Response format: visual analogue scale with the poles very bad - very good)

b) 1 item on arousal: I feel… Response format: visual analogue scale with the poles passive - active)

c) 1 item on social context: Who are you with right now? Response options: I am alone, I am with my partner, I am with a family member, a friend or acquaintance, my colleagues, strangers (e.g. public transportation etc.)

d) How do you feel in this situation? Response format: visual analogue scale with the poles disconnected - connected)

- The last (5th) survey (8 p.m.): IAD + (+ = plus three items).

During the ChangePDD treatment phase the assessment will be once a day in the evening (e.g. 8 p.m.) containing the IAD.

Table 4: Item overview of the Interpersonal-Activation- Diary (IAD)

No.	Construct	Item*
	Interpersonal Strength	
1	„Connect“	I liked being with other people.
2	“Engage”	I was more outgoing, in order to get in touch with others.
3	“Lead”	I was able to ask other people for what I wanted.
4	“Direct”	I could fend for myself.
5	“Balance”	I was able to say “no” to others.
6	“Restrain”	I was able to listen and think before acting in relationships.
7	“Cooperate”	I was cooperative.
8	“Consider”	I felt enriched when I was able to help others.
	Activation-Avoidance	
1	Activation 1	I was an active person and achieved the goals I set for myself.
2	Activation 2	I made good decisions regarding which activities I partake in and which situations I seek out.
3	Activation 3	I did many and different activities.

4	Activation 4	I am content with the kind and number of activities I did.
5	Activation 5	I did things I enjoy.
6	Avoidance 1	I was mainly focused on avoiding uncomfortable things or fleeing from them.
7	Avoidance 2	There were things to do, which I did not complete.
8	Avoidance 3	I spent a lot of my time thinking about my problems again and again.
	Social Stress	
1	Social Stress	I was ignored, dismissed or rejected by others.
2	Social Stress	I was let down by a person close to me.
3	Social Stress	I was accused, criticized or talked down by someone.
4	Social Stress	I was used or betrayed by someone.
	Loneliness	
1	Loneliness	I was alone or had little social contacts.
2	Loneliness	I felt lonely today.
3	Loneliness	I felt excluded today.

*Note: eight items each on interpersonal strength and behavioral activation and avoidance four items on social stress (modified according to Zimmermann et al., 2019) with the addition of another item on loneliness from the Personality Dynamics Diary (PDD; Zimmermann et al., 2019) as well as two items on loneliness from the Psychological Item Pool for Corona Outbreak (PIPCO; Buecker et al., 2020).

Data Analysis
All data assessed in the context of the ChangePDD-EMA Add-on study will be analyzed using Dynamic Structural Equation Models (Asparouhov et al., 2018).

10.2. Effort Task

In addition to the goals of the ChangePDD study, in this add-on study moderators and mediators of change of BA are examined. These mediators and moderators will be assessed by means of combining a behavioral effort task with computational modelling, allowing us to estimate mechanisms underlying depressive symptoms and processes assumed to lead to change due to BA. The task and design could also allow us to identify predictors of response to BA on an individual patient level. Dr. Isabel Berwian (PI of this add on study), Prof. Henrik Walter, Prof. Quentin Huys and Prof. Eva-Lotta Brakemeier are responsible for this add-on study. As already mentioned, participation in this supplementary study is optional and does not influence inclusion in the main ChangePDD study.

10.2.1. Theoretical motivation and hypotheses

Patients with depression show reduced engagement in rewarding activities (APA, 2013). The decision to engage in rewarding activities (e.g. going out, meeting friends) compared to "depressive" behaviors (staying in bed) can be viewed as a trade-off between the anticipated reward and the anticipated effort for each behaviour (Berwian et al., 2020). The reduction in rewarding activities seen in depression might hence result from decreased anticipated reward

or from increased anticipated effort. Behavioral Activation (BA), a widely disseminated first-line therapy for depression (Lewinsohn, 1974; Nagy et al., 2020) contains component interventions that aim to directly address these aspects: planning, scheduling and monitoring of rewarding activities. The aim of planning is to ensure activities are realistic and achievable, thereby reducing the probability that effort will be spent without achieving a goal. The aim of scheduling rewarding activities is to ensure rewards are experienced. Finally, monitoring one's responses and feelings after rewarding activities helps to compare it to earlier expectation of effort and reward. The underlying assumption is that the experience of successful planning and rewarding activities re-establish reward and effort expectations.

These theoretical assumptions lead to the following two core hypotheses:

A) Experience of reward or effort moderates and predicts response to BA.
B) Anticipation of effort or reward is a mediator of this response.

As a secondary hypothesis, we suggest:

C) The above effects are stronger in patients receiving BA compared to patients receiving CBASP

10.2.2. Task and computational model

We propose to employ an online physical effort for reward task to mimic decisions and behavior of effort and reward.

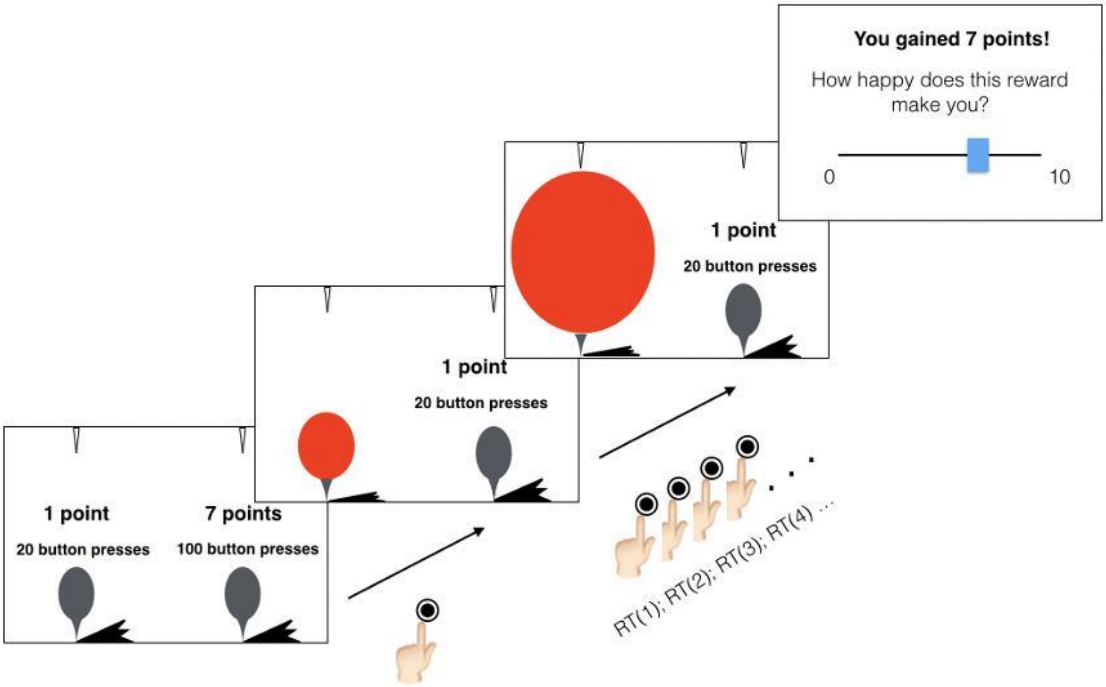
Task: The task is illustrated in Figure 5. Participants perform the task on a computer. On each trial, patients need to decide between investing little effort (few button presses) for a small reward or more effort (more button presses) for a larger reward. Patients need to indicate their decision with the first button press within 4 seconds and afterwards have 40 seconds to execute their effortful behavior allowing to measure effort experience. On a subset of trials, participants are asked to rate their momentary happiness which we use as a proxy to assess reward experience. The task duration is around 20 min. The task is written in javascript and can hence be run in any modern web browser. The data is saved on a GDPR-compliant cloud server within the EU (Google Firebase). Data will be pseudonymized throughout.

Analysis: To disentangle and quantify anticipation and experience separately for effort and reward we employ a generative computational model that captures the entire decision-making process. The model computes the values of a high effort/reward and a low effort/reward option including parameters relating to the effort and reward sensitivity implemented as a trade-off between necessary effort and the resulting reward (anticipation), the vigour used to execute the effortful behavior and the reaction to the reward (experience). The computed values are fed into a softmax function to determine the probability of making a high effort/reward choice (Niv et al., 2007; Huys et al. 2013; Hauser et al., 2017; Berwian et al., 2020).

In our previous work (Berwian et al., 2020), we could show with the application of a computational model to the data collected by means of an earlier version of the task, that remitted, previously depressed, patients invested less effort for reward due to increased effort anticipation and that longer decision times prior to discontinuation (captured by larger boundaries in a drift-diffusion model) predicted later relapse better than chance in a validation sample. Hence, the task is established, could be used to disentangle effort anticipation and experience in a patient sample and provided robust effects. Based on our

experience, we optimized the task as described above and established its validity by means of pilot data from healthy controls.
Analyses will be pre-registered. Moderation and mediation will be analyzed with linear mixed models with covariates x time x group interactions and mediation with dynamic panel models as outlined in the study protocol. Prediction will be examined using logistic regression in combination with an elastic net. The data will be split in advance into a training and validation sample.

Figure 5: Physical effort for reward task



10.2.3 Study design

The study design of the ChangePDD study is already established and depicted in Table 2. The additional task will be conducted at trial visits V2, V5, and V11 (see Table 2 add-on). Data collected at V2 allows us to test hypothesis 1, while data collected at V5 and V11 allows us to assess hypothesis 2.

10.3. Study design and instruments supplemented by add-on studies

In order to get an overview of the design and the instruments when patients participate in both add-on studies in addition to ChangePDD, we have adapted Table 2 accordingly.

Table 2 add-on: Frequency and scope of trial visits of ChangePDD and the two add-on studies

	pre-Screenir	Baseline	Inpatient				Dayclinic			Continuationphase			Naturalistic follow-up					
Main Measurement Timepoints (T)	Tpre	T0	T1			T2			T3			T4						T5
Trial Visits (V)	V1a	V1b-d	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11[1]	V12	V13	V14	V15	V16	V17[1]
Week	pre		1	2	4	5	6	8	10	12	14	16	24	32	40	48	56	64
Telephone screening for elegibility	x																	
Informed Consent		x																
Randomization[2]		x																
In-/Exclusion criteria		x																
Patients master data		x																
Patient preference		x																
ATHF / concomitant medication		x																
DIPS		x										x						x
SCID-5-PD		x										x						x
Primary Efficacy																		
HDRS-24[3]		x	X	x	x	X	x	x	X	x	x	X						x
Secondary endpoints																		
IDS-SR		x	x	x	x		x	x	x	x	x	x	x	x	x	x	x	x
BSI, GAF[3], WHOQoL		x	x			x			x			x						x
Cost Interview		x										x						x
Further endpoints																		
BDI-II, BRS, DAS, ECRRD8, ES, GSE, IMI-R[3], LQPT, MINI-ICF[3], MPQ, PID5BF+M, RSQ, R-GPTS, SNI, UCLA, WBI		x	x			x			x			x						x
Moderators of Change																		
CTQ		x																
BDNF methylation			x															
Mediators of Change																		
IIP-32-R, BADS, Step counts[8]		x	x	x	x		x	x	x	x	x	x						x
Add-on Study Effort Task			x			x						x						
Add-on Study EMA IAD * +		x	x	x	x	x	x	x	x	x	x	xx						
Add-on Study EMA social context, valence & arousal*		x										xx						
Side effects /(Serious) Adverse events																		
SAEs and medication			x	x	x	x	x	x	x	x	x	x						x
SEPIPS						x			x			x						x
CSSRS[5]		x	x			x			x			x						x
Therapeutical Relationship, Adherence- and Competence Rating, Subjective Evaluation of Important Domains, Therapist																		
WAI			x	x	x	x	x	x	x	x	x	x						
CBASP-CAR[3], BA-CAR[3]			x[6]															
ReviewW[3]			x	x x	x	x	x x	x x	x x	x x	x x	x						
THAT[7]			x															

Primary endpoint is marked red

1 Visit can be divided into smaller units and may take up to one week

2 Randomization will be performed between T0 and T1

3 blinded observer ratings, bold capital letters are primary efficacy

4 two crosses per cell because the questionnaire Review is done weekly

5 may be used voluntarily in any other visit if deemed necessary

6 one rating per patient randomly drawn out of a pool of at least 6 videos per patient

7 will be filled in by each active study therapist once certified

8 step counter will be given out to T0 and are collected at T4, for T5 step counter will be given out one week prior (week 63)

* IAD and social context & valence & arousal items will be done five times/day for one week before admission and in week 17

\+ IAD will be done once daily from week 1 to week 16 and will include three additional items at pre and post treatment measurements

11. Safety

11.1. Adverse reactions

Adverse Event (AE) is defined as any disadvantageous incident that occurs a person receiving either psychotherapeutic intervention, regardless of possible associations with the treatment received.

The following AES are defined for the study ChangePDD:

- Exacerbation of symptoms, e.g., generalization of symptoms
- Appearance of new symptoms
- Appearance of passive suicidal thoughts
- Appearance of active suicidal plans or intentions

- Occurrence of problems in the patient-therapist relation
- Further disadvantageous incidents as assessed by the therapist

Adverse Treatment Reaction (ATR) is defined as any AE due to a received treatment. The decision on the causality of AEs is made by the therapists and is supervised and controlled by the PI and Co-PIs and the DMC.

Serious Adverse Events (SAE) and Serious Adverse Treatment Reactions (SATR) are defined as an AE or ATR resulting in:

- Death
- Life-threatening event, e.g. suicidal attempt
- An incident requiring hospitalization
- An incident leading to significant or permanent disability or invalidity.

(S)AEs and (S)ATRs are documented after each study treatment session (see 9.7 and 9.8) using an Adverse Event eCRF. In the eCRF, the corresponding therapist is asked to describe any adverse event, its duration (start/end date), intensity (mild, moderate, severe), assessment of causality (treatment related, probably related, unlikely related, not related, not assessable), the actions taken and the outcome of the action taken. In addition, the corresponding therapist is asked to assess whether the documented AEs and ATRs are judged serious (SAE, SATR).
In case of changing the individual therapists, the reasons for this change are documented in a separate form.
Adverse Event documentation is monitored during the study as part of the regulatory Monitoring conducted by the KKS Greifswald.
SAEs and SATRs must be reported electronically (via e-mail) to the PI and the KKS Greifswald immediately within 24 hrs using a Serious Adverse Event report form that provides further details on the incident.
Patients who withdraw from study interventions due to one or more of the above mentioned reasons will be followed up in accordance with good clinical practice until a solution is found or the event is no longer considered clinically significant.

11.2. Risk-benefit-assessment

11.2.1. Potential risks

As all patients are treatment-resistant and there is no placebo group, ethical concerns seem limited. Study participants will be treated with methods for which efficacy has been demonstrated in prior studies in severely depressed patients. The in/exclusion criteria were chosen to minimize the risks to patients.
However, in any psychotherapeutic treatment, there can be a temporary burden of actively dealing with topics discussed in the therapy sessions and possibly avoided so far. Under certain circumstances this can lead to the occurrence or increase of suicidal tendencies (suicidal thoughts or plans). Patients are regularly questioned on the subject of suicidal thoughts; in addition, they are asked to contact the study staff or appropriate emergency services at any time if they have suicidal thoughts.

Completing the questionnaires and conducting the interviews throughout the study (especially at the beginning) can also be potentially stressful for patients.
Patients are asked to immediately report any deterioration in their health status to the study staff, regardless of whether it is related to the scientific study. During the inpatient stay, patients can visit therapists from their treatment team at any time and during the dayclinic phase they can contact study staff (contact details are provided on the study information sheet). If stress becomes too great, patients can stop filling out questionnaires, conducting interviews or even participating in the entire study at any time without experiencing any disadvantages. If the study is discontinued, the patients will continue to be treated in the clinic as a 'non-study patient' according to the indication.
During the clinical trial, patients are also given a one-time blood sample (approx. 7 ml). The taking of a blood sample is usually associated with a very low risk. There may be slight pain at the puncture site or bruising, which may be visible for a few days. In extremely rare cases, a blood clot may form (thrombosis), a localised inflammation or infection may occur at the puncture site, or permanent damage to blood vessels or nerves may occur.
The DMC will monitor safety issues every 6 to 12 months. The informed consent process will be carefully conducted.

11.2.2. Potential benefit

In this study, two psychotherapy programs (CBASP and BA) are examined with regard to their effectiveness in treating PDD with TR. It is known that both therapies have a positive influence on PDD. Whether one of the two therapies is better than the other in this indication is to be found out with this study. By participating, the study patients generally make a valuable scientific and health policy contribution to improving inpatient psychotherapy concepts in the short and long term.
The following concrete advantages and opportunities may also result from participation in the study for study-patients:

- Shortening of the waiting time until admission to the clinic
- Valuable and comprehensive diagnostics of the individual problems during the entire treatment
- An intensive psychotherapeutic inpatient and dayclinic depression treatment
- Participation in an outpatient group therapy after discharge to maintain the success and to prevent relapse
- Being part of a larger scientific study with close supervision by trained staff who are always available to patients

The overall results of this scientific study should contribute to finding an effective treatment for the group of PDD patients with treatment-resistance and increase the allocation of the patient to the individually more suitable therapy approach.
With regard to the health policy perspective, the following potential benefits should be pointed out: Considering the seriousness of the disease with its high risks for suicidality, low response to standard treatments as well as the enormous economic burden of an estimated 1 billion € annually in Germany, new evidence-based treatment programs are urgently needed to overcome TR and severely improve the current treatment of patients with PDD. The results provided by this study then have the potential to enable the establishment of the inpatient

CBASP program in Germany (as well as other countries) and thereby vastly improving the current treatment of this serious disease.

11.2.3. Conclusion

In view of the limited ethical concerns and potential risks mentioned and the continuous monitoring of safety issues, the overall potential risks in conducting the study appear to be low. Therefore, the described benefits of conducting the study, which have the potential to provide the results needed to significantly improve the current treatment of severe PDD with treatment-resistance, will outweigh the costs and potential risks.

11.3. Discontinuation criteria

11.3.1. Premature discontinuation of a patient

In accordance with the Declaration of Helsinki, the patient's participation in the study is voluntary and each patient may withdraw from the study at any time without giving reasons for this decision. The decision to withdraw from the study treatment must be without any prejudice for the patient.
Study treatment of a patient may be terminated by the investigator for one or more of the following reasons:

- Active suicidality
- Physical health of the patient is a risk due to clinical judgement
- Occurrence of an AE/SAE (Averse Event/Serious Adverse Event) with therapeutic implications
- A newly emerging exclusion criterion
- Withdrawn of the informed consent
- Non-compliance with the study protocol

If the investigator terminates the treatment of the patient prematurely, he or she has to inform the patient about the decision and has to record the primary reason for withdrawal in the patient file and to document the end of treatment in the eCRF. If the patient caused the premature withdrawal the data collected before termination may be used if the patient agrees and an informed consent for follow up is signed by the patient.

11.3.2. Premature discontinuation of the study

Single site
If a Leading Investigator has ethical concerns because of the performance at one of the sites, the Coordinating Investigator (PI) and the Co-PIs must be informed immediately.
The Coordinating Investigator together with the KKS Greifswald are authorized to discontinue this study at any time in any single site. Possible reasons for termination of the site could be but are not limited to:

- Unsatisfactory enrollment with respect to quantity or quality
- Inaccurate or incomplete data collection

- Unexpected accumulation of safety issues
- Major failure to adhere to the study protocol

Study as a whole
The Coordinating Investigator together with the KKS Greifswald have the right to terminate this clinical study as a whole at any time. Possible reasons for termination of the study could be but are not limited to:

- Unexpected accumulation of safety issues
- Change of risk-benefit considerations

A premature discontinuation of a single site or of the study as a whole must be documented adequately with reasons being stated and information must be conveyed according to national requirements (e.g. Ethics Committee).

11.4. Data Monitoring Committee (DMC)

A Data Monitoring Commitee (DMC) has been established for this study consisting of one psychologist (Prof. Dr. Matthias Berking), one psychiatrist (Prof. Dr. Stefan Röpke), and one biostatistician (Prof. Dr. Steffen Nestler) – all highly experienced researchers in the field of clinical trials. The function of the DMC is to monitor the course and progress of the study against the predefined milestones and – if necessary – to give recommendations to the study administration for discontinuation, modification, or continuation of the study. The underlying principles for the DMC are ethical and safety aspects for the patients. It is the task of the DMC to examine whether the conducting of the study is still ethically justifiable, whether security of the patients is ensured, and whether the process of the study is acceptable. For this, the DMC is informed about the adherence to the protocol, patient recruitment, and the observed adverse events. The DMC will meet regularly, but at least three times:

1) 6 months after "first patient in"
2) 18 months after "first patient in" an
3) 30 months after "first patient in", which should correspond to "last patient in" according to the study plan.

The outcome of the meetings is communicated to the Trial Steering Committee and the Leading Investigators of each site so that any administrative action required can be implemented.
In addition, Prof. Dr. Pim Cuijpers, Prof. Dr. Giovanni Fava, and Prof. Dr. Martin Hautzinger constitute the international Scientific Advisory Board (SAB). Due to their excellent expertise in conducting and analyzing clinical trials, they have been invited for providing independent advice and consulting regarding scientific, ethical, and data security issues, the dissemination process and external developments that are relevant to the progress and impact of the project.

12. Ethical and regulatory aspects

12.1. Laws and regulations

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human patients. The study will be conducted in compliance with the guidelines of GCP and the applicable national laws and regulations (Berufsordnung der Ärzte und Psychotherapeuten) to assure that the rights, safety, and well-being of the participating patients are protected in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

12.2. Independent ethics committee

The study will only be started after consultation with the responsible ethics committee and only if there are no ethical concerns. The principal investigator (Prof. Dr. Brakemeier) is responsible for submitting the application to the Ethics Committee.

12.3. Changes to the study protocol

After the commencement of the clinical study, the Coordinating Investigator may amend the protocol. If those amendments are substantial and are likely to have an impact on the safety of the study patients or to change the interpretation of the scientific documents in support of the conduct of the study, or if they are otherwise significant, the Coordinating Investigator shall notify the involved ethics committees.
If the opinion of the Ethics Committee is favourable the Coordinating Investigator shall proceed to conduct the clinical study following the amended protocol.
Amendments will be signed by all signatories of the protocol. All investigators will acknowledge the receipt and confirm by their signature on the amendment that they will adhere to the amendment. A copy of the signature page will be filed in the Investigator Study the original will be filed in the Trial Master File.

12.4. Informed consent and insurance

A patient can only be included to the study if he/she has given his/her consent. A physician/therapist has to inform the patient verbally and in written form about the nature, meaning and scope of the study in an appropriate and understandable manner. The patient must have had sufficient time to make the decision. At the same time, with the consent, he/she must have declared that he/she agreed to the data being recorded as part of the study. The patient is informed that he/she can withdraw his/her consent at any time and without giving reasons without incurring disadvantages. If new information emerges during the course of the study that could influence the patient's willingness to participate, the Informed Consent Form will be changed accordingly. The patient is informed of the changes by a physician/therapist. Subsequently (assuming sufficient time to consider), the consent of the investigating physician/therapist and the patient must be signed again. An original of the patient's written information and consent is given to the patient. A second original is kept safe at the study site in the Investigator Site File (ISF).
During the study, no additional invasive or stressful examinations are carried out. The course of the study corresponds to the clinical routine. There are no study-related risks for the patient. Accordingly, it is not planned to take out subject insurance. An accident insurance is taken out for all patients for their dayclinic visits and the subsequent follow-up visits.

12.5. Data safety

The provisions of the data protection laws (EU-DSGVO) are observed. It is ensured that all examination data are pseudonymized adequately in accordance with the data protection regulations before scientific exploitation. An assignment of the personal data to the study data is only possible by the locally responsible study physician/therapist.
The study management (Prof. Dr. Eva-Lotta Brakemeier) receives the pseudonymized study data only for the purpose of scientifically evaluating the observational study. Exceptions to this are the video-based data of psychotherapies, which are used as described for supervision purposes, the CAR Ratings and research (concerning psychotherapy and depression research).

13. Statistics

13.1. Sample size

Analysis populations

The Intent-to-treat (ITT) population will be defined as all patients randomized, regardless of whether they actually received treatment.
The Per Protocol (PP) population will be a subgroup of the ITT population comprising all patients who started the treatment assigned to them by randomization and who received a therapy dosage of at least ten sessions of individual therapy and ten sessions of group therapy.

Safety population

The safety population will be defined as all patients randomized who received at least one session of CBASP or BA.

Sample size

We intended the sample size to be large enough so that the power to detect a difference in the changes between treatment groups (CBASP vs. BA) of at least three HDRS points after 16 weeks is 90% (assuming alpha = .05). This target effect size is in line with the NICE guidelines (Middleton et al., 2005), stating that a difference between treatment groups of at least three points on the HDRS-24 is clinically relevant. It is also consistent with empirical findings on CBASP in outpatient settings: Schramm et al. (2017) reported a significant difference between CBASP and nonspecific psychotherapy of 2.5 points on the HDRS-24 after 20 weeks of outpatient treatment (d = 0.31), and a meta-analysis found a significant combined overall effect of small to moderate magnitude of CBASP versus other treatments or treatment as usual (TAU) (g = 0.34–0.44) (Negt et al., 2016).
Sample size calculation was based on a simulation study (Gelman & Hill, 2007). We defined a latent growth curve model (LGCM) (including latent/random intercepts and slopes) assuming that outcome changes during treatments as a function of log transformed weeks after treatment onset (i.e., with larger improvements in earlier compared to later treatment phases). The focal parameter (i.e., the effect of treatment groups on the latent slope) was selected to represent a three point difference in HRDS-24 between treatments after 16 weeks. The remaining parameter values (e.g., latent variances and covariances) were selected according to the results of Schramm et al. (2017), who shared their original HDRS-24 data with us. Given these parameter values, the expected standard deviation of HRDS-24 scores after 16 weeks was *SD* = 8.85, and thus the target effect of three HRDS-24 points corresponded to a standardized effect of d = 0.34. Moreover, we assumed that each person is assessed four times across the 16 weeks interval, including a 14% dropout at the primary endpoint (assuming a linear increase of missing data across time). Given these parameters, the

simulation (performed with the statistical platform R using 2,000 resamples) suggested that a total sample size of N = 396 yields a power of 90% to detect the target treatment effect. Simulations including effects of covariates (e.g., recruitment sites) resulted in virtually identical estimates.

13.2. Statistical evaluation

13.2.1. Primary endpoint

The primary outcome will be investigated using a LGCM to estimate the effect of treatment group (CBASP vs. BA) on changes in HDSR-24 scores over 16 weeks of treatment (T4) in the intention-to-treat (ITT) population. For the specification and estimation of the LGCM, we will use a structural equation modeling (SEM) approach with the package "lavaan" (Rosseel, 2012) from the statistical environment R, or alternatively with Mplus. Compared with the model used in the power analysis, we will deviate in two respects: assessments before randomization will be included in the model as a baseline (T0), and no particular function will be assumed for the course of outcome over time. This LGCM is equivalent to a "latent basis model" (McNeish & Matta, 2018), using the syntax of the R package "lavaan". To account for possible deviations from a normal distribution in the primary outcome, we will use a scaled test statistic and robust standard errors. The focal parameter in this model is the effect of treatment group on the latent slope. In these and subsequent models, we will adopt a 5% significance level for testing the focal parameter and report the corresponding 95% confidence intervals (CIs). A standardized effect size (d) will be computed by dividing the focal parameter from the LGCM by the pooled standard deviation of HDRS-24 scores at 16 weeks (T4).
For sensitivity analyses, we will statistically control for the effect of selected baseline variables. These include the latent intercept of the LGCM (representing HDRS-24 scores at baseline) as well as sociodemographic and diagnostic variables for which significant differences between treatment groups occur despite randomization. To examine whether the treatment effect depends on study sites, we will use a multiple-group LGCM (with sites representing the groups) and test whether allowing the focal parameter to vary between groups significantly improves model fit. We will also estimate the focal parameter in the per protocol (PP) population. The per protocol population comprises all patients who started the treatment assigned to them by randomization and who received a therapy dosage of at least ten sessions of individual therapy and ten sessions of group therapy. The safety population will be defined as all patients randomized who received at least one session of CBASP or BA.
Other details of the statistical analysis are fixed in the Statistical Analysis Plan, to be prepared before start of the study (first patient in). All statistical analysis will be done with the software R (current version: 4.4.1).

13.2.2. Secondary endpoints

For continuous secondary and further exploratory outcomes that are measured repeatedly, we will use the LGCM with the same settings as for the primary outcome, as well as for analyses that include follow-up time points. Logistic regression analyses are planned for dichotomous outcomes such as response, remission, relapse, and dropout, which by definition cannot be measured at baseline. In all cases, focal parameters will be estimated primarily for the ITT population and additionally reported for the PP population in terms of sensitivity analyses.

All moderator and mediator analyses will be preregistered in a public repository (e.g., osf.io) before running the analyses. Preregistration will include a rationale, hypothesis, variables and analytic strategy used. Briefly, for the moderator analyses, we will respecify the LGCM as a two-group model (with CBASP and BA representing the two groups) and include the hypothesized moderator variables as predictors of the latent slope. We will then test whether allowing the effects of the hypothesized moderator variables to vary between groups significantly improves model fit. In this case, we would conclude that the mean difference of latent slopes between groups (i.e., the focal parameter in the respecified model) depends on the level of the baseline variables and, to that extent, they moderate the treatment effect. For the mediator analyses, we will consider all ten assessments of the primary outcome and both mediators between T0 and T4. Following recommendations by Berli et al. (2021), we will first look descriptively at the trajectories and correlations of these variables and then select an appropriate statistical model. For this purpose, we will consider dynamic panel models (Falkenström, 2024), dynamic SEM (McNeish & MacKinnon, 2022), and latent growth mediation models (Selig & Preacher, 2009).

13.2.3. Safety and tolerability endpoints

Safety data will be analyzed for all patients having started one of the treatments. Rates of adverse events and SAEs will be calculated with corresponding two-sided 95% confidence intervals.

13.2.4. Handling of dropouts

In our power analysis, we expected that 5% of the patients will drop out of the study directly after randomization (defined as “non-starter”), and a further 10% will drop out of treatment (defined as “treatment dropout”) or will drop out of the study during treatment (defined as "study dropout"). Therefore, we expect 95% x 90% = 85.5% of randomized patients to have HDRS-24 non-missing in week 16. To include earlier data points from non-starters, treatment dropouts, and study dropouts (as long as they do not withdraw consent), the LGCM will be estimated using full information maximum likelihood estimation (FIML; Enders & Bandalos, 2001). When using FIML, missing data regarding the primary outcome variable is considered missing at random (MAR) (i.e., missing at random conditional on other information in the model). To make this assumption plausible, we will first correlate all available baseline variables with missingness in the primary outcome variable at later time points and then include baseline variables that predict missingness as auxiliary variables when estimating the LGCM (Graham, 2003).

14. Data Management

14.1. Data collection

All data on patients collected in eCRFs and CRFs during the course of the study will be documented pseudonymously, i.e. the patient will be identified only by the pseudonymized identification number. Investigator must ensure that the patient’s encryption is maintained. The patient identification list should be kept in strict confidence at the study site in the ISF. The investigator at each study site is responsible for keeping the identification list and informed consent forms locked up.

Most of the information required by the protocol and collected during the trial is entered directly into the eCRF electronically by patients or by the investigators or a designated representative. Some information required under the protocol that cannot be entered directly into the eCRF electronically is entered into the CRF by the investigators or a designated representative.
The investigator will maintain a list of individuals authorized to enter or correct data (study delegation log).

14.2. Data processing

14.2.1 EDC-System (eCRF)

The data of the patients are documented within the EDC (Electronic Data Capture) system eHealth-Platform. Data will be entered by study personnel as well as directly by patients. The data of the actimeter are read from the clock during the bi-weekly study visit and entered into the eCRF by the study personnel (rater). Data are entered directly via web browser to the eCRF. Detailed instructions for using the EDC system are specified in the EDC Manual, which is part of the ISF.
In order to use the EDC system all staff who are entering and monitoring data are provided with training materials and required documentation by the KKS Greifswald. All data which are collected during the trial have to be documented in the eCRF by authorized persons according to the Delegation log. Specific user roles within the system enforce accordance with the Delegation Log.
The EDC system has an implemented audit trail. This assures that any documentation and/or changes to database items are traceable anytime. Changes or corrections are permitted to authorized persons who have access to the system with user specific access rights. This access is documented in the audit trail. Users with monitoring function are not able to enter or change patient's data. They view the data in read-only and they can create SDV marks in case of queries. Discrepancies which appear at data management are forwarded to the monitors or to the site directly.

14.2.2 Data concealment for electronic transfer

The eHealth-Platform uses personalized certificate to ensure authorized access. Stored data are further secured with regular backups. At the end of study, the database will be closed after data cleaning process.

14.2.3 Data discrepancies

In a multistage procedure, the obtained data will be checked electronically for their plausibility and consistency. Detected inconsistencies and missing or implausible data will be clarified with queries and necessary changes will be carried out.

14.2.4 Registration

Before recruitment and data collection starts, the trial will be registered at Clinical trials (http://clinicaltrials.gov). Prof. Dr. Eva-Lotta Brakemeier is responsible for the first registration and following updates.

14.2.5 Publication

The study results are presented at scientific symposia and published in international journals according to the criteria of the CONSORT declaration, regardless of the result. At least within one year after completion of the study, the main manuscript will be completed for publication. Any formal presentation or publication of data collected as a direct or indirect result of this study will be considered by the investigators as a joint publication. It therefore requires the agreement of the Coordinating Investigator and the Co-Principal Investigators. The authorship will be determined by mutual agreement.
The results of this study may be presented at scientific symposia or published in a scientific journal only after review and written approval by the Coordinating Investigator and the Co-Principal Investigators. The Investigators of the participating centers agree not to make presentations based on data collected individually or from a subset of centers prior to the publication of the first main publication, unless otherwise agreed by all other investigators, the Coordinating Investigator, and the Co-Principal Investigators.
The Coordinating Investigator, the Co-Principle Investigators and all Leading Investigators will receive copies of all communications, presentations or publications within a reasonable time in advance (at least 10 working days for an abstract or oral presentation material and 35 working days for a manuscript). These guidelines are provided to check the communications for accuracy, to ensure that confidential information is not inadvertently disclosed, to allow for appropriate input or additional information that may not have been available to the Investigator, and to allow for co-authorship.

14.2.6 Open Data

In accordance with the Open Science specifications of the German Psychological Association (DGPs), anonymized data is made available to the public via the Open Data portal of the Open Science Foundation (ww.osf.io). The data will be stored when data collection is completed, but not before 01.01.2028. This step allows third parties to reproduce the analyses reported in scientific publications and to perform ad hoc analyses. The data is permanently stored on servers located in Germany. As soon as they are uploaded and published, these anonymized data cannot be deleted and are therefore also excluded from the deletion of the data in case of revocation of the study participation.

14.3. Quality assurance and quality control

14.3.1. Source data and subject files

The investigator has to keep a written or electronic subject/patient file for every subject participating in the clinical study. In this file, the available demographic and medical information of a subject has to be documented, in particular the following: name, date of birth, sex, height, weight, subject history, concomitant diseases and concomitant drug (including changes during the study), statement of entry into the study, study identification, subject number, the date and process of informed consent, all study visit dates, predefined performed examinations and clinical findings, observed (S)AEs (if applicable), and reason for withdrawal from the study if applicable. lt must be possible to identify each subject by using this patient file.

Additionally, any other documents with source data, especially original printouts of data that were generated by technical equipment have to be filed. All these documents have to bear at least subject identification and the printing date printed by the recording device to indicate to which subject and to which study procedure the document belongs. The medical evaluation of such records should be documented as necessary and signed/dated by the investigator.

For the current study, documents considered to be source data include (but are not limited to):

- Patient's record (patient's clinic and/or office chart, hospital chart).
- Patient Informed Consent Form
- Laboratory results
- Pharmacy records
- Treatment notes
- Scores
- Any other records maintained to conduct and evaluate the clinical study

14.3.2. Monitoring

During the course of the study each participating site will be visited for monitoring before, during and after the study. During each of these visits, source data verification will be performed based on the monitoring plan, generated by the KKS Greifswald. The monitoring of the study takes place by the trained staff of the KKS Greifswald. Content, amount and details of the monitoring visits are described in the monitoring plan. Additionally, on-site and remote-monitoring visits are defined.
In general, any discrepancies in the data collection should be discussed and clarified with the study team during the monitoring visit and corrections/additions should be done according to GCP requirements.
All Monitoring visits are documented according to KKS-specific SOPs.

15. Literature

Angermeyer, M. C., Kilian, R., & Matschinger, H. (2000). *WHOQOL-100 und WHOQOL-BREF. Handbuch für die deutschprachige Version der WHO Instrumente zur Erfassung von Lebensqualität*. Hogrefe.

Angst, J., Gamma, A., Rössler, W., Ajdacic, V., & Klein, D. N. (2009). Long-term depression versus episodic major depression: Results from the prospective Zurich study of a community sample. *Journal of Affective Disorders*, *115*(1–2), 112–121. https://doi.org/10.1016/j.jad.2008.09.023

American Psychiatric Association (2013). Diagnostic and statistical manual of mental disorders (5th ed.). https://doi.org/10.1176/appi.books.9780890425596

Asparouhov, T., Hamaker, E. L., & Muthén, B. (2018). Dynamic Structural Equation Models. *Structural Equation Modeling: A Multidisciplinary Journal*, *25*(3), 359–388. https://doi.org/10.1080/10705511.2017.1406803

Association, A. P. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5®)*. (American Psychiatric Pub, 2013).

Bach, B., Kerber, A., Aluja, A., Bastiaens, T., Keeley, J. W., Claes, L., Fossati, A., Gutierrez, F., Oliveira, S. E. S., Pires, R., Riegel, K. D., Rolland, J. P., Roskam, I., Sellbom, M., Somma, A., Spanemberg, L., Strus, W., Thimm, J. C., Wright, A. G. C., & Zimmermann, J. (2020).

International Assessment of DSM-5 and ICD-11 Personality Disorder Traits: Toward a Common Nosology in DSM-5.1. *Psychopathology*, *53*(3-4), 179–188. https://doi.org/10.1159/000507589

Bajbouj, M., Aust, S., Spies, J., Herrera-Melendez, A.-L., Mayer, S. V., Peters, M., Plewnia, C., Fallgatter, A. J., Frase, L., Normann, C., Behler, N., Wulf, L., Brakemeier, E.-L., & Padberg, F. (2018). PsychotherapyPlus: Augmentation of cognitive behavioral therapy (CBT) with prefrontal transcranial direct current stimulation (tDCS) in major depressive disorder—study design and methodology of a multicenter double-blind randomized placebo-controlled trial. *European Archives of Psychiatry and Clinical Neuroscience*, *268*(8), 797–808. https://doi.org/10.1007/s00406-017-0859-x

Beesdo-Baum, K., Zaudig, M., Wittchen, H.-U., (2019). *Strukturiertes Klinisches Interview für DSM-5-Persönlichkeitsstörungen. Deutsche Bearbeitung des Structured Clinical Interview for DSM-5 – Personality Disorders von Michael B. First, Janet B.W. Williams, Lorna Smith Benjamin, Robert L. Spitzer.* Hogrefe.

Berli, C., Inauen, J., Stadler, G., Scholz, U., & Shrout, P. E. (2021). Understanding Between-Person Intervebrsntions With Time-Intensive Longitudinal Outcome Data: Longitudinal Mediation Analyses, *Annals of Behavioral Medicine,* 55(5), 476-488, https://doi.org/10.1093/abm/kaaa066

Bernstein, D.P., Stein, J.A., Newcomb, M.D., Walker, E., Pogge, D., Ahluvalia, T., Stokes, J., Handelsman, L., Medrano, M., Desmond, D., Zule, W. (2003). Development and validation of a brief screening version of the Childhood Trauma Questionnaire. *Child Abuse & Neglect, 27,* 169–190. https://doi.org/10.1016/S0145-2134(02)00541-0

Bernstein, D.P. & Fink, L. (1998). Childhood Trauma Questionnaire: A retrospective self-report. *The Psychological Corporation*, Harcourt Brace & Company.

Berwian, I. M., Wenzel, J., Collins, A.G.E., Seifritz, E., Stephan, K.E., Walter, H., Huys, Q.J.M., (2020). Computational mechanisms of effort and reward decisions in patients with depression and their association with relapse after antidepressant discontinuation. *JAMA psychiatry* . https://doi.org/10.1001/jamapsychiatry.2019.4971

Bird T., Tarsia M., Schwannauer M. (2018). Interpersonal styles in major and chronic depression: A systematic review and meta-analysis. *J Affect Disord., 239*, 93-101. doi: 10.1016/j.jad.2018.05.057.

Brakemeier, E.-L., Dobias, J., Hertel, J., Bohus, M., Limberger, M. F., Schramm, E., Radtke, M., Frank, P., Padberg, F., Sabass, L., Jobst, A., Jacob, G. A., Struck, N., Zimmermann, J., & Normann, C. (2018). Childhood Maltreatment in Women with Borderline Personality Disorder, Chronic Depression, and Episodic Depression, and in Healthy Controls. *Psychotherapy and Psychosomatics*, *87*(1), 49–51. https://doi.org/10.1159/000484481

Brakemeier, E.-L., Engel, V., Schramm, E., Zobel, I., Schmidt, T., Hautzinger, M., Berger, M., & Normann, C. (2011). Feasibility and Outcome of Cognitive Behavioral Analysis System of Psychotherapy (CBASP) for Chronically Depressed Inpatients: A Pilot Study. *Psychotherapy and Psychosomatics*, *80*(3), 191–194. https://doi.org/10.1159/000320779

Brakemeier, E.-L., Herzog, P., Radtke, M., Schneibel, R., Breger, V., Becker, M., Spies, J., Jacobi, F., Heider, J., & Normann, C. (2018). CBASP als stationäres Behandlungskonzept der therapieresistenten chronischen Depression: Eine Pilotstudie zum Zusammenhang von Nebenwirkungen und Therapieerfolg. *PPmP - Psychotherapie · Psychosomatik · Medizinische Psychologie*, *68*(09/10), 399–407. https://doi.org/10.1055/a-0629-7802

Brakemeier, E.-L., Marchner, J., Gutgsell, S., Engel, V., Radtke, M., Tuschen-Caffier, B., Normann, C., & Berking, M. (2013). CBASP@home: Ein internetbasiertes Situationsanalysen-Training zur Stabilisierung des Therapieerfolgs nach stationärer

Therapie für chronisch depressive Patienten. *Verhaltenstherapie*, *23*(3), 190–203. https://doi.org/10.1159/000354814

Brakemeier, E.-L., Merkl, A., Wilbertz, G., Quante, A., Regen, F., Bührsch, N., & Kathmann, N. (2014). Continuation treatment after electroconvulsive therapy in patients with unipolar depression. *Biological Psychology, 76,* 194–202. https://doi.org/10.1016/j.biopsych.2013.11.030

Brakemeier, E.-L., & Normann, C. (2012). *Praxisbuch CBASP: Behandlung chronischer Depression; mit Online-Materialien* (1. Aufl). Beltz.

Brakemeier, E.-L., Guhn, A., & Normann, C. (2021). *Praxisbuch CBASP: Behandlung chronischer Depression und Modifikationen für weitere interpersonelle Störungen; mit E-Book inside und Arbeitsmaterial;* (2., überarbeitete und erweiterte Auflage). Beltz.

Brakemeier, E.-L., Radtke, M., Engel, V., Zimmermann, J., Tuschen-Caffier, B., Hautzinger, M., Schramm, E., Berger, M., & Normann, C. (2015). Overcoming Treatment Resistance in Chronic Depression: A Pilot Study on Outcome and Feasibility of the Cognitive Behavioral Analysis System of Psychotherapy as an Inpatient Treatment Program. *Psychotherapy and Psychosomatics*, *84*(1), 51–56. https://doi.org/10.1159/000369586

Bschor, T., Bauer, M., & Adli, M. (2014). Chronic and Treatment Resistant Depression. *Deutsches Aerzteblatt Online, 111,* 766-776. https://doi.org/10.3238/arztebl.2014.0766

Buecker, S., Horstmann, K. T., Terwiel, S., Krasko, J., Kritzler, S., Kaiser, T., & Luhmann, M. (2020). Psychological Item Pool for Corona Outbreak (PIPCO). Retrieved from osf.io/62dmf

Casper, F., Fingerle, H., & Werner, M. (2000). Der IMI (Impact Message Inventory): Ein Instrument zur interpersonalen Fremdbeurteilung. *Forschungsbericht aus dem psychologischen Institut der Universität Freiburg*. Thieme.

Carrozzino, D., Patierno, C., Fava, G.A., & Guidi, J. (2020). The Hamilton Rating Scales for Depression: A Critical Review of Clinimetric Properties of Different Versions. *Psychotherapy and Psychosoma*tics, 89(3), 133–150. https://doi:10.1159/000506879

Carrozzino, D., Svicher, A., Patierno, C., Berrocal, C., & Cosci, F. (2019). The Euthymia Scale: A Clinimetric Analysis. *Psychotherapy and Psychosoma*tics, 88(2), 119–121. https://doi:10.1159/000496230

Chaix, R., Alvarez-López, M. J., Fagny, M., Lemee, L., Regnault, B., Davidson, R. J., Lutz, A., & Kaliman, P. (2017). Epigenetic clock analysis in long-term meditators. *Psychoneuroendocrinology*, *85*, 210–214. https://doi.org/10.1016/j.psyneuen.2017.08.016

Cohen, S., Doyle, W. J., Skoner, D. P., Rabin, B. S., & Gwaltney, J. M. (1997). Social ties and susceptibility to the common cold. *Jama*, *277*(24), 1940–1944. https://doi.org/10.1001/jama.1997.03540480040036

Constantino, M. J., Manber, R., DeGeorge, J., McBride, C., Ravitz, P., Zuroff, D. C., Klein, D. N., Markowitz, J. C., Rothbaum, B. O., Thase, M. E., & Arnow, B. A. (2008). Interpersonal styles of chronically depressed outpatients: Profiles and therapeutic change. *Psychotherapy: Theory, Research, Practice, Training*, *45*(4), 491–506. https://doi.org/10.1037/a0014335

Cuijpers, P., Clignet, F., van Meijel, B., van Straten, A., Li, J., & Andersson, G. (2011). Psychological treatment of depression in inpatients: A systematic review and meta-analysis. *Clinical Psychology Review*, *31*(3), 353–360. https://doi.org/10.1016/j.cpr.2011.01.002

Cuijpers, P., van Straten, A., Schuurmans, J., van Oppen, P., Hollon, S. D., & Andersson, G. (2010). Psychotherapy for chronic major depression and dysthymia: A meta-analysis. *Clinical Psychology Review*, *30*(1), 51–62. https://doi.org/10.1016/j.cpr.2009.09.003

Cuijpers, P., van Straten, A., & Warmerdam, L. (2007). Behavioral activation treatments of depression: A meta-analysis. *Clinical Psychology Review*, *27*(3), 318–326. https://doi.org/10.1016/j.cpr.2006.11.001

Derogatis, L. R., & Spencer, P. M. (1993). *Brief symptom inventory: BSI*. Pearson, Upper Saddle River, NJ.

DGPPN, BÄK, KBV, AWMF (2015). *S3-Leitlinie/Nationale Versorgungsleitlinie Unipolare Depression- Langfassung: Bd. Version 5* (2. Aufl.). Springer.

Dimidjian, S., Hollon, S. D., Dobson, K. S., Schmaling, K. B., Kohlenberg, R. J., Addis, M. E., Gallop, R., McGlinchey, J. B., Markley, D. K., Gollan, J. K., Atkins, D. C., Dunner, D. L., & Jacobson, N. S. (2006). Randomized trial of behavioral activation, cognitive therapy, and antidepressant medication in the acute treatment of adults with major depression. *Journal of Consulting and Clinical Psychology*, *74*(4), 658–670. https://doi.org/10.1037/0022-006X.74.4.658

Döring, N., & Bortz, J. (1993). Psychometrische Einsamkeitsforschung: Deutsche Neukonstruktion der UCLA Loneliness Scale. *Diagnostica, 39,* 224–239.

Downey, G., & Feldman, S. I. (1996). Implications of rejection sensitivity for intimate relationships. *Journal of personality and social psychology*, *70* (6), 1327. https://doi.org/10.1037/0022-3514.70.6.1327

Drummond, M. F. (Hrsg.). (2007). *Methods for the economic evaluation of health care programmes* (3. Aufl.). Oxford University Press.

Ehrenthal, J.C., Zimmermann, J., Brenk-Franz, K. et al. (2021). Evaluation of a short version of the Experiences in Close Relationships-Revised questionnaire (ECR-RD8): results from a representative German sample. *BMC Psychol 9,* 140. https://doi.org/10.1186/s40359-021-00637-z

Ekers, D., Richards, D., & Gilbody, S. (2008). A meta-analysis of randomized trials of behavioural treatment of depression. *Psychological Medicine*, *38*(5), 611–623. https://doi.org/10.1017/S0033291707001614

Enders, C. K. & Bandalos, D. L. (2001). The Relative Performance of Full Information Maximum Likelihood Estimation for Missing Data in Structural Equation Models, Structural Equation Modeling: A Multidisciplinary Journal, 8(3), 430-457, DOI: 10.1207/S15328007SEM0803_5

Falkenström, F. (2024). Time-lagged panel models in psychotherapy process and mechanisms of change research: Methodological challenges and advances. Clinical Psychology Review, 110, 102435. https://doi.org/10.1016/j.cpr.2024.102435

Fava, G.A., Tomba, E., Brakemeier, E.-L., et al. (2019). Mental Pain as a Transdiagnostic Patient-Reported Outcome Measure. *Psychotherapy and Psychosomatics*, *88*(6), 341–349. https://doi:10.1159/000504024

Forbes, C. N. (2020). New directions in behavioral activation: Using findings from basic science and translational neuroscience to inform the exploration of potential mechanisms of change [published online ahead of print, 2020 May 5]. *Clinical Psychology Review*, 79, 101860. https://doi:10.1016/j.cpr.2020.101860

Freeman, D. *et al.* (2019). The revised Green et al., Paranoid Thoughts Scale (R-GPTS): psychometric properties, severity ranges, and clinical cut-offs. *Psychological Medicine,* 1–10. https://doi.org/10.1017/S0033291719003155

Frieling, H., & Tadić, A. (2013). Value of genetic and epigenetic testing as biomarkers of response to antidepressant treatment. *International Review of Psychiatry*, *25*(5), 572–578. https://doi.org/10.3109/09540261.2013.816657

Gelman, A., & Hill, J. (2007). *Data analysis using regression and multilevel/hierarchical models*. Cambridge University Press.

Geyer, E.C., Fua, K.C., Daniel, K.E., Chow, P.I., Bonelli, W., Huang, Y., Barnes, L.E., and Teachman, B.A. (2018). I Did OK, but Did I Like It? Using Ecological Momentary Assessment to Examine Perceptions of Social Interactions Associated With Severity of Social Anxiety and Depression. *Behav Ther* 49**,** 866-880. https://doi.org/10.1016/j.beth.2018.07.009

Graham, J. W. (2003). Adding Missing-Data-Relevant Variables to FIML-Based Structural Equation Models, Structural Equation Modeling: A Multidisciplinary Journal, 10(1), 80-100, DOI: 10.1207/S15328007SEM1001_4

Guhn, A., Köhler, S., Brakemeier, E.-L., & Sterzer, P. (2019). Cognitive Behavioral Analysis System of Psychotherapy for inpatients with persistent depressive disorder: a naturalistic trial on a general acute psychiatric unit. *European Archives of Psychiatry and Clinical Neuroscience*. 2019 Jul 12. https://doi.org/10.1007/s00406-019-01038-5

Hall, R. C. W. (1995). Global Assessment of Functioning. *Psychosomatics*, *36*(3), 267–275. https://doi.org/10.1016/S0033-3182(95)71666-8

Hamilton, M. (1960). A Rating Scale for Depression. *Journal of Neurology, Neurosurgery & Psychiatry*, *23*(1), 56–62. https://doi.org/10.1136/jnnp.23.1.56

Härter, M., Sitta, P., Keller, F. et al. (2004). Stationäre psychiatrisch-psychotherapeutische Depressionsbehandlung. *Nervenarzt 75*, 1083–1091 (2004). https://doi.org/10.1007/s00115-004-1705-8

Hauser, T.U. et al. Separate mesocortical and mesolimbic pathways encode effort and reward learning signals*. Proc Natl Acad Sci USA* (2017). https://doi.org/10.1073/pnas.1705643114

Hautzinger, M., Joormann, J., & Keller, F. (2005). *DAS: Skala dysfunktionaler Einstellungen; Manual*. Hogrefe.

Hautzinger, M., Keller, F., & Kühner, C. (2006). *Das Beck Depressionsinventar II*. Hogrefe.

Herzog, P., Kaiser, T., Gärtner, T., Rief, W., & Brakemeier, E.-L. (in prep). Detecting and monitoring side effects of psychological interventions: Development and Validation of the Side Effects of Psychological Interventions Process Scale (SEPIPS)

Hopko, D. R., Lejuez, C. W., Lepage, J. P., Hopko, S. D., & McNeil, D. W. (2003). A Brief Behavioral Activation Treatment for Depression: A Randomized Pilot Trial within an Inpatient Psychiatric Hospital. *Behavior Modification*, *27*(4), 458–469. https://doi.org/10.1177/0145445503255489

Horowitz, L. M., Alden, L. E., Kordy, H., & Strauß, B. (2000). *Inventar zur Erfassung interpersonaler Probleme: Deutsche Version; IIP-D*. Beltz.

Hörter, M., Sitta, P., Keller, F., Metzger, R., Wiegand, W., Schell, G., Stieglitz, R.-D., Wolfersdorf, M., Felsenstein, M., & Berger, M. (2004). Stationäre psychiatrisch-psychotherapeutische Depressionsbehandlung: Prozess- und Ergebnisqualität anhand eines Modellprojekts in Baden-Württemberg. *Der Nervenarzt*, *75*(11), 1083–1091. https://doi.org/10.1007/s00115-004-1705-8

Hölzel, L., Wolff, A. von, Kriston, L., & Härter, M. (2010). Unter welchen Bedingungen bleibt eine stationäre Depressionsbehandlung erfolglos? *Psychiatrische Praxis*, *37*(01), 27–33. https://doi.org/10.1055/s-0029-1223348

Huys, Q.J.M. et al. Mapping anhedonia onto reinforcement learning: a behavioural meta-analysis. *Biol Mood Anxiety Disord* (2013). https://doi.org/10.1186/2045-5380-3-12

Jacobs, I., & Scholl, W. (2005). Interpersonale Adjektivliste (IAL). *Diagnostica*, *51*(3), 145–155. https://doi.org/10.1026/0012-1924.51.3.145

Jobst, A., Brakemeier, E.-L., Buchheim, A., Caspar, F., Cuijpers, P., Ebmeier, K. P., Falkai, P., Jan van der Gaag, R., Gaebel, W., Herpertz, S., Kurimay, T., Sabaß, L., Schnell, K., Schramm, E., Torrent, C., Wasserman, D., Wiersma, J., & Padberg, F. (2016). European Psychiatric Association Guidance on psychotherapy in chronic depression across Europe. *European Psychiatry*, *33*, 18–36. https://doi.org/10.1016/j.eurpsy.2015.12.003

Kahl, K. G., Winter, L., & Schweiger, U. (2012). The third wave of cognitive behavioural therapies: What is new and what is effective? *Current Opinion in Psychiatry*, *25*(6), 522–528. https://doi.org/10.1097/YCO.0b013e328358e531

Kanter, J. W. (2009). *Behavioral Activation: Distinctive Features* (1. Aufl.). Routledge. https://doi.org/10.4324/9780203876060

Kanter, J. W., Mulick, P. S., Busch, A. M., Berlin, K. S., & Martell, C. R. (2007). The Behavioral Activation for Depression Scale (BADS): Psychometric Properties and Factor Structure. *Journal of Psychopathology and Behavioral Assessment*, *29*(3), 191–202. https://doi.org/10.1007/s10862-006-9038-5

Keller, F., Härter, M., Metzger, R., Wiegand, W., & Schell, G. (2001). Prozess-und Ergebnisqualität in der stationären Behandlung ersterkrankter und chronisch depressiver Patienten. *Krankenhauspsychiatrie*, *12*(1), 50–56. http://dx.doi.org/10.1055/s-2001-17668

Keller, Martin B., McCullough, J. P., Klein, D. N., Arnow, B., Dunner, D. L., Gelenberg, A. J., Markowitz, J. C., Nemeroff, C. B., Russell, J. M., Thase, M. E., Trivedi, M. H., Blalock, J. A., Borian, F. E., Jody, D. N., DeBattista, C., Koran, L. M., Schatzberg, A. F., Fawcett, J., Hirschfeld, R. M. A., … & Zajecka, J. (2000). A Comparison of Nefazodone, the Cognitive Behavioral-Analysis System of Psychotherapy, and Their Combination for the Treatment of Chronic Depression. *New England Journal of Medicine*, *342*(20), 1462–1470. https://doi.org/10.1056/NEJM200005183422001

Keller, M.B., Warshaw, M. G., Dyck, I., Dolan, R. T., Shea, M. Y., Riley, K., & Shapiro, R. (1997). *LIFE-IV: The Longitudinal Interval Follow-up Evaluation for DSM-IV*.

Kerber, A., Schultze, M., Müller, S., Rühling, R. M., Wright, A. G. C., Spitzer, C., Krueger, R. F., Knaevelsrud, C., & Zimmermann, J. (2022). Development of a Short and ICD-11 Compatible Measure for *DSM-5* Maladaptive Personality Traits Using Ant Colony Optimization Algorithms. *Assessment*, *29*(3), 467–487. https://doi.org/10.1177/1073191120971848

Klein, J. P., Erkens, N., Schweiger, U., Kriston, L., Bausch, P., Zobel, I., Hautzinger, M., Schoepf, D., Serbanescu, I., Bailer, J., Backenstrass, M., Wambach, K., Walter, H., Härter, M., & Schramm, E. (2018). Does Childhood Maltreatment Moderate the Effect of the Cognitive Behavioral Analysis System of Psychotherapy versus Supportive Psychotherapy in Persistent Depressive Disorder? *Psychotherapy and Psychosomatics*, *87*(1), 46–48. https://doi.org/10.1159/000484412

Klug, G., Huber, D., & Kächele, H. (2002). *Psychotherapeutische Haltung (ThAt). Ein Fragebogen zur Ausbildung, Erfahrung, Stil und Werten*.

Kocsis, J. H. (2009). Cognitive Behavioral Analysis System of Psychotherapy and Brief Supportive Psychotherapy for Augmentation of Antidepressant Nonresponse in Chronic

Depression. The REVAMP Trial. *Archives of General Psychiatry, 66*(11), 1178. https://doi.org/10.1001/archgenpsychiatry.2009.144

Köhler, S., Sterzer, P., Normann, C., Berger, M., & Brakemeier, E.-L. (2016). Überwindung der Therapieresistenz bei chronischer Depression: Die Bedeutung der stationären Psychotherapie. *Der Nervenarzt*, *87*(7), 701–707. https://doi.org/10.1007/s00115-015-0034-4

Koy, J. (2019). S*pecific and non-specific working mechanisms of inpatient psychotherapy concepts in patients with depression: Validation of the questionnaire "Review of last Week (RevieW)*. Masterthesis. Philipps-Universität Marburg.

Krieger, T., Zimmermann, J., Huffziger, S., et al. (2014). Measuring depression with a well-being index: further evidence for the validity of the WHO Well-Being Index (WHO-5) as a measure of the severity of depression. *Journal of Affective Disorders, 156,* 240–244. https://doi.org/10.1016/j.jad.2013.12.015

Kriston, L., von Wolff, A., Westphal, A., Hölzel, L. P., & Härter, M. (2014). Efficacy and Acceptability of acute treatments for Persistent Depressive Disorder: A Network Meta-Analysis: Acute Treatments for Persistent Depressive Disorder. *Depression and Anxiety, 31*(8), 621–630. https://doi.org/10.1002/da.22236

Köhler, S., Fischer, T., Brakemeier, E.-L., & Sterzer, P. (2015). Successful Treatment of Severe Persistent Depressive Disorder with a Sequential Approach: Electroconvulsive Therapy Followed by Cognitive Behavioural Analysis System of Psychotherapy. *Psychotherapy and Psychosomatics, 84*(2), 127–128. https://doi.org/10.1159/000369847

Köhler, S., Chrysanthou, S., Guhn, A., & Sterzer, P. (2019). Differences between chronic and nonchronic depression: Systematic review and implications for treatment. *Depression and Anxiety, 36*(1), 18–30. https://doi.org/10.1002/da.22835

Kühnen, T., Knappke, F., Otto, T., Friedrich, S., Klein, J., Kahl, K., Hüppe, M., Sipos, V. & Schweiger, U. (2011). Chronic depression: development and evaluation of the luebeck questionnaire for recording preoperational thinking (LQPT). *BMC Psychiatry, 11,* 199. https://doi.org/10.1186/1471-244X-11-199

Lewinsohn, P. M. A behavioral approach to depression*. Essential papers on depression*, 150-172 (1974).

Lieb, K., Dreimüller, N., Wagner, S., Schlicht, K., Falter, T., Neyazi, A., Müller-Engling, L., Bleich, S., Tadić, A., & Frieling, H. (2018). BDNF Plasma Levels and BDNF Exon IV Promoter Methylation as Predictors for Antidepressant Treatment Response. *Frontiers in Psychiatry*, *9*, 511. https://doi.org/10.3389/fpsyt.2018.00511

Linden, M., & Baron, S. (2005). Das „Mini-ICF-Rating für psychische Störungen (Mini-ICF-P)". Ein Kurzinstrument zur Beurteilung von Fähigkeitsstörungen bei psychischen Erkrankungen. *Die Rehabilitation*, *44*(3), 144–151. https://doi.org/10.1055/s-2004-834786

Luborsky, L., Diguer, L., Seligman, D. A., Rosenthal, R., Krause, E. D., Johnson, S., ... & Schweizer, E. (1999). The researcher's own therapy allegiances: A "wild card" in comparisons of treatment efficacy. *Clinical Psychology: Science and Practice*, *6*(1), 95–106. https://doi.org/10.1093/clipsy.6.1.95

Luppa, M., Heinrich, S., Angermeyer, M. C., König, H.-H., & Riedel-Heller, S. G. (2007). Cost-of-illness studies of depression. *Journal of Affective Disorders*, *98*(1–2), 29–43. https://doi.org/10.1016/j.jad.2006.07.017

Margraf, J., Cwik, J. C., von Brachel, R., Suppiger, A., & Schneider, S. (2021). *DIPS Open Access 1.2: Diagnostisches Interview bei psychischen Störungen*. Ruhr-Universität Bochum (RUB). https://doi.org/10.46586/rub.172.149

Martell, C. R., Dimidjian, S., Hermann-Dunn, R., Winter, L., & Lewinsohn, P. M. (2015). *Verhaltensaktivierung bei Depression: Eine Methode zur Behandlung von Depression* (1. Aufl). Kohlhammer.

McCullough, J. P., Schramm, E., Penberthy, K. (2014). *CBASP as a Distinctive Treatment for Persistent Depressive Disorder*. Routledge. https://doi.org/10.4324/9781315743196

McNeish, D., & Matta, T. (2018). Differentiating between mixed-effects and latent-curve approaches to growth modeling. Behav Res, 50, 1398–1414. https://doi.org/10.3758/s13428-017-0976-5

McNeish, D., & MacKinnon, D. P. (2022). Intensive longitudinal mediation in M*plus*. *Psychological Methods.* Advance online publication. https://doi.org/10.1037/met0000536

Menke, A., & Binder, E. B. (2014). Epigenetic alterations in depression and antidepressant treatment. *Dialoges in Clinical Neuroscience*, *16*(3), 395–404. https://doi.org/10.1159/000491431

Michalak, J., Schultze, M., Heidenreich, T., & Schramm, E. (2015). A randomized controlled trial on the efficacy of mindfulness-based cognitive therapy and a group version of cognitive behavioral analysis system of psychotherapy for chronically depressed patients. *Journal of Consulting and Clinical Psychology*, *83*(5), 951–963. https://doi.org/10.1037/ccp0000042

Middleton, H., Shaw, I., Hull, S., & Feder, G. (2005). NICE guidelines for the management of depression. *BMJ*, *330*(7486), 267–268. https://doi.org/10.1136/bmj.330.7486.267

Montgomery, S. A., & Åsberg, M. (1979). A New Depression Scale Designed to be Sensitive to Change. *British Journal of Psychiatry*, *134*(4), 382–389. https://doi.org/10.1192/bjp.134.4.382

Munder, T., Bruetsch, O., Leonhart, R., Gerger, H., & Barth, J. (2013). Researcher allegiance in psychotherapy outcome research: an overview of reviews. *Clinical Psychology Review, 33*(4), 501–511. https://doi.org/10.1016/j.cpr.2013.02.002

Murphy, J. A., & Byrne, G. J. (2012). Prevalence and correlates of the proposed DSM-5 diagnosis of Chronic Depressive Disorder. *Journal of Affective Disorders*, *139*(2), 172–180. https://doi.org/10.1016/j.jad.2012.01.033

Murphy, J. A., Sarris, J., & Byrne, G. J. (2017). A Review of the Conceptualisation and Risk Factors Associated with Treatment-Resistant Depression. *Depression Research and Treatment*, *2017*, 1–10. https://doi.org/10.1155/2017/4176825

Nagy, G. A. et al. Reward network modulation as a mechanism of change in behavioral activation. *Behavior modification* 44, 186-213 (2020). https://doi.org/10.1177%2F0145445518805682

Negt, P., Brakemeier, E.-L., Michalak, J., Winter, L., Bleich, S., & Kahl, K. G. (2016). The treatment of chronic depression with cognitive behavioral analysis system of psychotherapy: A systematic review and meta-analysis of randomized-controlled clinical trials. *Brain and Behavior*, *6*(8), e00486. https://doi.org/10.1002/brb3.486

Nemeroff, C. B., Heim, C. M., Thase, M. E., Klein, D. N., Rush, A. J., Schatzberg, A. F., Ninan, P. T., McCullough, J. P., Weiss, P. M., Dunner, D. L., Rothbaum, B. O., Kornstein, S., Keitner, G., & Keller, M. B. (2003). Differential responses to psychotherapy versus pharmacotherapy in patients with chronic forms of major depression and childhood

trauma. *Proceedings of the National Academy of Sciences*, *100*(24), 14293–14296. https://doi.org/10.1073/pnas.2336126100

Niv, Y. et al. Tonic dopamine: opportunity costs and the control of response vigor. *Psychopharmacology (Berl)* (2007). https://doi.org/10.1007/s00213-006-0502-4

Norcross, J. C., & Wampold, B. E. (2011). Evidence-based therapy relationships: Research conclusions and clinical practices. *Psychotherapy*, *48*(1), 98–102. https://doi.org/10.1037/a0022161

Posner, K., Brown, G. K., Stanley, B., Brent, D. A., Yershova, K. V., Oquendo, M. A., Currier, G. W., Melvin, G. A., Greenhill, L., Shen, S., & Mann, J. J. (2011). The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *The American journal of psychiatry*, *168*(12), 1266–1277. https://doi.org/10.1176/appi.ajp.2011.10111704

Reinhard, M.A., Zentz, K., Nenov-Matt, T., Barton, B.B., V. Rek, S., Goerigk, S., Brakemeier, E.L., Musil, R., Jobst, A., Padberg, F. (accepted). Cognitive Behavioral Analysis System of Psychotherapy reduces loneliness in patients with persistent depressive disorder. *Journal of Affective Disorders Reports*

Richards, D. A., Ekers, D., McMillan, D., Taylor, R. S., Byford, S., Warren, F. C., Barrett, B., Farrand, P. A., Gilbody, S., Kuyken, W., O'Mahen, H., Watkins, E. R., Wright, K. A., Hollon, S. D., Reed, N., Rhodes, S., Fletcher, E., & Finning, K. (2016). Cost and Outcome of Behavioural Activation versus Cognitive Behavioural Therapy for Depression (COBRA): A randomised, controlled, non-inferiority trial. *The Lancet*, *388*(10047), 871–880. https://doi.org/10.1016/S0140-6736(16)31140-0

Robinson, L. A., Berman, J. S., & Neimeyer, R. A. (1990). Psychotherapy for the treatment of depression: a comprehensive review of controlled outcome research. *Psychological Bulletin, 108*(1), 30. https://doi.org/10.1037/0033-2909.108.1.30

Rosseel, Y. (2012). lavaan: An R Package for Structural Equation Modeling. *Journal of Statistical Software*, *48*(2), 1–36. https://doi.org/10.18637/jss.v048.i02

Rosenbaum, S., Sherrington, C., & Tiedemann, A. (2015). Exercise augmentation compared with usual care for post-traumatic stress disorder: A randomized controlled trial. *Acta Psychiatrica Scandinavica*, *131*(5), 350–359. https://doi.org/10.1111/acps.12371

Russell, D. W. (1996). UCLA Loneliness Scale (Version 3): Reliability, validity, and factor structure. *Journal of personality assessment*, *66*(1), 20–40. https://doi.org/10.1207/s15327752jpa6601_2

Rush, A. J., Carmody, T., & Reimitz, P.-E. (2000). The Inventory of Depressive Symptomatology (IDS): Clinician (IDS-C) and Self-Report (IDS-SR) ratings of depressive symptoms. *International Journal of Methods in Psychiatric Research*, *9*(2), 45–59. https://doi.org/10.1002/mpr.79

Sabaß, L., Padberg, F., Normann, C., Engel, V., Konrad, C., Helmle, K., Jobst, A., Worlitz, A., & Brakemeier, E.-L. (2018). Cognitive Behavioral Analysis System of Psychotherapy as group psychotherapy for chronically depressed inpatients: A naturalistic multicenter feasibility trial. *European Archives of Psychiatry and Clinical Neuroscience*, *268*(8), 783–796. https://doi.org/10.1007/s00406-017-0843-5

Sackeim, H. A., Aaronson, S. T., Bunker, M. T., et al. (2019). The assessment of resistance to antidepressant treatment: Rationale for the Antidepressant Treatment History Form: Short Form (ATHF-SF). *Journal of Psychiatry Research*, 113, 125–136. https://doi:10.1016/j.jpsychires.2019.03.021

Schefft, C., Guhn, A., Brakemeier, E.-L., Sterzer, P., & Köhler, S. (2019). Efficacy of inpatient psychotherapy for major depressive disorder: a meta-analysis of controlled trials. *Acta Psychiatrica Scandinavica, 139*(4), 322–335. https://doi.org/10.1111/acps.12995

Schramm, E., Kriston, L., Zobel, I., Bailer, J., Wambach, K., Backenstrass, M., Klein, J. P., Schoepf, D., Schnell, K., Gumz, A., Bausch, P., Fangmeier, T., Meister, R., Berger, M., Hautzinger, M., & Härter, M. (2017). Effect of Disorder-Specific vs Nonspecific Psychotherapy for Chronic Depression: A Randomized Clinical Trial. *JAMA Psychiatry*, *74*(3), 233. https://doi.org/10.1001/jamapsychiatry.2016.3880

Schramm, E., Schneider, D., Zobel, I., van Calker, D., Dykierek, P., Kech, S., Härter, M., & Berger, M. (2008). Efficacy of Interpersonal Psychotherapy plus pharmacotherapy in chronically depressed inpatients. *Journal of Affective Disorders*, *109*(1–2), 65–73. https://doi.org/10.1016/j.jad.2007.10.013

Schramm, E., van Calker, D., Dykierek, P., Lieb, K., Kech, S., Zobel, I., Leonhart, R., & Berger, M. (2007). An Intensive Treatment Program of Interpersonal Psychotherapy Plus Pharmacotherapy for Depressed Inpatients: Acute and Long-Term Results. *American Journal of Psychiatry*, *164*(5), 768–777. https://doi.org/10.1176/ajp.2007.164.5.768

Schramm, E., Zobel, I., Dykierek, P., Kech, S., Brakemeier, E.-L., Külz, A., & Berger, M. (2011). Cognitive behavioral analysis system of psychotherapy versus interpersonal psychotherapy for early-onset chronic depression: A randomized pilot study. *Journal of Affective Disorders*, *129*(1–3), 109–116. https://doi.org/10.1016/j.jad.2010.08.003

Schramm, E., Zobel, I., Schoepf, D., Fangmeier, T., Schnell, K., Walter, H., Drost, S., Schmidt, P., Brakemeier, E.-L., Berger, M., & Normann, C. (2015). Cognitive Behavioral Analysis System of Psychotherapy versus Escitalopram in Chronic Major Depression. *Psychotherapy and Psychosomatics*, *84*(4), 227–240. https://doi.org/10.1159/000381957

Schwarzer, R., & Jerusalem, M. (1995). Generalized Self-Efficacy scale. In J. Weinman, S. Wright, & M. Johnston, Measures in health psychology: A user's portfolio. Causal and control beliefs (pp. 35-37). Windsor, UK: NFER-NELSON.

Seidl, H., Bowles, D., Bock, J.-O., Brettschneider, C., Greiner, W., König, H.-H., & Holle, R. (2014). FIMA – Fragebogen zur Erhebung von Gesundheitsleistungen im Alter: Entwicklung und Pilotstudie. *Das Gesundheitswesen*, *77*(01), 46–52. https://doi.org/10.1055/s-0034-1372618

Selig, J. P., & Preacher, K. J. (2009). Mediation models for longitudinal data in developmental research. *Research in Human Development, 6*(2-3), 144–164. https://doi.org/10.1080/15427600902911247

Shinohara, K., Honyashiki, M., Imai, H., Hunot, V., Caldwell, D. M., Davies, P., Moore, T. H., Furukawa, T. A., & Churchill, R. (2013). Behavioural therapies versus other psychological therapies for depression. *Cochrane Database of Systematic Reviews*. https://doi.org/10.1002/14651858.CD008696.pub2

Smith, B. W., Dalen, J., Wiggins, K., Tooley, E., Christopher, P., & Bernard, J. (2008). The brief resilience scale: assessing the ability to bounce back. *International journal of behavioral medicine*, *15*(3), 194-200. https://doi.org/10.1080/10705500802222972

Snarski, M., Scogin, F., DiNapoli, E., Presnell, A., McAlpine, J., & Marcinak, J. (2011). The Effects of Behavioral Activation Therapy With Inpatient Geriatric Psychiatry Patients. *Behavior Therapy*, *42*(1), 100–108. https://doi.org/10.1016/j.beth.2010.05.001

Spates, C. R., Pagoto, S. L., & Kalata, A. (2006). A qualitative and quantitative review of behavioral activation treatment of major depressive disorder. *The Behavior Analyst Today*, *7*(4), 508–521. https://doi.org/10.1037/h0100089

Staebler, K., Helbing, E., Rosenbach, C., & Renneberg, B. (2011). Rejection sensitivity and borderline personality disorder. *Clinical psychology & psychotherapy*, *18*(4), 275–283. https://doi.org/10.1002/cpp.705

Tadić, A., Müller-Engling, L., Schlicht, K. F., Kotsiari, A., Dreimüller, N., Kleimann, A., Bleich, S., Lieb, K., & Frieling, H. (2014). Methylation of the promoter of brain-derived neurotrophic factor exon IV and antidepressant response in major depression. *Molecular Psychiatry*, *19*(3), 281–283. https://doi.org/10.1038/mp.2013.58

Vinkers, C. H., Geuze, E., van Rooij, S. J. H., Kennis, M., Schür, R. R., Nispeling, D. M., Smith, A. K., Nievergelt, C. M., Uddin, M., Rutten, B. P. F., Vermetten, E., & Boks, M. P. (2021). Successful treatment of post-traumatic stress disorder reverses DNA methylation marks. *Molecular Psychiatry*, *26*(4), 1264–1271. https://doi.org/10.1038/s41380-019-0549-3

Wagner, T., Fydrich, T., Stiglmayr, C., Marschall, P., Salize, H-J., Renneberg, B., Fleßa, S., & Roepke, S. (2014). Societal cost-of-illness in patients with borderline personality disorder one year before, during and after dialectical behavior therapy in routine outpatient care. *Behaviour Research and Therapy, 61*, 12–22. https://doi.org/10.1016/j.brat.2014.07.004

Weck, F., Hautzinger, M., Heidenreich, T., & Stangier, U. (2010). Erfassung psychotherapeutischer Kompetenzen: Validierung einer deutschsprachigen Version der Cognitive Therapy Scale. *Zeitschrift für Klinische Psychologie und Psychotherapie*, *39*(4), 244–250. https://doi.org/10.1026/1616-3443/a000055

Wiersma, J. E., Van Schaik, D. J. F., Hoogendorn, A. W., Dekker, J. J., Van, H. L., Schoevers, R. A., Blom, M. B. J., Maas, K., Smit, J. H., McCullough Jr., J. P., Beekman, A. T. F., & Van Oppen, P. (2014). The Effectiveness of the Cognitive Behavioral Analysis System of Psychotherapy for Chronic Depression: A Randomized Controlled Trial. *Psychotherapy and Psychosomatics*, *83*(5), 263–269. https://doi.org/10.1159/000360795

Wingenfeld, K., Spitzer, C., Mensebach, C., Grabe, H.J., Hill, A., Gast, U., Schlosser, N., Höpp, H., Beblo, T., Driessen, M., 2010. The German Version of the Childhood Trauma Questionnaire (CTQ): Preliminary Psychometric Properties. *PPmP: Psychotherapie Psychosomatik Medizinische Psychologie, 60*, 442–450. https://doi.org/10.1055/s-0030-1247564

Williams, J. B. (1988). A structured interview guide for the Hamilton Depression Rating Scale. *Archives of General Psychiatry*, 45(8), 742–747.

Wilmers, F., Munder, T., Leonhart, R., Herzog, T., Plassmann, R., Barth, J., & Linster, H. W. (2008). Die deutschsprachige Version des Working Alliance Inventory - Short revised (WAI-SR) - Ein schulenübergreifendes, ökonomisches und empirisch validiertes Instrument zur Erfassung der therapeutischen Allianz. *Klinische Diagnostik und Evaluation* (1. Aufl.),. Vandenhoeck & Ruprecht GmbH.

Zheleznyakova, G. Y., Cao, H., & Schiöth, H. B. (2016). BDNF DNA methylation changes as a biomarker of psychiatric disorders: Literature review and open access database analysis. *Behavioral and Brain Functions.*

Zimmermann, J., Woods, W. C., Ritter, S., Happel, M., Masuhr, O., Jaeger, U., Spitzer, C., & Wright, A. (2019). Integrating structure and dynamics in personality assessment: First steps toward the development and validation of a personality dynamics diary. *Psychological assessment*, *31*(4), 516–531. https://doi.org/10.1037/pas0000625