A comparison of Cognitive Behavioral Analysis System of Psychotherapy (CBASP) and System of Supportive Psychotherapy (SYSP) for Early Onset Chronic Depression

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<tr>
<td>AE</td>
<td>Adverse Events</td>
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<tr>
<td>ANCOVA</td>
<td>Analysis of covariance</td>
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<td>ATR</td>
<td>Adverse Treatment Reaction</td>
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<td>BSI</td>
<td>Brief Symptom Inventory</td>
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<td>CALPAS</td>
<td>California Psychotherapy Alliance Scales</td>
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<tr>
<td>CBASP</td>
<td>Cognitive Behavioural Analysis System of Psychotherapy</td>
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<tr>
<td>CRA</td>
<td>Clinical Research Associate</td>
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<td>CRF</td>
<td>Case Report Form</td>
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<td>CTQ</td>
<td>Childhood Trauma Questionnaire</td>
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<td>DSMB</td>
<td>Data Safety Monitoring Board</td>
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<tr>
<td>DSM-IV</td>
<td>Diagnostic and Statistical Manual of Mental Disorders</td>
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<tr>
<td>E-IDS</td>
<td>30-item Inventory of Depressive Symptomatology-Expectation</td>
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<tr>
<td>ETI</td>
<td>Early Trauma Inventory</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>GAD7</td>
<td>7-item Generalized Anxiety Disorder Scale</td>
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<td>GAF</td>
<td>Global Assessment Functioning Scale</td>
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<td>GCP</td>
<td>Good Clinical Practice</td>
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<td>HAQ</td>
<td>Helping Alliance Questionnaire</td>
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<tr>
<td>HRQoL</td>
<td>Health-Related Quality of Life</td>
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<tr>
<td>HRSD</td>
<td>24-item Hamilton Rating Scale of Depression</td>
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<tr>
<td>ICD</td>
<td>International Classification of Diseases</td>
</tr>
<tr>
<td>ICH</td>
<td>The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use</td>
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<tr>
<td>IDS-SR</td>
<td>30-item Inventory of Depressive Symptomatology</td>
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<td>IIP-64</td>
<td>Inventory of Interpersonal Problems</td>
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<td>IPT</td>
<td>Interpersonal Psychotherapy</td>
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<tr>
<td>IRC/IRB</td>
<td>Institutional Ethics Committee</td>
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<td>ITT</td>
<td>Intention to treat</td>
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<tr>
<td>LOCF</td>
<td>Last observation carried forward</td>
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<tr>
<td>MDD</td>
<td>Major depressive disorder</td>
</tr>
<tr>
<td>MS</td>
<td>Milestone</td>
</tr>
<tr>
<td>PI</td>
<td>Principal investigator</td>
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<tr>
<td>QIDS-C16</td>
<td>16-item Inventory of Depressive Symptomatology, clinician-rated</td>
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<td>QLDS</td>
<td>Quality of Life in Depression Scale</td>
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<tr>
<td>QoL</td>
<td>Quality of Life</td>
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<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
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<tr>
<td>SAP</td>
<td>Statistical Analysis Plan</td>
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<td>SASS</td>
<td>Social Adaptation Self-Evaluation Scale</td>
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<td>SATR</td>
<td>Serious Adverse Treatment Reaction</td>
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<tr>
<td>SCID</td>
<td>Structured Clinical Interview for DSM-IV</td>
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<tr>
<td>SCL</td>
<td>Symptom Checklist</td>
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<td>SF-36</td>
<td>Medical Outcome Study 36-item Short Form Health Survey</td>
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<td>SF-12</td>
<td>The 12-item Short Form Survey</td>
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<tr>
<td>STAI</td>
<td>The State-Trait Anxiety Inventory</td>
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<td>SYSP</td>
<td>System of Supportive Psychotherapy</td>
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<tr>
<td>WAI</td>
<td>Working Alliance Inventory</td>
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1 General Information

1.1 Title
A comparison of Cognitive Behavioral Analysis System of Psychotherapy (CBASP) and System of Supportive Psychotherapy (SYSP) for early onset chronic depression
Short title: CBASP vs. SYSP
Identifying number: UKF001906
ClinicalTrials.gov ID: NCT00970437
Amendments: no
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1.7 Treatment Responsibility

E. Schramm, a certified and experienced CBASP clinician as well as supervisor for Cognitive Behavior and Interpersonal Therapy, will be responsible for training and supervision of the CBASP study therapists.

M. Hautzinger, a certified and experienced clinician and supervisor for Cognitive Behavior Therapy and for Supportive Psychotherapy, will be responsible for training and supervision of the SYSP study therapists.

1.8 Qualified physician

M. Härter, one of the Principle Investigators for the study, is a trained physician and will be responsible for all trial-site related medical issues.
2 Background Information

2.1 Investigational product

Cognitive Behavioral Analysis System of Psychotherapy (CBASP) is a manualized psychotherapeutic method (McCullough, Treatment for Chronic Depression; 2000; German version: Schramm et al., 2006) specifically designed for the psychological treatment of chronic depression. Its success is contingent on how well the therapist is able to implement the techniques to demonstrate to patients that they are responsible for the life dilemma they bring to psychotherapy. The patient’s chronic feelings of helplessness and hopelessness are prominent signs signaling (a) that the persons are disengaged perceptually from the interpersonal environment they live in (perceived dysfunctionality) and (b) that they are unable to recognize the interpersonal consequences of their behavior.

CBASP is a contingency training program that relies predominantly on the administration of negative reinforcement. Being able to identify the consequences of one’s behavior (perceived functionality) and learning to recognize one’s stimulus value for others, as well as the stimulus value others have for the patient (empathy), are the essential goals of treatment. Therapists are taught to keep patients on the participant hot seat at every turn by exposing behavioral consequences. A discomforting state of affairs frequently characterizes sessions so that when patients make important changes, the discomforting state is often reduced. Two CBASP techniques are designed to arrange in-session negative reinforcement contingencies: Situation Analysis and the Interpersonal Discrimination Exercise. A third technique contains Behavioral Skill Training and Rehearsal.

System of Supportive Psychotherapy (SYSP) is an active but less specific, manualized control treatment (Hautzinger 2001; Hautzinger et al. 2005, 2006; Hautzinger & Welz, 2008; Markowitz et al., 2008). SYSP - defined as non-interpersonal and non-cognitive-behavioral therapy - resembles the client-centered therapy of Rogers with added psychoeducation about depression. SYSP is defined as a therapy wherein the therapist strives to create a supportive relationship by emphasizing non-specific therapeutic interactions and techniques that convey to the patient the therapist’s interest, concern, and understanding. It emphasizes the patient’s strengths and assets. It utilizes the so-called common factors that have been assumed to account for much of the effect of all tested psychotherapies. These common or non-specific factors include:

- Facilitation of affect
- Helping the patient to feel understood (Relationship)
- A framework for understanding (Rationale)
- Empathy
- A treatment ritual (Ritual)
- Success experiences
- Hope and therapeutic optimism (Remoralization).
2.2 Summary of previous findings from clinical and non-clinical trials

Chronic depressions account for roughly a third of all mood disorders. In the USA, about 3% of the population suffers from chronic depression (Kessler et al., 1994). It is a particularly disabling disorder which is associated with greater comorbidity, more significant impairments in functioning, increased health care utilization, and more frequent suicide attempts and hospitalizations than acute major depressive episodes (Arnow et al., 2003). It therefore accounts for a considerable proportion of the enormous economic burden associated with depression (Greenberg et al., 2003). In more than 70% of all cases, chronic depression begins early in life (Cassano et al., 1992), is often associated with early interpersonal trauma and frequently persists life long. Early-onset chronic depression results in an even more substantial human capital loss compared with late-onset (Berndt et al., 2000). In addition, the disorder has a more malignant course than the late-onset group (Klein et al., 1999) and shows a high rate of relapse after an initial response to medication treatment (Agosti, 1999).

Specific and effective treatment strategies for chronic depression are urgently needed since it is not only a highly prevalent and particularly impairing disorder, but is also considered “difficult-to-treat” or even treatment resistant by most clinicians.

Although psychotherapy is commonly applied to chronically depressed patients with early-onset there is little data on the efficacy of psychological interventions for this disorder. One large study (n=681; Keller et al., 2000) showed that for the subgroup of chronically depressives with an early childhood trauma (Nemeroff et al., 2003) a psychotherapeutic method specifically designed for chronic depression (CBASP) was particularly effective. In contrast, medication (nefazodone) alone had a weak effect in this subgroup of patients as only 33% reached remission (48% with CBASP). The combination of CBASP and nefazodone resulted in a higher remission rate (54%) than both monotherapies. Similarly, imipramine but also more traditional psychotherapies (Interpersonal Psychotherapy/IPT, and Cognitive Behavioral Therapy/CBT) performed relatively poorly in the subgroup of early-onset chronic MDD as shown by an older reanalysis (Agosti et al., 1997) of the data of the NIMH-Collaborative study. In a randomized pilot study (Schramm et al., 2009) of our work group on 28 chronically depressed outpatients with early onset, highly significant differences were found between CBASP and IPT regarding the reduction of both self- and clinician-rated depressive symptoms in the first 14 completed subjects in favor of CBASP. The remission rate in the CBASP-group was very high (71.4% vs. 14.3% for IPT) probably due to the extended course of therapy (22 sessions) and sample characteristics (82% early traumatized, mostly physician-referred). The study proved to be feasible. However, we expected IPT as a depression-specific approach to be more efficient.

Based on these data, CBASP with and without medication seems to be a highly promising method for early onset chronic depression. Yet, CBASP was never compared to a placebo control. A control treatment consisting of active but non-specific supportive psychotherapy was used by Markowitz et al. (2005) with early-onset dysthymic patients as a comparator to IPT. Surprisingly, supportive psychotherapy did not perform significantly less than IPT (both with low remission rates of 12% and 22%) supporting the argument of Wampold et al. (2005) that psychological placebos - when properly designed and structurally equivalent – are as effective as psychotherapy in depressive disorders. However, in chronic depression the response to medication placebo is reported to be low (12%; Kocsis et al., 1988).
Based on the results of these studies, our primary hypothesis is that: CBASP is more effective in reducing depressive symptoms in patients with early-onset chronic MDD than a non-specific psychological control treatment (SYSP).

2.3 Potential risks and benefits to human subjects

Psychotherapeutic treatment with CBASP as well as with SYSP involves the chance of improvement of the depressive symptomatology. Possible undesired „side-effects” may include transient worsening of symptoms and transient risk of suicidality at the beginning of therapy (due to breaking out of avoidance behavior), but was rarely observed (e.g. Hoyer et al., 2006).

2.4 Rationale for dosage and treatment period

The available data up-to-date support the need for a greater number of psychotherapy sessions and a longer course of treatment to unfold its effects in chronic depression. Both CBASP and SYSP are conducted with two weekly individual sessions for the first 4 weeks and 1 weekly session for the remaining 16 weeks in the acute phase (=24 sessions, see Fig. 1 & 2), followed by 8 continuation sessions over the next 28 weeks (2 sessions in the first 4 weeks, and 1 session every 4 weeks thereafter). All patients will be free of medication (at least a 2-week drug-free period) before beginning of the trial.

Evidence indicates that effective treatment involves besides acute, also longer-term maintenance treatment (Gelenberg et al., 2003). A 12-months naturalistic follow-up is planned for a second study phase (not applied for here) since sustainment of response is particularly relevant given the chronic nature of the disorder. Furthermore, the only study using CBASP (Keller et al., 2000) did not report a follow-up. All non-protocol treatments that the patient may have obtained during the follow-up period will be assessed.

2.5 Compliance with the protocol, GCP, and applicable regulatory requirements

The trial will be conducted in compliance with the protocol, GCP, and the applicable regulatory requirements. In particular, the following aspects will be taken into consideration: a) submission of the proposed trial (trial protocol, patient information, informed consent form) to the IRB/IEC of the University of Freiburg (Ethik-Kommission der Albert-Ludwigs-Universität) and continued review of the ongoing trial by the committee. The IRB/IEC has been constituted according to the usual German regulations (landesrechtliche Statuten) and is organized and operates in accordance to GCP. In addition, the local ethics committees of the participating trial sites will be informed and asked for confirmation; and b) informed consent from all participating patients prior to clinical interview, randomization and intervention.

Any change or addition to this protocol requires a written protocol amendment. No change to the protocol may be made without the joint agreement of the Coordinating Investigator and the Co-Principle Investigator. Any amendment must be signed by all parties before the
change of or addition to the final protocol is effective. For major changes, the Data Monitoring and Safety Committee (DSMB) must be incorporated into the considerations. An amendment becomes an integral part of the protocol. All centers will be informed immediately after approval by the Coordinating or the Co-Principle Investigators.

2.6 Description of the population to be studied

Patients with chronic Major Depressive Disorder according to DSM IV.

Chronic depression, which is marked, often despite several trials of adequate psychiatric treatment, by a course of illness lasting 2 years or more, encompasses 4 subtypes of depressive illness: (1) chronic major depressive disorder, (2) dysthymic disorder, (3) dysthymic disorder with major depressive disorder ("double depression"), and (4) major depressive disorder with poor interepisodic recovery (i.e., in incomplete remission). Patients with pure dysthymic disorder will not be included in this study. Chronic depression not only causes chronic suffering, it compromises interpersonal functioning. Chronically depressed patients typically are passive, unassertive, avoid confrontation, and feel extremely uncomfortable in tolerating and expressing anger or taking social risks. They often lead marginalized lives, trying to avoid the social spotlight and pass as normal, hoping that other people will not notice their self-perceived inner defects (Markowitz, 2003).

3 Trial Objectives and Purposes

Effective treatment strategies for chronic depression are urgently needed since it is not only a common and particularly disabling disorder, but is also considered treatment resistant by most clinicians. There are only a few studies on chronic depression indicating that traditional interventions are not as effective as in acute, episodic depression. In addition, most of the studies had methodological weaknesses, such as the very short courses of psychotherapy. With the present multicentre study, the efficacy of the only specific psychotherapy for chronic depression (Cognitive Behavioral Analysis System of Psychotherapy/CBASP) is compared with a non-specific supportive psychotherapy (SYSP - a well-designed psychological placebo) in early onset chronically depressives. CBASP faired very well in one large trial but has never been directly compared to a placebo control. Another innovative aspect of the study is the use of an extended course of psychotherapy (32 sessions).

Primary hypothesis: CBASP is more effective in reducing depressive symptoms than SYSP.

Our secondary hypothesis is: Remission rates are higher in CBASP than in SYSP.

In summary, this trial will generate important new evidence, because it addresses the proof of concept that CBASP works.
4 Trial Design

4.1 Primary and secondary endpoints

Determination of primary and secondary measures

Primary endpoint:
Depressive symptoms 20 weeks after randomization (after acute treatment phase) as measured by the HRSD.

Secondary endpoints:
- Depressive symptoms after 12 and 48 weeks as measured by the HRSD, and remission after 12, 20, and 48 weeks as measured by the IDS-SR. Remission is defined a priori as a score of 13 or less for at least three consecutive weeks in the acute phase for those who completed the 12-week/20-week protocol and at the time of withdrawal for those who did not complete the study. For calculation of remission in the continuation phase, the IDS-SR-Value has to be 13 or less at week 44 and 48. Furthermore, the proportion of patients who demonstrate clinical response will be analyzed, where response is defined by a reduction of at least 50% in the baseline at week 12, 20, and 48.
- Changes in QIDS-C16 (from baseline to week 12, 20, and 48)
- Temporal changes in IDS-SR – Total sum score between baseline assessment and follow-up assessments (time course of 27 time points)
- Changes in GAF (from baseline to week 12, 20, and 48)
- Changes in Anxiety-subscalse\(^1\) (sum score anxiety items BSI and GAD7, changes from baseline to week 12, 20, and 48)
- SASS (sum score, changes from baseline to week 12, 20, and 48)
- Changes in IIP-subscales from baseline to week 12, 20, and 48
- Changes in QoL-Scales SF-12 and QLDS (from baseline to week 12, 20, and 48)

A Number needed to treat (NNT) of 8 and a difference in relapse rates during continuation treatment of 5% is considered to be clinically relevant. In addition, the HRSD-remission rates (HRSD \(\leq 8\)) and HRSD –response rates (HRSD score by at least 50 percent from baseline) will be calculated for the main measurement time points.

Rationale and description of endpoints, parameters and instruments\(^2\)
All measures of outcomes are widely used internationally, are reliable and valid, also for usage in Germany.

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\(^1\) Compared to the proposal, the STAI was replaced by a more symptoms-related measure of anxiety

\(^2\) For an overview of methods and time points of assessment see 7.2
Primary endpoint

Severity of depression

The HRSD is the most frequently-used clinician-rated measures of depression severity (Moran et al. 2005). The 24-item-version has been implemented in the study by Keller et al. (2000) and will therefore ascertain internationally comparable study results.

Evidence suggests that the Hamilton Depression Scale is psychometrically and conceptually somewhat flawed (Bugby et al., 2004). Many scales and instruments used in psychiatry today are based on—or at least include—current DSM symptoms. Therefore we include the QIDS-C (see description below), as in the Star*D-study (Rush et al., 2004).

Secondary endpoints

Severity of depression – self-rating and clinician-rated

The 16-item Quick Inventory of Depressive Symptomatology, clinician-rated (QIDS-C16) and the 30-item Inventory of Depressive Symptomatology, Self-Report (IDS-SR; Rush et al., 1996) have been used to assess acute and longer-term outcomes and have highly acceptable psychometric properties (Rush et al. 2005). The IDSs were intended to comprise all areas of depressive symptoms according to the Diagnostic and Statistical Manual of Mental Disorders, DSM-III-R and DSM-IV, assessed in a clear and steady graduation (Rush et al., 1996). The IDS-SR contains 30 items. Only 28 of 30 items count for the sum-score, because the two questions addressing change of weight and appetite distinguish between ‘loss’ and ‘increase’. All items are rated on a scale from ‘0’ (symptom is not present) to ‘3’ (strongest impairment). A cut-off-point of 26 (IDS-SR) and 11 (QIDS-C16) indicate a clinical relevant depressive symptomatology (Trivendi et al., 2004).

Expectation and importance

We will use a modified version of the IDS-SR to measure expectation (E-IDS). Patient will be asked what they expect to answer in the IDS-SR at the end of therapy. Furthermore, the patient will give information about the importance of being symptom-free.

Severity of anxiety

In elderly depressed patients, anxiety predicted slower recovery (Dew et al. 2007), and lower baseline anxiety predicted response at 12 weeks (Andreecdu et al. 2007). In order to identify anxiety as a predictor, the following instruments will be applied: Symptoms of anxiety will be measured using the anxiety scale and the phobic anxiety scale from the Brief Symptom Inventory (BSI). The BSI is a validated self-report scale developed from the SCL-90-R with strong test-retest and internal consistency reliabilities. Factor analytic studies of the internal structure of the scale have demonstrated its construct validity (Derogatis et al. 1983). The anxiety subscale consists of six items: nervousness, suddenly scared, feeling fearful, feeling tense, feeling restless, and spells of panic. In the original version, each item is rated on a 5-point scale (0=symptom not present, 4=extremely severe). To get an uniform scale with the GAD-7, each item will be rated on a 4-point scale (0=symptoms
not present, 3=severe). The GAD-7 (Spitzer et al., 2006) is a valid and efficient tool with 7 items for screening for generalized anxiety disorder. It also assesses the severity of GAD.

Quality of life

The Medical Outcome Study 36-item Short Form Health Survey (SF-36; Ware et al., 1992) is an internationally approved, generic instrument to assess Health-Related Quality of Life (HRQoL). The 12-item Short Form Survey (SF-12), derived from the SF-36, has been demonstrated to be reliable and valid in clinical and population-based applications in the U.S. and other countries (Ware et al., 1996; Gandek et al. 1998; Sugar et al. 1998; Jenkinson et al. 1997). The physical health and mental health summary scores that reproduce the summary scores derived from the SF-36, have been demonstrated to account for most of the variance in the eight subscales of health functioning (Ware et al., 1996). SF-12 scores range from 0 to 100, with 100 being complete absence of impairment.

A more disease-specific instrument is the Quality of Life in Depression Scale (QLDS). This 34-item measure was developed to measure the impact of depression symptoms and treatment on quality of life (Hunt and McKenna, 1992). The QLDS has evidence of reliability, construct and content validity, and sensitivity to change in depressed patients (Whalley and McKenna, 1995). All items are rated on a scale with 'yes' (statement is true) or 'no'. The score is an index ranging from 0 to 34, with a higher score indicating worse QOL.

Interpersonal problems

Interpersonal problems will be measured with the German translation of the 64-item Inventory of Interpersonal Problems (IIP-64; Horowitz et al. 2000). The IIP-64 is a self-report questionnaire. Its strength is that it simultaneously assesses multiple aspects of interpersonal malfunctioning. Psychometric research on the instrument in English-speaking communities as well as in German-speaking populations (Horowitz et al., 2000) demonstrated the validity and the reliability (good internal consistency and test-retest reliability) of the IIP-64.

Social functioning

Assessment of functional status is increasingly important in clinical trials and outcome research. To measure global psychological, social, and occupational functioning, the widely utilized Global Assessment of Functioning (GAF, Axis V in DSM-IV) scale will be used. Another measurement is the Social Adaptation Self-Evaluation Scale (SASS, Duschek et al., 2003), specifically for self-assessment of social functioning by patients with depression. This scale has been used in European clinical trials and is currently being studied in the United States. It contains 21 items covering the different aspects of social interactions, global social attitude, and self-perception. The SASS has been validated and found to be simple to use and sensitive to changes in the different areas of social functioning (Weissman, 2001).

Childhood trauma

At baseline, the Childhood Trauma Questionnaire (CTQ; Bernstein et al., 1994) will be completed. The CTQ is a 28-item retrospective self-report questionnaire which determines 4 se-
verity categories of emotional/physical/sexual abuse, and emotional/physical neglect. “Early trauma” is defined as one of these experiences before the age of 18 to a degree of at least “moderate to severe”. In addition, we will use the Early Trauma Inventory (ETI; Bremner et al., 2000), a 56-item semi-structured interview. The ETI assesses also the domain of general trauma (not assessed by CTQ). The psychometric properties of both instruments have shown to be favorable (Bremner et al., 2007).

**Process analyses of therapies**

In addition to outcome analyses, this study aims to investigate the therapy processes.

After each session, the patients and therapists will be requested to fill out the Helping Alliance questionnaire (HAQ)\(^3\) developed by Luborsky (1985). It is an 11-item self-report questionnaire rated on a six-point rating-scale (from -3, I strongly feel that it isn’t true, to +3, I strongly feel that it is true). The instrument assesses two types of alliance: patient’s experience of feeling helped and supported by the therapist (seven items) and patient’s experience of working together with the therapist in a joint effort in order to overcome the difficulties (four items).

The HAQ is correlated to other well validated instruments (0.74 to CALPAS and 0.74 to WAI according to Hatcher & Barends, 1996), is highly correlated with outcome (Martin et al., 2000) and shows at least similar psychometric properties to other alliance instruments (Luborsky, 2000).

To identify therapy-induced changes those constitute a negative effect, the HAQ (patient's version) will be extended by further questions:

- Would you recommend this kind of treatment to someone with similar problems?
- Would you recommend this therapist to someone with similar problems?'
- To what extent did the therapy help you?
- Do you experience any undesirable “side-effects” of the therapy (such as increased rumination, suicidal thoughts, etc.)?

**Adherence**

All sessions will be videotaped and site-supervisors will review the videotapes regularly on a random basis to assess psychotherapists’ adherence to the treatment procedures using specific rating-scales (McCullough, 2000 and Markowitz, 2003). In addition, a separate team of independent raters trained to reliability will randomly evaluate several of the tapes from early, middle, and late therapy phase of each treatment for adherence and therapist competence.

**Evaluation by a relative**

We will use a new questionnaire for close relatives of the patient to measure changes in depression perceived by them. At the end of the therapy, a relative of the patient will be asked

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\(^3\) Compared to the proposal, the WAI was replaced by the HAQ. The therapist and the patient form of this questionnaire are available in German.
to evaluate 14 items of depressive symptoms before and after therapy. Each item will be rated on a 5-point scale (0=symptoms not present, 4=extremely severe).

**Screening**

The initial screening visit consists of a medical and psychiatric history. Diagnoses will be derived using the Structured Clinical Interview for DSM-IV (SCID-I and II; First et al., 1997) during the screening evaluation as well as after 20 and 48 weeks of treatment.

The *Structured Clinical Interview for DSM-IV (SCID-I)* (German Version: Wittchen et al., 1997) is a diagnostic interview which is widely used by health care professionals and has been implemented in cross-national epidemiological and treatment studies. It includes an introductory overview followed by nine modules, seven of which represent the major Axis I diagnostic classes (e.g., mood disorders, anxiety disorders, adjustment disorders, somatoform disorders). Because of its modular construction, it can be adapted for use in studies in which particular diagnoses are not of interest. Using a decision-tree approach, the SCID guides the clinician in testing diagnostic hypotheses as the interview is conducted. Although the semi-structured interview consists of standardized questions, it allows the experienced clinician to tailor questions to fit the patient's understanding; to ask additional questions that clarify ambiguities; to challenge inconsistencies; and to make clinical judgments about the seriousness of symptoms. The output of the SCID is a record of the presence or absence of each of the disorders being considered, for a current episode (past month) and for lifetime occurrence. Interrater reliability has been reported to be between .88 and .95 for the diagnoses of major depressive episode (Gorman et al., 2004).

The *Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II)* is a semi-structured diagnostic interview for assessing the 10 DSM-IV (German Version: Wittchen et al., 1997) Axis II personality disorders, as well as Depressive Personality Disorder and Passive-Aggressive Personality Disorder (included in DSM-IV's Appendix B, "Criteria Sets and Axes Provided for Further Study"). SCID-II can be used to make Axis II diagnoses, either categorically (present or absent) or dimensionally (by noting the number of personality disorder criteria for each diagnosis that are coded "3")

The SCID-II is a two-stage method consisting of a questionnaire for screening personality disorders and a structured interview.

**Sociodemographic and medical data**

a) **Sociodemographic data**

Sex, age, nationality, marital status, education, occupation, measure of household income, and employment

b) **Medical data**

Previous or present diseases, outpatient and/or inpatient psychiatric and/or psychotherapeutic treatments; suicidal attempts and risk factors for suicide
**Therapist data**

The name of the therapist (coded as digits: center digit _individual therapist digit) of each patient will be registered. In addition, a therapist form will be used for descriptive values (e.g. age, sex, clinical experience) and qualification of therapists.

To evaluate therapist attitudes toward CBASP und SYSP, specific questionnaires will be applied at the therapy training, after the first study patient, and after study termination.

**Safety/Acceptance Outcomes**

- Drop-out rates
- Rates of drop-out due to AEs
- Rates of drop-out due to suicidality
- Rates of patient with AEs
- Rates of patients with suicidality
- Time to drop-out

**4.2 Type and design of the trial**

Multicentre, observer blind, prospective, randomized, controlled study, active control, 2 treatment phases (acute and continuation) (trial design see Figure 1)

A stratified block randomization with randomly varying block size will be performed, stratified by trial center.

**Interventions**

*CBASP* and *SYSP* are conducted with two weekly individual sessions of 50 minutes each for the first 4 weeks and 1 weekly session for the remaining 16 weeks in the acute phase (=24 sessions, see Figure 1 & 2), followed by 8 continuation sessions over the next 28 weeks (2 sessions in the first 4 weeks, and 1 session every 4 weeks thereafter).

See description of interventions in Section 2.1. and 4.4.
Patients declining participation / refusers

This group of patients will be aimed to be assessed to gain information about characteristics of patients refusing treatment. As part of standard care within each treatment center, individual consultations will be available for all patients outside of the study protocol (randomization etc.).

4.3 Measures taken to minimize/avoid bias

a) Randomization

Randomization will be conducted according to a central computerized randomization schedule, with a 1:1 treatment allocation ratio, stratified by centre, in blocks of variable size, to
guarantee concealment. The internet based randomization allows investigators at the centers to randomize patients from anywhere through the convenience of their web browser. Investigators require a valid username, password and PIN number to access the randomization application, and randomize patients by simply completing an on-screen form with patient details, inclusion and exclusion criteria. Investigators are immediately shown the treatment allocation.

Randomizations are conducted via SSL encryption for added security. No-one can delete records from the randomization database, so that all randomizations have to be accounted for. Audit log files detailing all activity on the randomization system are available to the trial coordinator.

**b) Blinding**

All clinical ratings will be completed by trained (high interrater-reliability and procedural integrity throughout the study, not just during training) and independent evaluators blinded to treatment assignment. Ideally, the same evaluator will rate the patients at all measurement times. Each of the sites will implement procedures to mask a patient treatment assignment from the person who will evaluate the results of the clinical ratings through the following: 1) locating the rater at a separate physical location, and 2) reminding the patients at each visit not to mention anything that might reveal their treatment condition to the independent evaluator.

**c) Control of therapy allegiance**

Over the past several years, therapy allegiance, i.e. treatment preference of the investigators, has been discussed as an important influencing factor for results in psychotherapy research (Luborsky et al., 1999). There have been several recommendations for how to minimize the allegiance effect: involving several investigators who represent a “mix of therapy allegiances”, comparing interventions of the same length and duration, using blinded raters for process and outcome analyses, and conducting both interventions in all sites (Thase, 1999). All recommendations will be realized in the present study.

**d) Control for overlapping treatments**

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

1. The therapists are obligated to adhere to the therapeutic procedures and interventions described within the manuals. Adherence to the treatment manuals will be continuously supervised by watching videotapes of the sessions using adherence scales (McCullough, 2000 and Markowitz, 2003). In addition, after each session the therapists will fill out a check list (containing therapeutic elements of both therapies) regarding the employed interventions. The validity of the therapist’s statements will be checked through external assessment of the video recordings. In the post-hoc analysis it will be checked if the expected differences regarding intervention characteristics appear within the therapies.

2. Each therapist will conduct only one of the two treatments.

3. To evaluate therapist attitudes toward CBASP und SYSP, questionnaires will be applied at the therapy training, after the first study patient, and after study termination.
Possible influences through qualification differences of the therapists will be controlled as follows:

1. All therapists have completed professional training (or they are in their second training year (out of three) for certification as a licensed psychotherapist).
2. All therapists have completed a comprehensive training (min. 24 hours) within the respective treatment approach. Therapists will conduct two pilot cases which will be intensively supervised.
3. Concerning their influence upon the effectiveness of treatment, level of training and professional experience of the therapists will be collected and reviewed.

**e) Control for confounding factors**

1. The influence of the trial site upon the effectiveness of the respective treatment approaches will be investigated as a separate factor.
2. Patients will be asked not to engage in off-study psychosocial (e.g., group therapy) or psychiatric interventions (e.g. antidepressive medication) during the treatment period.

**f) Control for measurement bias**

1. All raters have completed training for rating HRSD.
2. Guidelines for rating scales are available.
3. Determination of the interrater reliability on the basis of at least 4 recorded HRSD ratings.

### 4.4 Trial treatments

CBASP as the experimental intervention will follow a manual (McCullough, 2000; German version: Schramm et al., 2006). The approach is specifically tailored for the treatment of chronic forms of depression, particularly with early-onset, by focusing on the problems resulting from an inhibition of maturation in early childhood and by using the therapeutic relationship in a personal, disciplined way as well as other specific techniques (e.g. Interpersonal Discrimination Exercise, Situation Analysis). CBASP integrates behavioral, cognitive, and interpersonal strategies.

The comparator for CBASP is SYSP, a system of supportive psychotherapy, an active but less specific, manualized control treatment (Hautzinger et al. 2005, 2006, 2008; Markowitz et al., 2008) previously used in several comparative trials. SYSP - defined as non-interpersonal and non-cognitive-behavioral therapy - resembles supportive clinical management, client-centered therapy, counseling, and psychoeducation about depression. It is assumed that many clinicians in private practice proceed in this unstructured manner. There is no specific explanatory mechanism for treatment effect offered to the patient and it does not focus on specific themes. The number and duration of sessions as well as the experience of the therapists in this treatment condition will be equivalent to CBASP. According to a meta-analysis of Baskin et al. (2003) structurally equivalent “placebos” produced negligible effects.
compared to active treatments (Hegerl et al. 2009). But there are also studies with depressed subjects which show significant effects for supportive interventions (Hautzinger & Welz, 2008; Wampold, 2005).

CBASP and SYSP will be implemented by 2 separate groups of psychotherapists, both trained (in a 2-day training workshop and 1 practice day) in one of the methods and meeting the criteria for mastery of CBASP or SYSP procedures as assessed by evaluation of their performance during two videotaped pilot cases. All psychotherapists have completed a 3-year psychotherapy training program or are in an advanced stage of training. All sessions will be videotaped and site-supervisors will review the videotapes regularly on a random basis to assess psychotherapists’ adherence to the treatment procedures using specific rating scales (McCullough, 2000 and Markowitz, 2003). In addition, a separate team of independent raters trained to reliability will randomly evaluate several of the tapes from early, middle, and late therapy phase of each treatment for adherence and therapist competence. Site-supervisors will be directly supervised by the trial-supervisors (E. Schramm & M. Hautzinger) in terms of two-weekly conference calls and meetings (twice a year or more if needed).

Evidence suggests the application of a greater number of psychotherapy sessions and a longer course of treatment is necessary to unfold the effects of psychological intervention in chronic depression. In our experience (both clinical and from the pilot study), two weekly individual sessions in the first 4 weeks facilitate the engagement of the patient and provides an intensive start. After the first 4 weeks, both CBASP and SYSP are conducted with 1 weekly session for the remaining 16 weeks in the acute phase (=24 sessions), followed by 8 continuation sessions over the next 28 weeks (2 sessions in the first 4 weeks, and 1 session every 4 weeks thereafter). The CBASP manual is designed as a longer intervention due to the chronic nature of the condition. Evidence indicates that effective treatment involves besides acute, also longer-term maintenance treatment to transfer the learning into daily life (Gelenberg et al., 2003). The duration of 50-minutes for each session is a common dosage in individual therapy.

A 12-months naturalistic follow-up is planned for a second study phase (not applied for here) since sustainment of response is particularly relevant given the chronic nature of the disorder.

4.5 Duration of subject participation

First patient in to last patient out: 30 months

Duration of the entire trial: 36 months

Duration of treatment per patient: 20 weeks of acute treatment followed by 28 weeks of continuation treatment = 48 weeks

Follow-up per patient: 48 weeks after randomization
4.6 Criteria for discontinuation

Individuals:
- Active suicidality,
- The physical health of the patient is at risk due to clinical judgment,
- Occurrence of an AE/SAE (Adverse Event/Serious Adverse Event) with therapeutic implications,
- Newly occurring exclusion criteria, or
- The informed consent is withdrawn.

Parts of the trial and entire trial:
If an investigator has ethical concerns because of the performance at one of the centers, the Coordinating Investigator or the Co-PI must be informed immediately. The Coordinating Investigator and the Co-PI are authorized to discontinue interventions in a trial centre because of insufficient and/or inadequate recruitment, insufficient quality of data or special problems unforeseeable in advance, which make the continuation of the study impossible at that specific centre.

A single treatment arm or the whole trial will be stopped if severe safety concerns become apparent to the DSMB or if stopping is recommended by the DSMB based on the adaptive interim analysis.

4.7 Accountability procedures
Therapists conducting the therapy sessions will be trained and will receive continuous supervision during the trial (see Section 4.3).
The supervisors of the site-supervisors are experienced psychotherapists with an official supervisory status. The supervisor of CBASP (E. Schramm) was the first certified CBASP-trainer and therapist in Europe (by J. McCullough), is active in the distribution of the approach, and has conducted previous trials with the intervention. Supervision for SYSP will be organized and lead by M. Hautzinger who conducted several studies in which supportive therapy was the control condition.

Supervisors meet at least bi-monthly for conference calls with their site-supervisors.

4.8 Randomization codes and procedures for breaking codes

If a patient appears to be eligible for the study, the Site Coordinating Investigator will inform the patient about the study and must then receive written informed consent from the patient before any further study specific examination. Then the Site Coordinating Investigator will register the patient on a patient identification list located at the trial center.

According to this list, the patient receives a consecutive patient identification number. This patient identification number consists of five digits:

- The first two digits are the number for the trial site.
- The next three digits stand for the successively screened patients (e.g., 001 for the first patient)

The Site Coordinating Investigator must record the following information about the patient on the patient identification list:

- Full name
- Date of birth
- Inclusion and exclusion criteria of the study fulfilled/ not fulfilled

Treatment assignments for this study will be made using separate randomization schedules for each of the 10 trial sites. 100 randomization lists will be prepared by the University Medical Center Hamburg-Eppendorf prior to the start of recruitment. From these lists, the Freiburg Trial Site Coordinator (I. Zobel) will randomly assign a randomization schedule to the participating centers, respectively. All randomization schedules will remain confidential and known only by the Freiburg Trial Site Coordinator, who is not involved in recruiting and patient's inclusion.

Once the forms have been checked to be sure the participant meets eligibility requirements, the Site Coordinating Investigator shall access the interactive, internet based randomization program. The program will verify through a defined set of questions that the participant is ready to be randomized and provide a randomized treatment assignment for that participant.

The information registered on the patient registration form will contain:

- Patient identification number
- Year of birth
- Inclusion criteria of the study fulfilled
The randomization assignment will be printable displayed on the screen and emailed to the Site Coordinating Investigator.

This randomization email will contain:

- Patient identification number
- Year of birth
- Treatment and treatment number (a single digit assigned by the Freiburg Trial Site Coordinator)

After receipt, the Site Coordinating Investigator will record the treatment number on the patient identification list.

The code will not be broken until the primary statistical analyses have been completed and reviewed by the investigators.

4.9 Identification of data to be recorded on the CRFs/source data

There will be CRFs for each study participant on which data will be recorded directly. The completed CRFs are collected at each site and sent at least bi-annual to the Coordinating Centre Freiburg. The originals of the completed CRFs will be stored in the Department of Psychiatry and Psychotherapy, University Hospital Freiburg for at least 10 years.

5 Selection and Withdrawal of Subjects

The large sample size and the inclusion of 10 recruitment sites in different regions of Germany and from different departments (psychiatry and psychotherapy, psychology and psychotherapy, and psychosomatic medicine) will assure wider (e.g. geographical) participation and therefore greater generalisability and representativeness of results. Furthermore, we kept exclusion criteria to a minimum (expecting a high rate of comorbidity) in order to extend the generalisability of our findings.

Patients will be recruited from private practitioners (primary care physicians, psychiatrists, and psychotherapists), outpatient clinics, through announcements in the media, and announcements in public health centers.

In case of recruitment without medical referral (i.e. general physician or psychiatrist), trial centers will organize a close cooperation with the treating physician. If a medication washout is required, the referring physician (or the cooperating physician) will be responsible for an adequate period of the washout.

5.1 Inclusion criteria

Participants must meet the following criteria:

1) DSM-IV criteria for a current episode of chronic MDD, MDD superimposed on a pre-existing dysthymic disorder or recurrent MDD with incomplete remission between episodes in a patient with a current MDD and a total duration of at least 2 years.
2) Early onset of the disorder according to DSM-IV (onset before the age of 21)
3) Age between 18 and 65
4) A score of at least 20 on the 24-item HRSD at screening and, after a 2-week drug-free period, at baseline
5) Fluent in German language
6) Provide informed consent

5.2 Exclusion criteria
1) Acute risk for suicide (as opposed to suicidal thoughts) assessed according to clinical practice guidelines. Suicidal patients are eligible, as long as outpatient treatment is deemed safe by the clinician.
2) A history of psychotic symptoms, bipolar disorder, or organic brain disorders
3) A primary diagnosis of another axis I disorder including anxiety disorders (e.g. Posttraumatic Stress Disorder), or any severe substance-related abuse or dependence disorder as evaluated with the SCID-I
4) Antisocial, schizotypical, or borderline personality disorder (SCID-II);
5) Severe cognitive impairment
6) Absence of a response to previous adequate trial of CBASP, and/or SYSP
7) Other ongoing psychotherapy or medication
8) A serious medical condition (i.e. a history of seizures, severe head trauma, stroke or heart attack within six months before the study began)

5.3 Withdrawal criteria
In case of occurrence of an AE/SAE with therapeutic implications, newly occurring exclusion criteria or if the informed consent is withdrawn the patient's participation in the trial will be terminated. Patients may withdraw from the study at any time at their request, for any reason, specified or unspecified and without penalty or loss of benefits the patients are otherwise entitled. Patients who are withdrawn from the study will not be allowed to re-enter later. Date of discontinuance, all recorded results at this time and if known the reasons for discontinuation will be documented in the CRF.

It is preferred that as few patients as possible prematurely discontinue treatment. All patients will be followed and documented after discontinuation of the treatment in order to record the data required according to the intention-to-treat principle. It is expected that only few patients will have to be withdrawn from treatment because of discontinuation criteria. They are accounted for in the general drop out rate included in sample size and power calculations (see Section 9.2). Therefore, withdrawn subjects will not have to be replaced.
6 Treatment of Subjects

6.1 Treatments to be administered
Treatments within this trial are described in Sections 2.1 and 4.4.

6.2 Medication/treatments permitted during trial
In cases of severe sleep problems, zolpidem is allowed for a limited period of time during the study (for a maximum of 3 weeks). Central acting drugs are not allowed during the study. Furthermore, illegal drugs are not allowed. Single dosages of non-steroid analgesics and other non-centrally acting drugs for medical conditions are allowed. General self-support groups can be maintained if already started.

6.3 Monitoring compliance
Patients’ attendance of therapy sessions will be documented. Therapists will immediately follow up on absent patients. Assessment forms for baseline, post-intervention and follow-up will be posted to patients and followed by reminders from the study center in case of no return.

7 Assessment of Efficacy

7.1 Efficacy parameters
See Section 4.1 primary and secondary endpoints

7.2 Assessing, recording and analyzing of efficacy parameters
For a description of endpoints, parameters and instruments see Section 4.1 primary and secondary endpoints. For an overview of patient’s study visits and measurement times and screening flow see Figure 3 and 4, respectively. The screening procedure contains six blocks from first phone screening (I) to baseline measurement (T0a and T0b). If required, the referring or cooperating physician will be consulted (e.g. for medication washout).

For analyzing of parameters see Section 9.1
Figure 3 Patient's study visits and measurement times (Marked in green and italic: primary self-ratings; for abbreviations see page 2).

Figure 4 Detailed screening flow
8 Assessment of Safety

8.1 Specification and Assessment of safety parameters

**Adverse Event (AE)** is defined as any disadvantageous incident occurring to a person receiving either psychotherapeutic intervention, irrespective of possible associations with the received treatment.

In the present study the following AEs are defined:

1. exacerbation of symptoms, e.g. generalization of symptoms
2. appearance of new symptoms
3. appearance of passive suicidal thoughts
4. appearance of active suicidal plans or intentions
5. occurrence of problems in the patient-therapist relation
6. further disadvantageous incidents as assessed by the therapist.

**Adverse Treatment Reaction (ATR)** is defined as any AE due to the received treatment.

The decision on causality of AEs will be made by the therapists and will be supervised and controlled by the PIs and the DSMB.

**Serious Adverse Event (SAE) and Serious Adverse Treatment Reaction (SATR)** are defined as an AE or ATR resulting in:

1. death;
2. life-threatening event, e.g. suicidal attempt;
3. an incident requiring hospitalization;
4. an incident leading to significant or permanent disability or invalidity.

**Adverse Event CRF**

(S)AEs and (S)ATRs will be documented after each session using an Adverse Event CRF. In the CRF the therapists will be asked to describe any adverse event, its duration (start/end date), intensity (mild, moderate, severe), assessment of causality (treatment related, probably related, possibly related, unlikely related, not related, not assessable), action taken, and outcome of the action taken. Furthermore, the therapist's will be asked to assess whether the documented AEs and ATRs are judged to be serious (SAE, STR).

In case of changing therapists, the reasons for this change will be documented in a separate form.

8.2 Report, recording and reporting adverse events

Adverse Event CRFs (see 8.1) will be analyzed three times during the study as part of the regulatory Monitoring Reports provided by the monitoring institute (University Medical Center Hamburg-Eppendorf).

Serious adverse events (SAEs) and serious adverse treatment reactions (SATRs) are to report within one week to the coordinating center per fax or electronically (e-mail) using a Serious Adverse Event report form that provides further details on the incident.
8.3 Follow-up of subjects after adverse events

Patients leaving the interventions due to one or more of the reasons mentioned above will be followed up in accordance with good clinical practice until resolved or judged no longer clinically significant.

9 Statistics

9.1 Statistical methods and interim analyses

Statistical analyses will be done using the program 'Statistical Analysis System' SAS or SPSS. All program scripts which run for analysis will be documented and saved.

The primary interim and final analyses will be performed in the intention to treat (ITT) population, allocating patients to treatment groups according to the arm to which they were randomized, and using the LOCF method in case of missing outcome data at week 20. Because of the chronic nature of the disorder, spontaneous remission is unlikely to happen.

Since it is anticipated that placebo (SYSP) might be substantially inferior to CBASP, one interim analysis allowing for early stopping with rejection of the null hypothesis is planned in a group sequential design. It is planned for the time when about a third of the planned patients (i.e. 90 patients) have been followed up for 20 weeks, plus the time needed for data cleaning and analysis. To avoid inflation of the type I error rate, the p-value for the interim analysis and the final analysis of the primary objective will be adjusted according to the a-spending function corresponding to an O’Brian and Fleming design (see Wassmer 1999, p. 59 and A.6). At the interim analysis, the null hypothesis of equal efficacy will be tested (two-sided test) using analysis of covariance (ANCOVA) controlled for pre-treatment scores and centre. If the null hypothesis can be rejected at the adjusted interim significance level, the trial will be stopped. If not, recruitment will carry on to the maximum target number of 268 randomized patients.

Secondary analyses of the primary endpoint will include a per-protocol approach, regression controlling for additional factors, and exploratory analyses of treatment effect modifiers. To examine changes over time, the MIXED model approach to repeated measures with 2 treatments by 4 measurement points will be used: baseline, after 12 weeks, after 20 weeks (acute intervention), and after 28 further weeks of continuation treatment. Analyses of continuous secondary variables will be performed using generalized linear mixed models. For remission rates, chi-squared tests and logistic regression will be used. The analysis of time to remission and time to response will be analyzed using standard survival analysis techniques.

Rates of (serious) adverse events with two-sided 95% confidence intervals will be reported separately for patients who attended at least one session of CBASP or of SYSP, respectively.

Standard methods will be used to provide tabular and graphical summaries as appropriate for continuous and categorical variables. To assess generalizability, demographic and clinical characteristics will be compared between participants who are subsequently randomized and participants who are screened but not randomized. The specific eligibility and exclusionary
criteria by which participants are excluded from randomization will be tabulated. Demo-
graphic and clinical characteristics will be compared among the clinical coordinating centers
and between the treatment groups to identify any imbalances.

Subgroup Analyses: Interaction terms between the treatment comparison and baseline fac-
tors in pre-specified participant subgroups will be used to test for differences in the treatment
comparison of the primary outcome and other outcomes between different subgroups. The
factors (moderators) to be considered in subgroup analyses (such as Childhood trauma, co-
morbidity, treatment expectation, suicidality and previous treatment), and further predictors,
mediators will specified in the detailed statistical analysis plan (SAP).

Before the start of the analysis the detailed SAP will be prepared by the responsible statisti-
cian. This will be completed during the 'blind review' of the data, at the latest. This blind re-
view, i.e., a checking and assessment of the data, will be performed after the end of the re-
cruitment period, and it will be conducted ignoring treatment assignment. If the SAP contains
any changes to the analyses outlined in the trial protocol, they will be marked as such, and
reasons for amendments will be given. The SAP will be appended to the trial protocol.

The randomization code will be broken in two steps. The participants will be identified as
belonging to group "1" or "2" without revealing which is the CBASP and SYSP group. The "1"
and "2" code will not be broken until the primary and secondary statistical analyses have
been completed and reviewed by the investigators.

9.2 Sample size/Recruitment

a) Power calculation

To be assessed for eligibility: n = 450

To be allocated to trial: n = 268

To be analyzed: intention-to-treat: n = 268; per protocol: n = 210

The sample size calculation starts by considerations for a fixed design, based on the primary
outcome (HRSD) and on the primary hypothesis testing CPASP against SYSP (null hypothe-
sis: identical expected HRSD). We considered a difference of five points on the HRSD be-
tween mean post-treatment scores of the treated groups as clinically relevant. In similar stud-
ies, standard deviations of post-intervention HRSD-scores of groups receiving CBASP,
SYSP, or combinations range from 5.4 to 10.4 points (Keller et al., 2000; Markowitz et al.,
2005). Assuming a common standard deviation of 10 points for two-group comparisons
yields a medium-sized effect of 0.5 (Cohen's d). To detect this effect by a two-tailed t-test
with a power (1-α) of 0.95 and type I error probability level of α=0.05 for significance, 210
patients (105 per group) are needed.

However, to allow for early stopping in case of substantial inferiority especially of the placebo
(SYSP) arm, an interim analysis allowing for early rejection of the null hypothesis was
planned for the time when data of about a third of the patients are available. A conservative
estimate of the inflation factor for the maximum sample size in this group sequential design
with one interim analysis compared with the fixed design is 1.007 (the factor valid for two groups of equal size and a power (1-α) of 0.9; see Jennison and Turnbull 1999, p. 30). Thus 214 patients should be available for analysis. Assuming a drop-out rate of 20% from baseline to week 20, the maximum sample size is fixed as 268 patients to be randomized. This is the number needed for an appropriately powered per-protocol analysis (only completers are analyzed). In the intention-to-treat analysis, the higher number of patients is expected to be compensated by a potential dilution of treatment effects, so that the power will be approximately the same.

Estimations of eligible patients, giving informed consent (61%) and dropouts (20%) are based on our own pilot study (informed consent: 66%, drop-out: 14%) and the trial of Keller et al. (2000; informed consent: 66%; drop-out: 23.8%)

b) Enrollments

a) We have finished a randomized pilot study with 29 early-onset chronically depressed outpatients receiving either 22 sessions of CBASP or of IPT (Schramm et al., 2009). Currently, we are completing a bi-center trial with 60 chronically depressed patients comparing CBASP against medication. As in previous own DFG-funded studies on depression (e.g. IPT plus medication vs. medication alone in severely depressed patients, N=124; IPT vs. CBT in Social Phobia with/without depression, N=118), we experienced no recruitment problems in primary care and speciality mental health settings. We included 29 chronically depressed patients with early onset in 14 months (42 patients were screened), and 10 more training cases before the beginning of the study. The protocol was found to be feasible (only two drop-outs in the IPT-group, no suicide attempts).

b) The trial sites have been selected according to their scientific and clinical expertise in the field of depression treatment, their experiences in conducting large-scale investigations, pre-existing collaborations with the PI-centre and the numbers of accessible patients. All participating sites have their clinical focus on the treatment and research of depression and have established structures for successful patient recruitment during the course of other studies on depression. The Tübingen site, for example, recruited in an earlier study a sample of 339 unipolar depressed patients over 3 years (at 3 sites) and diagnosed 45% chronic depression (19% dysthymia). At the Heidelberg site app. 250 patients with depression are annually seen in the psychiatric out-patient clinic (app. 50% chronic). Additionally, 200 patients with depression are treated as inpatients. Some of the sites also participated in the “Competence Network on Depression and Suicidality” funded by the BMBF.

The recruitment and intervention phases will last 30 months (see Figure 2), i.e., patients can be enrolled continuously during 18 months. In order to achieve the total number (N=450) of screened patients in that period, an average of 25 patients have to be contacted every month. Consequently, an average number of 3 screened patients are required in each of the 10 trial sites per month. See Table 1 for detailed numbers of patients at each participating site. Participating Sites will produce summary recruitment reports 3-monthly for the Coordinating Center.
Table 1 Recruiting centers & numbers of allocated subjects projected for each trial site

<table>
<thead>
<tr>
<th>#</th>
<th>Recruiting center</th>
<th>Expected no. of patients allocated for the trial</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>University of Leipzig, Dept. of Psychiatry</td>
<td>15</td>
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<tr>
<td>2</td>
<td>University of Tübingen, Dept. of Psychology and Psychology Clinic</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>EOS-Clinic for Psychotherapy, Muenster</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>University of Marburg, Psychological Outpatient Clinic</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>University Medical Center Bonn, Dept. of Psychiatry and Psychotherapy</td>
<td>24</td>
</tr>
<tr>
<td>6</td>
<td>University Medical Center Hamburg-Eppendorf and Clinic Center Eilbek, Dept. of Psychosomatic Medicine and Psychotherapy</td>
<td>16</td>
</tr>
<tr>
<td>7</td>
<td>University of Lübeck, Dept. of Psychiatry and Psychotherapy</td>
<td>36</td>
</tr>
<tr>
<td>8</td>
<td>University of Heidelberg, Dept. of Psychiatry</td>
<td>40</td>
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<tr>
<td>9</td>
<td>Central Institute of Mental Health, Mannheim</td>
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<td>University Medical Center Freiburg, Dept. of Psychiatry and Psychotherapy</td>
<td>45</td>
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<tr>
<td></td>
<td></td>
<td>306</td>
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</table>

9.3 Level of significance

Will be set at $a=.05$

9.4 Criteria for termination of the trial

See Section 4.6

9.5 Missing, unused and spurious data

The primary interim and final analyses will be performed in the intention to treat (ITT) population, allocating patients to treatment groups according to the arm to which they were randomized, and using the LOCF method in case of missing outcome data at week 20. Because of the chronic nature of the disorder, spontaneous remission is unlikely to happen. During data entry missing examinations will be performed and documented (see also Section 13).

9.6 Reporting of deviations from the original statistical plan

Protocol deviations: All important deviations related to study inclusion or exclusion criteria, conduct of the trial, patient management or patient assessment will be described. Deviations will be summarized by trial site, grouped by those who entered the study even though they did not satisfy the inclusion criteria and those who developed withdrawal criteria during the study but were not withdrawn.

Deviation from the Statistical Analysis Plan: If the SAP contains any changes to the analyses outlined in the trial protocol, they will be marked as such, and reasons for amendments will be given. The SAP will be appended to the trial protocol.
9.7 Subjects included in the analysis

The trial will be analyzed according to the ITT-principle. That means, the primary analysis for comparison of the treatment groups with regard to the primary endpoint will be based on the 'full analysis set'. The full analysis set includes all randomized patients, and patients are analyzed as belonging to their randomized arm, regardless of whether they refused or discontinued therapy, or whether other protocol deviations are known. In order to preserve the ITT principle as far as possible and to minimize bias, patients randomized to one of the treatment arms who do not start with the assigned therapy, will be included in the analysis, since the decision not to start therapy might be influenced by the knowledge of the treatment assignment.

The 'per-protocol set' is a subset of the patients in the full analysis set and includes only patients for whom no serious protocol violations are known. Comparisons of the treatments in the per-protocol set will be performed for the purpose of sensitivity analysis.

10 Access to Source Data/Documents

In the framework of the clinical trial, quality-assurance will be guaranteed by monitoring, auditing and authorized supervision. In this case access to source data/documents will be provided.

See also Sponsor declaration in the appendices of the full application.

11 Quality Control and Quality Assurance

The investigators grant the monitor access to patient files for verification of proper documentation of study data. The laws on data confidentiality ("Bundesdatenschutzgesetz") fully apply. Persons authorized by the Sponsor as well as the competent authorities are allowed to verify data.

During the course of the study, a well trained monitor from the University Medical Center Hamburg-Eppendorf will visit the investigators regularly, depending on enrollment rates and study progression, approximately every 6 months. The investigator will need to set aside a reasonable amount of their time and the time of the designated members of their staff who are involved in the study for monitoring visits. After initializing the study the monitor will stay in regular contact with the study centers on short notice to get information about the compliance with the study protocol requirements, consensus of the data in the CRF and the originals, dating of the randomization, the updated patient identification lists, and the archiving system. These visits and telephone calls are supposed to control the progress of the trial, realize problems early and potentially solve them. The monitor will review the case report forms of the patients in the study to make certain that the items have been completed and that the data provided are accurate and obtained in the manner specified within the protocol.

The investigators will allow the monitor to have access to all original documents which prove the data on the CRFs. The monitor signs to handle all data that are under professional secrecy or show the patient’s identity confidentially, and will use the data only for the purpose
the patient gave informed consent for. No data disclosing the identity of patients should leave the study centre as a result of the monitoring procedure. The monitor, the investigators and the Sponsor will maintain confidentiality of all patient records.

In addition to the routine monitoring procedures outlined above, a further quality assurance measure will be implemented. Summaries of the regular monitoring reports and further information on the trial progress (number of patients recruited, adverse events etc.) will be translated in English and sent to the members of the DSMB for inspection each half year. Thus, as an independent committee, the DSMB performs a second-level quality assurance step similar to internal audits in clinical trials of pharmacological interventions.

Further procedures:

- Regular supervision and monitoring of adherence
- Video recording of the psychotherapy sessions
- All therapists and raters will be asked to remind patients on a continuous basis to complete the questionnaires and to check the questionnaires for appropriateness

Certification of Participating Sites

A site will be considered certified when the following have been submitted to the PIs:

1. Name of study coordinator (or, if no study coordinator is designated, name of back up investigator)
2. Date the IRB affiliated with the Participating Site has approved the CT Protocol
3. Date of contract with Coordinating Center (Contracts will include the plans for payments and data entry, and will note that the Participating Site agrees to abide by the study’s publications policies)
4. Name of center supervisor for CBASP and SYSP

12 Ethics

According to law regulations the patients will be appropriately educated about the nature, the relevance, and the meaning of the planned study. Written informed consent will be obtained prior to randomization and after the study has been fully explained to the patients. Patients can withdraw at any point without any disadvantage.

The education includes the following:

1. Goals and procedure of the trial
2. Deliberate character of the participation and the right to withdraw at any point without any disadvantage and without giving reasons
3. Benefits expected due to the participation in the study
4. Offer of more detailed information
5. Explanation of treatments
6. Obligations of the participant/insurance conditions
Side effects of evidence-based psychotherapies are fortunately rather rare (Hoffmann et al., 2008). A transient worsening of symptoms at the beginning of therapy may be due to giving up avoidance behavior but is rather rare. All patients will be regularly seen by his therapist and checked for acute suicidal risk and other AE/SAE according to clinical practice guidelines. In case of high risk for suicide or other severe psychiatric events, the patient will be transferred to inpatient psychiatric treatment. Further procedures are: Continuous monitoring (video recording of therapy sessions) and supervision of therapies for adherence and for the detection of psychiatric crisis or intolerable side-effects (AE); Immediate report of SAE to the PIs and initiation of specific intervention (e.g. hospitalization) to offer best possible treatment (see 8.1 and 8.2). All therapists and supervisors will be professionally trained therapists, safeguarding confidentiality of patient information.

To allow for early stopping in case of substantial inferiority especially of the placebo (SYSP) arm, an adaptive interim analysis (see section 9.1) is planned. The study has to be approved by the Ethical Committee of the University of Freiburg and the other sites, respectively. Any subsequent protocol amendments will be submitted to the Ethical Committee of the University of Freiburg for approval. The trial will be conducted in accordance with the Guidelines for Good Clinical Practice (GCP) following the principles of the Declaration of Helsinki.

### 13 Data Handling and Record Keeping

All protocol-required information collected during the study will be entered by the investigators, or designated representative in the CRF. The investigator will maintain a list of individuals who are authorized to enter or correct data. Data on patients collected on CRFs in the course of this trial will be documented in an anonymous fashion, i.e., the patient will be identified only by a patient identification number. Throughout the trial, all findings will be documented on the CRFs by the responsible investigator or an authorized person (according to the signature form of the centers). Paper forms will be signed by either of them. They will be complete, clear, accurate, legible, and plausible. Missing examinations or data must be marked along with an explanation. Corrections will be made according to the GCP-guidelines.

The CRF data will be transferred into the data base by double entry. Procedures for transfer and transformation of data will be validated. If data are transformed during processing, this is done in a way that it is always possible to compare the original data and observations with the processed data. Patients’ data will be checked for plausibility.

For coding, the following systems will be used: International Classification of Diseases (ICD) 10 for coding the illnesses and diseases.

Throughout this study, all data will be saved on electronic files and treated confidentially. For protection of the data, methods are implemented for prevention of passing of data to unauthorized third persons. Throughout the whole data-recording and analysis, patients will be identified only by a patient identification number - never by their full name, initials or date of birth.
The legal provisions by the respective laws will be heeded. The investigator will keep sufficient information for every patient (name, date of birth, internal clinic number, patient identification number, gender, informed consent), in order to identify the patient. According to the ICH-GCP-guidelines, these documents (Patient Identification List) will be archived for at least 10 years. By conducting this study, the investigators agree that they and their staff will maintain all information provided by patients in strict confidence. Study documents provided (protocols, CRFs and other material) will be stored appropriately to further ensure their confidentiality. It is understood that the confidential information provided to the investigator will not be disclosed to others without direct written authorization from, except to the extent necessary to obtain informed consent from the patients, who are possibly eligible and might choose to participate in this trial. Such information will not be communicated by telephone to potential or enrolled patients or to any other individual.

The evaluation of the study will be done by the Principle Investigators exclusively. Scores, CRFs and all other documents used are the property of the Sponsor and may not be used differently or passed on without permission.

## 14 Organizational Structure

The organizational structure of the trial includes a steering committee, whose members participate in at least quarterly conference calls, and a data safety monitoring board (DSMB).

**Steering Committee** Topics for discussion and decision: e.g. set-up of inclusion of patients and recruitment procedures, set-up of data management. Decision of the trial's discontinuation, modification or continuation of the study after interim analysis. Data analysis, preparation of publications.

The role of the DSMB committee is to monitor the progress of the trial, adherence to protocol and treatments, and give recommendations to the steering committee of the trial for discontinuation, modification or continuation of the study. In particular the DSMB will advise on potential stopping of treatment arms. For this, the committee will receive a corresponding report at the time of the adaptive interim analysis, which will be prepared by the responsible biostatistician and finalized by the DSMB statistician (see 3.5 and 4). Furthermore, the DSMB will receive and monitor reports on serious adverse events (SAEs) at regular intervals.

The DSMB committee will be invited for three meetings (one day) at the PI-centre in the course of the trial. The first meeting will be scheduled at the beginning, when training of therapists has been accomplished and recruitment and treatment has started. The second meeting will be organized at the time of the interim analysis, in order to allow for the committee to examine and comment on the unblinded data. The third meeting will be scheduled at the end of the trial to discuss data analysis, preparation of publications, etc. Three experts have been invited and have agreed to serve as members of the DSMB committee for the proposed trial (see Table 2). The members cover different fields of expertise important to the trial.
In addition, Mr. Ch.F. Reynolds will review this study protocol.

**Table 2** Members of the DMSB and Steering Committee

<table>
<thead>
<tr>
<th>Data Monitoring and Safety Board (DMSB)</th>
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<th>Steering Committee</th>
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<td>3</td>
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<td>4</td>
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## 15 Financing and Insurance

Financial plan: see full application.

All cooperating sites and clinical facilities have a standard public liability insurance (allgemeine Betriebshaftpflichtversicherung).

## 16 Publication Policy

Before recruitment and data collection starts, the trial will be registered at www.clinicaltrials.gov.

Study results will be published in accordance to the criteria of the CONSORT-Statement. At least within one year of termination of the study, a manuscript for publication will be finalized.

Any formal presentation or publication of data collected as a direct or indirect result of this trial will be considered as a joint publication by the investigators. It requires the agreement of the Coordinating Investigator and the Co-Principle Investigator. Authorship will be determined by mutual agreement.

The results of the study may be presented during scientific symposia or published in a scientific journal only after review and written approval by the Coordinating Investigator and the Co-Principle Investigator. Investigators from the participating trial sites agree not to engage in presentations based on data gathered individually or by a subgroup of centers before publication of the first main publication, unless this has been agreed otherwise by all other investigators, the Coordinating Investigator and the Co-Principle Investigator.

The Coordinating Investigator and the co-Principle Investigator will receive copies of any intended communication, presentation or publication reasonably in advance (at least 15
working days for an abstract or material to be presented orally and 45 working days for a manuscript). This request is made so as to allow to review the communications for accuracy, to verify that confidential information is not inadvertently being divulged, to allow adequate input or supplementary information that my not have been available to the investigator, and to allow establishment of co-authorship.

17 References


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Thase ME: Commentary. What is the investigator allegiance effect and what should we do about it?. Clinical Psychology: Science and Practice 1999; 6(1):113-115

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Ware J Jr, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care 1996;34(3):220-33


18 Appendices
Protocol approval

Coordinating Investigator  

01.07.2009  

Signature Date

Co-Principal Investigator  

06.07.2009  

Signature Date

Statistician  

06.07.2009  

Signature Date
A comparison of Cognitive Behavioral Analysis System of Psychotherapy (CBASP) and System of Supportive Psychotherapy (SYSP) for Early Onset Chronic Depression

Amendment #1: July 30, 2010

Protocol Draft no. 2.2
Amendment #1

Rationale
Amendment #1 contains the abandonment of the a priori planned interim analysis as a result of the recommendation of the Data Safety Monitoring Board (DSMB). It also includes the announcement of a change in participating trial sites and the introduction of the clinical procedures manual (ProcMan). This amendment does not contain any changes in the design of the study.

Discussion of the appropriateness of the interim analysis
Concerns were raised by the official reviewer of the study protocol and by the DSMB if an interim efficacy analysis in this trial is appropriate because: 1) it is unusual in mental health clinical trials; 2) until results of the interim analysis are available, approx. 80% patients will have already been included, thus gain (i.e. abandonment of withholding a clearly efficacious treatment) is limited; and 3) clinicians need to have the full set of outcome data with narrow confidence intervals to assess the true utility and applicability of the tested interventions, which in the event of a possible early termination would not be the case.

All participants of the first DSMB meeting agreed that an interim efficacy analysis is not necessary in this trial. However, periodic safety checks (Summary Monitoring Reports on a half year basis) will inform the DSMB regularly and an early termination of the trial is still possible due to safety reasons, even without a statistical analysis.

The abandonment of the a priori planned interim analysis is a technical (rather than a content-related) change in the study protocol and will be reported to the ethics committees of the study centers and the DFG (German Research Association).

As a result the following chapters were changed: 4.6 Criteria for discontinuation, 9.1 Statistical methods, 9.2 Sample size/Recruitment, 12 Ethics, 14 Organizational Structure

As that the planned interim analysis inflated the required sample size only by the factor 1.007, (see 9.2) an adjustment of the sample size to the updated analysis plan (i.e. without interim analysis) does not seem to be necessary.

Lost trial sites
Two of the initial 10 sites have dropped out before start:

- University of Leipzig, Department of Psychiatry, Semmelweisstraße 10, 04103 Leipzig, Germany: Ulrich Hegerl, MD; Claudia Dahm-Mory, PhD.
- EOS-Clinic for Psychotherapy, Hammer Str. 18, 48151 Münster, Germany: Markus Pawelzik, MD.

The following chapter was changed: 1.6 Seven additional trial sites
As the trial sites had already given agreement on participating in the trial when it included three study arms (first draft), the confirmed recruitment load was considerably higher than needed to achieve the required power described in 9.2. Losing the two mentioned trial sites leads to a reduced sample size, that is, however, still provides the a priori targeted power. Thus, an adjustment of the recruitment rates of the remaining centers does not seem to be necessary.

ProcMan
For an overview of patient's study visits and measurement times, screening flow and further details on clinical procedures a separate manual called ProcMan (ProzedurenManual) was introduced. This document of 60 pages summarizes most study-related tasks and serves as a quality assurance measure to uniform study procedures across sites and involved staff.
<table>
<thead>
<tr>
<th>Chapter</th>
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<td>11</td>
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### Abbreviation

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AE</td>
<td>Adverse Events</td>
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<tr>
<td>ANCOVA</td>
<td>Analysis of covariance</td>
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<tr>
<td>ATR</td>
<td>Adverse Treatment Reaction</td>
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<tr>
<td>BSI</td>
<td>Brief Symptom Inventory</td>
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<td>CALPAS</td>
<td>California Psychotherapy Alliance Scales</td>
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<td>CBASP</td>
<td>Cognitive Behavioural Analysis System of Psychotherapy</td>
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<tr>
<td>CRA</td>
<td>Clinical Research Associate</td>
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<tr>
<td>CRF</td>
<td>Case Report Form</td>
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<td>CTQ</td>
<td>Childhood Trauma Questionnaire</td>
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<td>Data Safety Monitoring Board</td>
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<td>DSM-IV</td>
<td>Diagnostic and Statistical Manual of Mental Disorders</td>
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<td>30-item Inventory of Depressive Symptomatology-Expectation</td>
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<td>ETI</td>
<td>Early Trauma Inventory</td>
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<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>GAD7</td>
<td>7-item Generalized Anxiety Disorder Scale</td>
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<td>GAF</td>
<td>Global Assessment Functioning Scale</td>
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<td>GCP</td>
<td>Good Clinical Practice</td>
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<td>HAQ</td>
<td>Helping Alliance Questionnaire</td>
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<td>HRQoL</td>
<td>Health-Related Quality of Life</td>
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<tr>
<td>HRSD</td>
<td>24-item Hamilton Rating Scale of Depression</td>
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<td>ICD</td>
<td>International Classification of Diseases</td>
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<td>ICH</td>
<td>The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use</td>
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<td>Inventory of Interpersonal Problems</td>
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<td>Interpersonal Psychotherapy</td>
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<td>Last observation carried forward</td>
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<td>Principal investigator</td>
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<td>SAE</td>
<td>Serious Adverse Event</td>
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<td>SAP</td>
<td>Statistical Analysis Plan</td>
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<td>SASS</td>
<td>Social Adaptation Self-Evaluation Scale</td>
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<td>SATR</td>
<td>Serious Adverse Treatment Reaction</td>
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<td>Structured Clinical Interview for DSM-IV</td>
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<td>System of Supportive Psychotherapy</td>
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<td>Working Alliance Inventory</td>
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1 General Information

1.1 Title

A comparison of Cognitive Behavioral Analysis System of Psychotherapy (CBASP) and System of Supportive Psychotherapy (SYSP) for early onset chronic depression

Short title: CBASP vs. SYSP
Identifying number:  UKF001906
ClinicalTrials.gov ID: NCT00970437
Amendments: 1
Date: Juli 30, 2010

1.2 Sponsor and monitor

Sponsor: University Medical Center Freiburg, Department of Psychiatry and Psychotherapy, Freiburg, Germany
Monitor: University Medical Center Hamburg-Eppendorf, Department of Medical Psychology, Hamburg, Germany

1.3 Persons authorized to sign protocol and amendments

Elisabeth Schramm, PhD
University Medical Center Freiburg, Department of Psychiatry and Psychotherapy

Martin Härter, MD, PhD
University Medical Center Hamburg-Eppendorf, Department of Medical Psychology

1.4 Sponsor's medical expert

Mathias Berger, MD
University Medical Center Freiburg, Department of Psychiatry and Psychotherapy

1.5 Responsible investigators

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Martin Härter, MD, PhD (Co-Principle Investigator)
University Medical Center Hamburg-Eppendorf

1.6 Seven additional trial sites

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University Clinic of Hamburg-Eppendorf and Clinic Center Eilbek, Department of Psychosomatic Medicine and Psychotherapy
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1.7 Treatment Responsibility

E. Schramm, a certified and experienced CBASP clinician as well as supervisor for Cognitive Behavior and Interpersonal Therapy, will be responsible for training and supervision of the CBASP study therapists.

M. Hautzinger, a certified and experienced clinician and supervisor for Cognitive Behavior Therapy and for Supportive Psychotherapy, will be responsible for training and supervision of the SYSP study therapists.

1.8 Qualified physician

M. Härter, one of the Principle Investigators for the study, is a trained physician and will be responsible for all trial-site related medical issues.
2 Background Information

2.1 Investigational product

Cognitive Behavioral Analysis System of Psychotherapy (CBASP) is a manualized psychotherapeutic method (McCullough, Treatment for Chronic Depression; 2000; German version: Schramm et al., 2006) specifically designed for the psychological treatment of chronic depression. Its success is contingent on how well the therapist is able to implement the techniques to demonstrate to patients that they are responsible for the life dilemma they bring to psychotherapy. The patient’s chronic feelings of helplessness and hopelessness are prominent signs signaling (a) that the persons are disengaged perceptually from the interpersonal environment they live in (perceived dysfunctionality) and (b) that they are unable to recognize the interpersonal consequences of their behavior.

CBASP is a contingency training program that relies predominantly on the administration of negative reinforcement. Being able to identify the consequences of one’s behavior (perceived functionality) and learning to recognize one’s stimulus value for others, as well as the stimulus value others have for the patient (empathy), are the essential goals of treatment. Therapists are taught to keep patients on the participant hot seat at every turn by exposing behavioral consequences. A discomforting state of affairs frequently characterizes sessions so that when patients make important changes, the discomforting state is often reduced. Two CBASP techniques are designed to arrange in-session negative reinforcement contingencies: Situation Analysis and the Interpersonal Discrimination Exercise. A third technique contains Behavioral Skill Training and Rehearsal.

System of Supportive Psychotherapy (SYSP) is an active but less specific, manualized control treatment (Hautzinger 2001; Hautzinger et al. 2005, 2006; Hautzinger & Welz, 2008; Markowitz et al., 2008). SYSP - defined as non-interpersonal and non-cognitive-behavioral therapy - resembles the client-centered therapy of Rogers with added psychoeducation about depression. SYSP is defined as a therapy wherein the therapist strives to create a supportive relationship by emphasizing non-specific therapeutic interactions and techniques that convey to the patient the therapist’s interest, concern, and understanding. It emphasizes the patient’s strengths and assets. It utilizes the so-called common factors that have been assumed to account for much of the effect of all tested psychotherapies. These common or non-specific factors include:

- Facilitation of affect
- Helping the patient to feel understood (Relationship)
- A framework for understanding (Rationale)
- Empathy
- A treatment ritual (Ritual)
- Success experiences
- Hope and therapeutic optimism (Remoralization).
2.2 Summary of previous findings from clinical and non-clinical trials

Chronic depressions account for roughly a third of all mood disorders. In the USA, about 3% of the population suffers from chronic depression (Kessler et al., 1994). It is a particularly disabling disorder which is associated with greater comorbidity, more significant impairments in functioning, increased health care utilization, and more frequent suicide attempts and hospitalizations than acute major depressive episodes (Arnow et al., 2003). It therefore accounts for a considerable proportion of the enormous economic burden associated with depression (Greenberg et al., 2003). In more than 70% of all cases, chronic depression begins early in life (Cassano et al., 1992), is often associated with early interpersonal trauma and frequently persists life long. Early-onset chronic depression results in an even more substantial human capital loss compared with late-onset (Berndt et al., 2000). In addition, the disorder has a more malignant course than the late-onset group (Klein et al., 1999) and shows a high rate of relapse after an initial response to medication treatment (Agosti, 1999).

Specific and effective treatment strategies for chronic depression are urgently needed since it is not only a highly prevalent and particularly impairing disorder, but is also considered “difficult-to-treat” or even treatment resistant by most clinicians.

Although psychotherapy is commonly applied to chronically depressed patients with early-onset there is little data on the efficacy of psychological interventions for this disorder. One large study (n=681; Keller et al., 2000) showed that for the subgroup of chronically depressives with an early childhood trauma (Nemeroff et al., 2003) a psychotherapeutic method specifically designed for chronic depression (CBASP) was particularly effective. In contrast, medication (nefazodone) alone had a weak effect in this subgroup of patients as only 33% reached remission (48% with CBASP). The combination of CBASP and nefazodone resulted in a higher remission rate (54%) than both monotherapies. Similarly, imipramine but also more traditional psychotherapies (Interpersonal Psychotherapy/IPT, and Cognitive Behavioral Therapy/CBT) performed relatively poorly in the subgroup of early-onset chronic MDD as shown by an older reanalysis (Agosti et al., 1997) of the data of the NIMH-Collaborative study. In a randomized pilot study (Schramm et al., 2009) of our work group on 28 chronically depressed outpatients with early onset, highly significant differences were found between CBASP and IPT regarding the reduction of both self- and clinician-rated depressive symptoms in the first 14 completed subjects in flavor of CBASP. The remission rate in the CBASP-group was very high (71.4% vs. 14.3% for IPT) probably due to the extended course of therapy (22 sessions) and sample characteristics (82% early traumatized, mostly physician-referred). The study proved to be feasible. However, we expected IPT as a depression-specific approach to be more efficient.

Based on these data, CBASP with and without medication seems to be a highly promising method for early onset chronic depression. Yet, CBASP was never compared to a placebo control. A control treatment consisting of active but non-specific supportive psychotherapy was used by Markowitz et al. (2005) with early-onset dysthymic patients as a comparator to IPT. Surprisingly, supportive psychotherapy did not perform significantly less than IPT (both with low remission rates of 12% and 22%) supporting the argument of Wampold et al. (2005) that psychological placebos - when properly designed and structurally equivalent – are as effective as psychotherapy in depressive disorders. However, in chronic depression the response to medication placebo is reported to be low (12%; Kocsis et al., 1988).
Based on the results of these studies, our primary hypothesis is that: CBASP is more effective in reducing depressive symptoms in patients with early-onset chronic MDD than a non-specific psychological control treatment (SYSP).

### 2.3 Potential risks and benefits to human subjects

Psychotherapeutic treatment with CBASP as well as with SYSP involves the chance of improvement of the depressive symptomatology. Possible undesired "side-effects" may include transient worsening of symptoms and transient risk of suicidality at the beginning of therapy (due to breaking out of avoidance behavior), but was rarely observed (e.g. Hoyer et al., 2006).

### 2.4 Rationale for dosage and treatment period

The available data up-to-date support the need for a greater number of psychotherapy sessions and a longer course of treatment to unfold its effects in chronic depression. Both CBASP and SYSP are conducted with two weekly individual sessions for the first 4 weeks and 1 weekly session for the remaining 16 weeks in the acute phase (=24 sessions, see Fig. 1 & 2), followed by 8 continuation sessions over the next 28 weeks (2 sessions in the first 4 weeks, and 1 session every 4 weeks thereafter). All patients will be free of medication (at least a 2-week drug-free period) before beginning of the trial.

Evidence indicates that effective treatment involves besides acute, also longer-term maintenance treatment (Gelenberg et al., 2003). A 12-months naturalistic follow-up is planned for a second study phase (not applied for here) since sustenance of response is particularly relevant given the chronic nature of the disorder. Furthermore, the only study using CBASP (Keller et al., 2000) did not report a follow-up. All non-protocol treatments that the patient may have obtained during the follow-up period will be assessed.

### 2.5 Compliance with the protocol, GCP, and applicable regulatory requirements

The trial will be conducted in compliance with the protocol, GCP, and the applicable regulatory requirements. In particular, the following aspects will be taken into consideration: a) submission of the proposed trial (trial protocol, patient information, informed consent form) to the IRB/IEC of the University of Freiburg (Ethik-Kommission der Albert-Ludwigs-Universität) and continued review of the ongoing trial by the committee. The IRB/IEC has been constituted according to the usual German regulations (landesrechtliche Statuten) and is organized and operates in accordance to GCP. In addition, the local ethics committees of the participating trial sites will be informed and asked for confirmation; and b) informed consent from all participating patients prior to clinical interview, randomization and intervention.

Any change or addition to this protocol requires a written protocol amendment. No change to the protocol may be made without the joint agreement of the Coordinating Investigator and the Co-Principle Investigator. Any amendment must be signed by all parties before the
change of or addition to the final protocol is effective. For major changes, the Data Monitoring and Safety Committee (DSMB) must be incorporated into the considerations. An amendment becomes an integral part of the protocol. All centers will be informed immediately after approval by the Coordinating or the Co-Principal Investigators.

2.6 Description of the population to be studied

Patients with chronic Major Depressive Disorder according to DSM IV.

Chronic depression, which is marked, often despite several trials of adequate psychiatric treatment, by a course of illness lasting 2 years or more, encompasses 4 subtypes of depressive illness: (1) chronic major depressive disorder, (2) dysthymic disorder, (3) dysthymic disorder with major depressive disorder ("double depression"), and (4) major depressive disorder with poor interepisodic recovery (i.e., in incomplete remission). Patients with pure dysthymic disorder will not be included in this study. Chronic depression not only causes chronic suffering, it compromises interpersonal functioning. Chronically depressed patients typically are passive, unassertive, avoid confrontation, and feel extremely uncomfortable in tolerating and expressing anger or taking social risks. They often lead marginalized lives, trying to avoid the social spotlight and pass as normal, hoping that other people will not notice their self-perceived inner defects (Markowitz, 2003).

3 Trial Objectives and Purposes

Effective treatment strategies for chronic depression are urgently needed since it is not only a common and particularly disabling disorder, but is also considered treatment resistant by most clinicians. There are only a few studies on chronic depression indicating that traditional interventions are not as effective as in acute, episodic depression. In addition, most of the studies had methodological weaknesses, such as the very short courses of psychotherapy. With the present multicentre study, the efficacy of the only specific psychotherapy for chronic depression (Cognitive Behavioral Analysis System of Psychotherapy/CBASP) is compared with a non-specific supportive psychotherapy (SYSP - a well-designed psychological placebo) in early onset chronically depressives. CBASP faired very well in one large trial but has never been directly compared to a placebo control. Another innovative aspect of the study is the use of an extended course of psychotherapy (32 sessions).

Primary hypothesis: CBASP is more effective in reducing depressive symptoms than SYSP.

Our secondary hypothesis is: Remission rates are higher in CBASP than in SYSP.

In summary, this trial will generate important new evidence, because it addresses the proof of concept that CBASP works.
4 Trial Design

4.1 Primary and secondary endpoints

Determination of primary and secondary measures

Primary endpoint:
Depressive symptoms 20 weeks after randomization (after acute treatment phase) as measured by the HRSD.

Secondary endpoints:
- Depressive symptoms after 12 and 48 weeks as measured by the HRSD, and remission after 12, 20, and 48 weeks as measured by the IDS-SR. Remission is defined a priori as a score of 13 or less for at least three consecutive weeks in the acute phase for those who completed the 12-week/20-week protocol and at the time of withdrawal for those who did not complete the study. For calculation of remission in the continuation phase, the IDS-SR-Value has to be 13 or less at week 44 and 48. Furthermore, the proportion of patients who demonstrate clinical response will be analyzed, where response is defined by a reduction of at least 50% in the baseline at week 12, 20, and 48.
- Changes in QIDS-C16 (from baseline to week 12, 20, and 48)
- Temporal changes in IDS-SR – Total sum score between baseline assessment and follow-up assessments (time course of 27 time points)
- Changes in GAF (from baseline to week 12, 20, and 48)
- Changes in Anxiety-subscalses¹ (sum score anxiety items BSI and GAD7, changes from baseline to week 12, 20, and 48)
- SASS (sum score, changes from baseline to week 12, 20, and 48)
- Changes in IIP-subscalses from baseline to week 12, 20, and 48)
- Changes in QoL-Scales SF-12 and QLDS (from baseline to week 12, 20, and 48)

A Number needed to treat (NNT) of 8 and a difference in relapse rates during continuation treatment of 5% is considered to be clinically relevant. In addition, the HRSD-remission rates (HRSD $\leq 8$) and HRSD –response rates (HRSD score by at least 50 percent from baseline) will be calculated for the main measurement time points.

Rationale and description of endpoints, parameters and instruments²

All measures of outcomes are widely used internationally, are reliable and valid, also for usage in Germany.

¹ Compared to the proposal, the STAI was replaced by a more symptoms-related measure of anxiety
² For an overview of methods and time points of assessment see 7.2
Primary endpoint

Severity of depression

The HRSD is the most frequently-used clinician-rated measures of depression severity (Moran et al. 2005). The 24-item version has been implemented in the study by Keller et al. (2000) and will therefore ascertain internationally comparable study results.

Evidence suggests that the Hamilton Depression Scale is psychometrically and conceptually somewhat flawed (Bugby et al., 2004). Many scales and instruments used in psychiatry today are based on—or at least include—current DSM symptoms. Therefore we include the QIDS-C (see description below), as in the Star*D-study (Rush et al., 2004).

Secondary endpoints

Severity of depression – self-rating and clinician-rated

The 16-item Quick Inventory of Depressive Symptomatology, clinician-rated (QIDS-C16) and the 30-item Inventory of Depressive Symptomatology, Self-Report (IDS-SR; Rush et al., 1996) have been used to assess acute and longer-term outcomes and have highly acceptable psychometric properties (Rush et al. 2005). The IDSs were intended to comprise all areas of depressive symptoms according to the Diagnostic and Statistical Manual of Mental Disorders, DSM-III-R and DSM-IV, assessed in a clear and steady graduation (Rush et al., 1996). The IDS-SR contains 30 items. Only 28 of 30 items count for the sum-score, because the two questions addressing change of weight and appetite distinguish between ‘loss’ and ‘increase’. All items are rated on a scale from ‘0’ (symptom is not present) to ‘3’ (strongest impairment). A cut-off-point of 26 (IDS-SR) and 11 (QIDS-C16) indicate a clinical relevant depressive symptomatology (Trivedi et al., 2004).

Expectation and importance

We will use a modified version of the IDS-SR to measure expectation (E-IDS). Patient will be asked what they expect to answer in the IDS-SR at the end of therapy. Furthermore, the patient will give information about the importance of being symptom-free.

Severity of anxiety

In elderly depressed patients, anxiety predicted slower recovery (Dew et al. 2007), and lower baseline anxiety predicted response at 12 weeks (Andreescu et al. 2007). In order to identify anxiety as a predictor, the following instruments will be applied:

Symptoms of anxiety will be measured using the anxiety scale and the phobic anxiety scale from the Brief Symptom Inventory (BSI). The BSI is a validated self-report scale developed from the SCL-90-R with strong test-retest and internal consistency reliabilities. Factor analytic studies of the internal structure of the scale have demonstrated its construct validity (Derogatis et al. 1983). The anxiety subscale consists of six items: nervousness, suddenly scared, feeling fearful, feeling tense, feeling restless, and spells of panic. In the original version, each item is rated on a 5-point scale (0=symptom not present, 4=extremely severe). To get an uniform scale with the GAD-7, each item will be rated on a 4-point scale (0=symptoms
not present, 3=severe). The GAD-7 (Spitzer et al., 2006) is a valid and efficient tool with 7 items for screening for generalized anxiety disorder. It also assesses the severity of GAD.

Quality of life

The Medical Outcome Study 36-item Short Form Health Survey (SF-36; Ware et al., 1992) is an internationally approved, generic instrument to assess Health-Related Quality of Life (HRQoL). The 12-item Short Form Survey (SF-12), derived from the SF-36, has been demonstrated to be reliable and valid in clinical and population-based applications in the U.S. and other countries (Ware et al., 1996; Gandek et al. 1998; Sugar et al. 1998; Jenkinson et al. 1997). The physical health and mental health summary scores that reproduce the summary scores derived from the SF-36, have been demonstrated to account for most of the variance in the eight subscales of health functioning (Ware et al., 1996). SF-12 scores range from 0 to 100, with 100 being complete absence of impairment.

A more disease-specific instrument is the Quality of Life in Depression Scale (QLDS). This 34-item measure was developed to measure the impact of depression symptoms and treatment on quality of life (Hunt and McKenna, 1992). The QLDS has evidence of reliability, construct and content validity, and sensitivity to change in depressed patients (Walley and McKenna, 1995). All items are rated on a scale with 'yes' (statement is true) or 'no'. The score is an index ranging from 0 to 34, with a higher score indicating worse QOL.

Interpersonal problems

Interpersonal problems will be measured with the German translation of the 64-item Inventory of Interpersonal Problems (IIP-64; Horowitz et al. 2000). The IIP-64 is a self-report questionnaire. Its strength is that it simultaneously assesses multiple aspects of interpersonal malfunctioning. Psychometric research on the instrument in English-speaking communities as well as in German-speaking populations (Horowitz et al., 2000) demonstrated the validity and the reliability (good internal consistency and test-retest reliability) of the IIP-64.

Social functioning

Assessment of functional status is increasingly important in clinical trials and outcome research. To measure global psychological, social, and occupational functioning, the widely utilized Global Assessment of Functioning (GAF, Axis V in DSM-IV) scale will be used. Another measurement is the Social Adaptation Self-Evaluation Scale (SASS, Duschek et al., 2003), specifically for self-assessment of social functioning by patients with depression. This scale has been used in European clinical trials and is currently being studied in the United States. It contains 21 items covering the different aspects of social interactions, global social attitude, and self-perception. The SASS has been validated and found to be simple to use and sensitive to changes in the different areas of social functioning (Weissman, 2001).

Childhood trauma

At baseline, the Childhood Trauma Questionnaire (CTQ; Bernstein et al., 1994) will be completed. The CTQ is a 28-item retrospective self-report questionnaire which determines 4 se-
verity categories of emotional/physical/sexual abuse, and emotional/physical neglect. “Early trauma” is defined as one of these experiences before the age of 18 to a degree of at least “moderate to severe”. In addition, we will use the Early Trauma Inventory (ETI; Bremner et al., 2000), a 56-item semi-structured interview. The ETI assesses also the domain of general trauma (not assessed by CTQ). The psychometric properties of both instruments have shown to be favorable (Bremner et al., 2007).

Process analyses of therapies

In addition to outcome analyses, this study aims to investigate the therapy processes.

After each session, the patients and therapists will be requested to fill out the Helping Alliance questionnaire (HAQ)\(^3\) developed by Luborsky (1985). It is an 11-item self-report questionnaire rated on a six-point rating-scale (from -3, I strongly feel that it isn't true, to +3, I strongly feel that it is true). The instrument assesses two types of alliance: patient’s experience of feeling helped and supported by the therapist (seven items) and patient’s experience of working together with the therapist in a joint effort in order to overcome the difficulties (four items).

The HAQ is correlated to other well validated instruments (0.74 to CALPAS and 0.74 to WAI according to Hatcher & Barends, 1996), is highly correlated with outcome (Martin et al., 2000) and shows at least similar psychometric properties to other alliance instruments (Luborsky, 2000).

To identify therapy-induced changes those constitute a negative effect, the HAQ (patient's version) will be extended by further questions:

- Would you recommend this kind of treatment to someone with similar problems?
- Would you recommend this therapist to someone with similar problems?'
- To what extent did the therapy help you?
- Do you experience any undesirable “side-effects” of the therapy (such as increased rumination, suicidal thoughts, etc.)?

**Adherence:** All sessions will be videotaped and site-supervisors will review the videotapes regularly on a random basis to assess psychotherapists’ adherence to the treatment procedures using specific rating-scales (McCullough, 2000 and Markowitz, 2003). In addition, a separate team of independent raters trained to reliability will randomly evaluate several of the tapes from early, middle, and late therapy phase of each treatment for adherence and therapist competence.

**Evaluation by a relative**

We will use a new questionnaire for close relatives of the patient to measure changes in depression perceived by them. At the end of the therapy, a relative of the patient will be asked

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\(^3\) Compared to the proposal, the WAI was replaced by the HAQ. The therapist and the patient form of this questionnaire are available in German.
to evaluate 14 items of depressive symptoms before and after therapy. Each item will be rated on a 5-point scale (0=symptoms not present, 4=extremely severe).

**Screening**

The initial screening visit consists of a medical and psychiatric history. Diagnoses will be derived using the Structured Clinical Interview for DSM-IV (SCID-I and II; First et al., 1997) during the screening evaluation as well as after 20 and 48 weeks of treatment.

The *Structured Clinical Interview for DSM-IV (SCID-I)* (German Version: Wittchen et al., 1997) is a diagnostic interview which is widely used by health care professionals and has been implemented in cross-national epidemiological and treatment studies. It includes an introductory overview followed by nine modules, seven of which represent the major Axis I diagnostic classes (e.g., mood disorders, anxiety disorders, adjustment disorders, somatoform disorders). Because of its modular construction, it can be adapted for use in studies in which particular diagnoses are not of interest. Using a decision-tree approach, the SCID guides the clinician in testing diagnostic hypotheses as the interview is conducted. Although the semi-structured interview consists of standardized questions, it allows the experienced clinician to tailor questions to fit the patient’s understanding; to ask additional questions that clarify ambiguities; to challenge inconsistencies; and to make clinical judgments about the seriousness of symptoms. The output of the SCID is a record of the presence or absence of each of the disorders being considered, for a current episode (past month) and for lifetime occurrence. Interrater reliability has been reported to be between .88 and .95 for the diagnoses of major depressive episode (Gorman et al., 2004).

The *Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II)* is a semi-structured diagnostic interview for assessing the 10 DSM-IV (German Version: Wittchen et al., 1997) Axis II personality disorders, as well as Depressive Personality Disorder and Passive-Aggressive Personality Disorder (included in DSM-IV’s Appendix B, “Criteria Sets and Axes Provided for Further Study”). SCID-II can be used to make Axis II diagnoses, either categorically (present or absent) or dimensionally (by noting the number of personality disorder criteria for each diagnosis that are coded “3”).

The SCID-II is a two-stage method consisting of a questionnaire for screening personality disorders and a structured interview.

**Sociodemographic and medical data**

a) **Sociodemographic data**

Sex, age, nationality, marital status, education, occupation, measure of household income, and employment

b) **Medical data**

Previous or present diseases, outpatient and/or inpatient psychiatric and/or psychotherapeutic treatments; suicidal attempts and risk factors for suicide
**Therapist data**

The name of the therapist (coded as digits: center digit _individual therapist digit) of each patient will be registered. In addition, a therapist form will be used for descriptive values (e.g. age, sex, clinical experience) and qualification of therapists.

To evaluate therapist attitudes toward CBASP und SYSP, specific questionnaires will be applied at the therapy training, after the first study patient, and after study termination.

**Safety/Acceptance Outcomes**

- Drop-out rates
- Rates of drop-out due to AEs
- Rates of drop-out due to suicidality
- Rates of patient with AEs
- Rates of patients with suicidality
- Time to drop-out

**4.2 Type and design of the trial**

Multicentre, observer blind, prospective, randomized, controlled study, active control, 2 treatment phases (acute and continuation) (trial design see Figure 1)

A stratified block randomization with randomly varying block size will be performed, stratified by trial center.

**Interventions**

CBASP and SYSP are conducted with two weekly individual sessions of 50 minutes each for the first 4 weeks and 1 weekly session for the remaining 16 weeks in the acute phase (=24 sessions, see Figure 1 & 2), followed by 8 continuation sessions over the next 28 weeks (2 sessions in the first 4 weeks, and 1 session every 4 weeks thereafter).

See description of interventions in Section 2.1. and 4.4.
Patients declining participation / refusers

This group of patients will be aimed to be assessed to gain information about characteristics of patients refusing treatment. As part of standard care within each treatment center, individual consultations will be available for all patients outside of the study protocol (randomization etc.).

4.3 Measures taken to minimize/avoid bias

a) Randomization

Randomization will be conducted according to a central computerized randomization schedule, with a 1:1 treatment allocation ratio, stratified by centre, in blocks of variable size, to
guarantee concealment. The internet based randomization allows investigators at the centers to randomize patients from anywhere through the convenience of their web browser. Investigators require a valid username, password and PIN number to access the randomization application, and randomize patients by simply completing an on-screen form with patient details, inclusion and exclusion criteria. Investigators are immediately shown the treatment allocation.

Randomizations are conducted via SSL encryption for added security. No-one can delete records from the randomization database, so that all randomizations have to be accounted for. Audit log files detailing all activity on the randomization system are available to the trial coordinator.

b) Blinding

All clinical ratings will be completed by trained (high interrater-reliability and procedural integrity throughout the study, not just during training) and independent evaluators blinded to treatment assignment. Ideally, the same evaluator will rate the patients at all measurement times. Each of the sites will implement procedures to mask a patient treatment assignment from the person who will evaluate the results of the clinical ratings through the following: 1) locating the rater at a separate physical location, and 2) reminding the patients at each visit not to mention anything that might reveal their treatment condition to the independent evaluator.

c) Control of therapy allegiance

Over the past several years, therapy allegiance, i.e. treatment preference of the investigators, has been discussed as an important influencing factor for results in psychotherapy research (Luborsky et al., 1999). There have been several recommendations for how to minimize the allegiance effect: involving several investigators who represent a “mix of therapy allegiances”, comparing interventions of the same length and duration, using blinded raters for process and outcome analyses, and conducting both interventions in all sites (Thase, 1999). All recommendations will be realized in the present study.

d) Control for overlapping treatments

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

1. The therapists are obligated to adhere to the therapeutic procedures and interventions described within the manuals. Adherence to the treatment manuals will be continuously supervised by watching videotapes of the sessions using adherence scales (McCullough, 2000 and Markowitz, 2003). In addition, after each session the therapists will fill out a check list (containing therapeutic elements of both therapies) regarding the employed interventions. The validity of the therapist’s statements will be checked through external assessment of the video recordings. In the post-hoc analysis it will be checked if the expected differences regarding intervention characteristics appear within the therapies.
2. Each therapist will conduct only one of the two treatments.
3. To evaluate therapist attitudes toward CBASP und SYSP, questionnaires will be applied at the therapy training, after the first study patient, and after study termination.
Possible influences through qualification differences of the therapists will be controlled as follows:

1. All therapists have completed professional training (or they are in their second training year (out of three) for certification as a licensed psychotherapist).
2. All therapists have completed a comprehensive training (min. 24 hours) within the respective treatment approach. Therapists will conduct two pilot cases which will be intensively supervised.
3. Concerning their influence upon the effectiveness of treatment, level of training and professional experience of the therapists will be collected and reviewed.

**e) Control for confounding factors**

1. The influence of the trial site upon the effectiveness of the respective treatment approaches will be investigated as a separate factor.
2. Patients will be asked not to engage in off-study psychosocial (e.g., group therapy) or psychiatric interventions (e.g. antidepressive medication) during the treatment period.

**f) Control for measurement bias**

1. All raters have completed training for rating HRSD.
2. Guidelines for rating scales are available.
3. Determination of the interrater reliability on the basis of at least 4 recorded HRSD ratings.

### 4.4 Trial treatments

CBASP as the experimental intervention will follow a manual (McCullough, 2000; German version: Schramm et al., 2006). The approach is specifically tailored for the treatment of chronic forms of depression, particularly with early-onset, by focusing on the problems resulting from an inhibition of maturation in early childhood and by using the therapeutic relationship in a personal, disciplined way as well as other specific techniques (e.g. Interpersonal Discrimination Exercise, Situation Analysis). CBASP integrates behavioral, cognitive, and interpersonal strategies.

The comparator for CBASP is SYSP, a system of supportive psychotherapy, an active but less specific, manualized control treatment (Hautzinger et al. 2005, 2006, 2008; Markowitz et al., 2008) previously used in several comparative trials. SYSP - defined as non-interpersonal and non-cognitive-behavioral therapy - resembles supportive clinical management, client-centered therapy, counseling, and psychoeducation about depression. It is assumed that many clinicians in private practice proceed in this unstructured manner. There is no specific explanatory mechanism for treatment effect offered to the patient and it does not focus on specific themes. The number and duration of sessions as well as the experience of the therapists in this treatment condition will be equivalent to CBASP. According to a meta-analysis of Baskin et al. (2003) structurally equivalent “placebos” produced negligible effects
compared to active treatments (Hegerl et al. 2009). But there are also studies with depressed subjects which show significant effects for supportive interventions (Hautzinger & Welz, 2008; Wampold, 2005).

CBASP and SYSP will be implemented by two separate groups of psychotherapists, both trained (in a 2-day training workshop and 1 practice day) in one of the methods and meeting the criteria for mastery of CBASP or SYSP procedures as assessed by evaluation of their performance during two videotaped pilot cases. All psychotherapists have completed a 3-year psychotherapy training program or are in an advanced stage of training. All sessions will be videotaped and site-supervisors will review the videotapes regularly on a random basis to assess psychotherapists’ adherence to the treatment procedures using specific rating scales (McCullough, 2000 and Markowitz, 2003). In addition, a separate team of independent raters trained to reliability will randomly evaluate several of the tapes from early, middle, and late therapy phase of each treatment for adherence and therapist competence. Site-supervisors will be directly supervised by the trial-supervisors (E. Schramm & M. Hautzinger) in terms of two-weekly conference calls and meetings (twice a year or more if needed).

Evidence suggests the application of a greater number of psychotherapy sessions and a longer course of treatment is necessary to unfold the effects of psychological intervention in chronic depression. In our experience (both clinical and from the pilot study), two weekly individual sessions in the first 4 weeks facilitate the engagement of the patient and provides an intensive start. After the first 4 weeks, both CBASP and SYSP are conducted with 1 weekly session for the remaining 16 weeks in the acute phase (=24 sessions), followed by 8 continuation sessions over the next 28 weeks (2 sessions in the first 4 weeks, and 1 session every 4 weeks thereafter). The CBASP manual is designed as a longer intervention due to the chronic nature of the condition. Evidence indicates that effective treatment involves besides acute, also longer-term maintenance treatment to transfer the learning into daily life (Gelenberg et al., 2003). The duration of 50-minutes for each session is a common dosage in individual therapy.

A 12-months naturalistic follow-up is planned for a second study phase (not applied for here) since sustainment of response is particularly relevant given the chronic nature of the disorder.

4.5 Duration of subject participation

First patient in to last patient out: 30 months

Duration of the entire trial: 36 months

Duration of treatment per patient: 20 weeks of acute treatment followed by 28 weeks of continuation treatment = 48 weeks

Follow-up per patient: 48 weeks after randomization
4.6 Criteria for discontinuation

Individuals:
- Active suicidality,
- The physical health of the patient is at risk due to clinical judgment,
- Occurrence of an AE/SAE (Adverse Event/Serious Adverse Event) with therapeutic implications,
- Newly occurring exclusion criteria, or
- The informed consent is withdrawn.

Parts of the trial and entire trial:
If an investigator has ethical concerns because of the performance at one of the centers, the Coordinating Investigator or the Co-PI must be informed immediately. The Coordinating Investigator and the Co-PI are authorized to discontinue interventions in a trial centre because of insufficient and/or inadequate recruitment, insufficient quality of data or special problems unforeseeable in advance, which make the continuation of the study impossible at that specific centre.

A single treatment arm or the whole trial will be stopped if severe safety concerns become apparent to the DSMB.

4.7 Accountability procedures

Therapists conducting the therapy sessions will be trained and will receive continuous supervision during the trial (see Section 4.3).

The supervisors of the site-supervisors are experienced psychotherapists with an official supervisory status. The supervisor of CBASP (E. Schramm) was the first certified CBASP-
trainer and therapist in Europe (by J. McCullough), is active in the distribution of the approach, and has conducted previous trials with the intervention. Supervision for SYSP will be organized and led by M. Hautzinger who conducted several studies in which supportive therapy was the control condition.

Supervisors meet at least bi-monthly for conference calls with their site-supervisors.

4.8 Randomization codes and procedures for breaking codes

If a patient appears to be eligible for the study, the Site Coordinating Investigator will inform the patient about the study and must then receive written informed consent from the patient before any further study specific examination. Then the Site Coordinating Investigator will register the patient on a patient identification list located at the trial center.

According to this list, the patient receives a consecutive patient identification number. This patient identification number consists of five digits:

- The first two digits are the number for the trial site.
- The next three digits stand for the successively screened patients (e.g., 001 for the first patient)

The Site Coordinating Investigator must record the following information about the patient on the patient identification list:

- Full name
- Date of birth
- Inclusion and exclusion criteria of the study fulfilled/ not fulfilled

Treatment assignments for this study will be made using separate randomization schedules for each of the 10 trial sites. 100 randomization lists will be prepared by the University Medical Center Hamburg-Eppendorf prior to the start of recruitment. From these lists, the Freiburg Trial Site Coordinator (I. Zobel) will randomly assign a randomization schedule to the participating centers, respectively. All randomization schedules will remain confidential and known only by the Freiburg Trial Site Coordinator, who is not involved in recruiting and patient's inclusion.

Once the forms have been checked to be sure the participant meets eligibility requirements, the Site Coordinating Investigator shall access the interactive, internet based randomization program. The program will verify through a defined set of questions that the participant is ready to be randomized and provide a randomized treatment assignment for that participant.

The information registered on the patient registration form will contain:

- Patient identification number
- Year of birth
- Inclusion criteria of the study fulfilled

The randomization assignment will be printable displayed on the screen and emailed to the Site Coordinating Investigator.
This randomization email will contain:

- Patient identification number
- Year of birth
- Treatment and treatment number (a single digit assigned by the Freiburg Trial Site Coordinator)

After receipt, the Site Coordinating Investigator will record the treatment number on the patient identification list.

The code will not be broken until the primary statistical analyses have been completed and reviewed by the investigators.

4.9 Identification of data to be recorded on the CRFs/source data

There will be CRFs for each study participant on which data will be recorded directly. The completed CRFs are collected at each site and sent at least bi-annual to the Coordinating Centre Freiburg. The originals of the completed CRFs will be stored in the Department of Psychiatry and Psychotherapy, University Hospital Freiburg for at least 10 years.

5 Selection and Withdrawal of Subjects

The large sample size and the inclusion of 10 recruitment sites in different regions of Germany and from different departments (psychiatry and psychotherapy, psychology and psychotherapy, and psychosomatic medicine) will assure wider (e.g. geographical) participation and therefore greater generalisability and representativeness of results. Furthermore, we kept exclusion criteria to a minimum (expecting a high rate of comorbidity) in order to extend the generalisability of our findings.

Patients will be recruited from private practitioners (primary care physicians, psychiatrists, and psychotherapists), outpatient clinics, through announcements in the media, and announcements in public health centers.

In case of recruitment without medical referral (i.e. general physician or psychiatrist), trial centers will organize a close cooperation with the treating physician. If a medication washout is required, the referring physician (or the cooperating physician) will be responsible for an adequate period of the washout.

5.1 Inclusion criteria

Participants must meet the following criteria:

1) DSM-IV criteria for a current episode of chronic MDD, MDD superimposed on a pre-existing dysthymic disorder or recurrent MDD with incomplete remission between episodes in a patient with a current MDD and a total duration of at least 2 years.

2) Early onset of the disorder according to DSM-IV (onset before the age of 21)

3) Age between 18 and 65
4) A score of at least 20 on the 24-item HRSD at screening and, after a 2-week drug-free period, at baseline
5) Fluent in German language
6) Provide informed consent

5.2 Exclusion criteria
1) Acute risk for suicide (as opposed to suicidal thoughts) assessed according to clinical practice guidelines. Suicidal patients are eligible, as long as outpatient treatment is deemed safe by the clinician.
2) A history of psychotic symptoms, bipolar disorder, or organic brain disorders
3) A primary diagnosis of another axis I disorder including anxiety disorders (e.g. Posttraumatic Stress Disorder), or any severe substance-related abuse or dependence disorder as evaluated with the SCID-I
4) Antisocial, schizotypal, or borderline personality disorder (SCID-II);
5) Severe cognitive impairment
6) Absence of a response to previous adequate trial of CBASP, and/or SYSP
7) Other ongoing psychotherapy or medication
8) A serious medical condition (i.e. a history of seizures, severe head trauma, stroke or heart attack within six months before the study began)

5.3 Withdrawal criteria
In case of occurrence of an AE/SAE with therapeutic implications, newly occurring exclusion criteria or if the informed consent is withdrawn the patient’s participation in the trial will be terminated. Patients may withdraw from the study at any time at their request, for any reason, specified or unspecified and without penalty or loss of benefits the patients are otherwise entitled. Patients who are withdrawn from the study will not be allowed to re-enter later. Date of discontinuance, all recorded results at this time and if known the reasons for discontinuation will be documented in the CRF.

It is preferred that as few patients as possible prematurely discontinue treatment. All patients will be followed and documented after discontinuation of the treatment in order to record the data required according to the intention-to-treat principle. It is expected that only few patients will have to be withdrawn from treatment because of discontinuation criteria. They are accounted for in the general drop out rate included in sample size and power calculations (see Section 9.2). Therefore, withdrawn subjects will not have to be replaced.

6 Treatment of Subjects

6.1 Treatments to be administered
Treatments within this trial are described in Sections 2.1 and 4.4.
6.2 Medication/treatments permitted during trial

In cases of severe sleep problems, zolpidem is allowed for a limited period of time during the study (for a maximum of 3 weeks). Central acting drugs are not allowed during the study. Furthermore, illegal drugs are not allowed. Single dosages of non-steroid analgesics and other non-centrally acting drugs for medical conditions are allowed. General self-support groups can be maintained if already started.

6.3 Monitoring compliance

Patients’ attendance of therapy sessions will be documented. Therapists will immediately follow up on absent patients. Assessment forms for baseline, post-intervention and follow-up will be posted to patients and followed by reminders from the study center in case of no return.

7 Assessment of Efficacy

7.1 Efficacy parameters

See Section 4.1 primary and secondary endpoints

7.2 Assessing, recording and analyzing of efficacy parameters

For a description of endpoints, parameters and instruments see Section 4.1 primary and secondary endpoints. For an overview of patient's study visits and measurement times, screening flow and further details on procedures see the separate manual ProcMan-ProzedurenManual.

For analyzing of parameters see Section 9.1

8 Assessment of Safety

8.1 Specification and Assessment of safety parameters

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

In the present study the following AEs are defined:
1. exacerbation of symptoms, e.g. generalization of symptoms
2. appearance of new symptoms
3. appearance of passive suicidal thoughts
4. appearance of active suicidal plans or intentions
5. occurrence of problems in the patient-therapist relation
6. further disadvantageous incidents as assessed by the therapist.

Adverse Treatment Reaction (ATR) is defined as any AE due to the received treatment. The decision on causality of AEs will be made by the therapists and will be supervised and controlled by the PIs and the DSMB.

Serious Adverse Event (SAE) and Serious Adverse Treatment Reaction (SATR) are defined as an AE or ATR resulting in:
1. death;
2. life-threatening event, e.g. suicidal attempt;
3. an incident requiring hospitalization;
4. an incident leading to significant or permanent disability or invalidity.

Adverse Event CRF
(S)AEs and (S)ATRs will be documented after each session using an Adverse Event CRF. In the CRF the therapists will be asked to describe any adverse event, its duration (start/end date), intensity (mild, moderate, severe), assessment of causality (treatment related, probably related, possibly related, unlikely related, not related, not assessable), action taken, and outcome of the action taken. Furthermore, the therapist’s will be asked to assess whether the documented AEs and ATRs are judged to be serious (SAE, STR).

In case of changing therapists, the reasons for this change will be documented in a separate form.

8.2 Report, recording and reporting adverse events
Adverse Event CRFs (see 8.1) will be analyzed three times during the study as part of the regulatory Monitoring Reports provided by the monitoring institute (University Medical Center Hamburg-Eppendorf).

Serious adverse events (SAEs) and serious adverse treatment reactions (SATRs) are to report within one week to the coordinating center per fax or electronically (e-mail) using a Serious Adverse Event report form that provides further details on the incident.

8.3 Follow-up of subjects after adverse events
Patients leaving the interventions due to one or more of the reasons mentioned above will be followed up in accordance with good clinical practice until resolved or judged no longer clinically significant.
9 Statistics

9.1 Statistical methods

Statistical analyses will be done using the program 'Statistical Analysis System' SAS or SPSS. All program scripts which run for analysis will be documented and saved.

The final analyses will be performed in the intention to treat (ITT) population, allocating patients to treatment groups according to the arm to which they were randomized, and using the LOCF method in case of missing outcome data at week 20. Because of the chronic nature of the disorder, spontaneous remission is unlikely to happen.

At main analysis, the null hypothesis of equal efficacy will be tested (two-sided test) using analysis of covariance (ANCOVA) controlled for pre-treatment scores and centre. Secondary analyses of the primary endpoint will include a per-protocol approach, regression controlling for additional factors, and exploratory analyses of treatment effect modifiers. To examine changes over time, the MIXED model approach to repeated measures with 2 treatments by 4 measurement points will be used: baseline, after 12 weeks, after 20 weeks (acute intervention), and after 28 further weeks of continuation treatment. Analyses of continuous secondary variables will be performed using generalized linear mixed models. For remission rates, chi-squared tests and logistic regression will be used. The analysis of time to remission and time to response will be analyzed using standard survival analysis techniques.

Rates of (serious) adverse events with two-sided 95% confidence intervals will be reported separately for patients who attended at least one session of CBASP or of SYSP, respectively.

Standard methods will be used to provide tabular and graphical summaries as appropriate for continuous and categorical variables. To assess generalizability, demographic and clinical characteristics will be compared between participants who are subsequently randomized and participants who are screened but not randomized. The specific eligibility and exclusionary criteria by which participants are excluded from randomization will be tabulated. Demographic and clinical characteristics will be compared among the clinical coordinating centers and between the treatment groups to identify any imbalances.

Subgroup Analyses: Interaction terms between the treatment comparison and baseline factors in pre-specified participant subgroups will be used to test for differences in the treatment comparison of the primary outcome and other outcomes between different subgroups. The factors (moderators) to be considered in subgroup analyses (such as Childhood trauma, comorbidity, treatment expectation, suicidality and previous treatment), and further predictors, mediators will specified in the detailed statistical analysis plan (SAP).

Before the start of the analysis the detailed SAP will be prepared by the responsible statistician. This will be completed during the 'blind review' of the data, at the latest. This blind review, i.e., a checking and assessment of the data, will be performed after the end of the recruitment period, and it will be conducted ignoring treatment assignment. If the SAP contains any changes to the analyses outlined in the trial protocol, they will be marked as such, and reasons for amendments will be given. The SAP will be appended to the trial protocol.
The randomization code will be broken in two steps. The participants will be identified as belonging to group “1” or “2” without revealing which is the CBASP and SYSP group. The “1” and “2” code will not be broken until the primary and secondary statistical analyses have been completed and reviewed by the investigators.

9.2 Sample size/Recruitment

a) Power calculation

To be assessed for eligibility: n = 450

To be allocated to trial: n = 268

To be analyzed: intention-to-treat: n = 268; per protocol: n = 210

The sample size calculation starts by considerations for a fixed design, based on the primary outcome (HRSD) and on the primary hypothesis testing CPASP against SYSP (null hypothesis: identical expected HRSD). We considered a difference of five points on the HRSD between mean post-treatment scores of the treated groups as clinically relevant. In similar studies, standard deviations of post-intervention HRSD-scores of groups receiving CBASP, SYSP, or combinations range from 5.4 to 10.4 points (Keller et al., 2000; Markowitz et al., 2005). Assuming a common standard deviation of 10 points for two-group comparisons yields a medium-sized effect of 0.5 (Cohen's d). To detect this effect by a two-tailed t-test with a power (1- ) of 0.95 and type I error probability level of a=0.05 for significance, 210 patients (105 per group) are needed.

However, to allow for early stopping in case of substantial inferiority especially of the placebo (SYSP) arm, an interim analysis allowing for early rejection of the null hypothesis was planned for the time when data of about a third of the patients are available. This interim analysis was dropped with the first amendment. The power analysis was not actualized!

A conservative estimate of the inflation factor for the maximum sample size in this group sequential design with one interim analysis compared with the fixed design is 1.007 (the factor valid for two groups of equal size and a power (1- ) of 0.9; see Jennison and Turnbull 1999, p. 30). Thus 214 patients should be available for analysis. Assuming a drop-out rate of 20% from baseline to week 20, the maximum sample size is fixed as 268 patients to be randomized. This is the number needed for an appropriately powered per-protocol analysis (only completers are analyzed). In the intention-to-treat analysis, the higher number of patients is expected to be compensated by a potential dilution of treatment effects, so that the power will be approximately the same.

Estimations of eligible patients, giving informed consent (61%) and dropouts (20%) are based on our own pilot study (informed consent: 66%, drop-out: 14%) and the trial of Keller et al. (2000; informed consent: 66%; drop-out: 23.8%)

b) Enrollments
a) We have finished a randomized pilot study with 29 early-onset chronically depressed outpatients receiving either 22 sessions of CBASP or of IPT (Schramm et al., 2009). Currently, we are completing a bi-center trial with 60 chronically depressed patients comparing CBASP against medication. As in previous own DFG-funded studies on depression (e.g. IPT plus medication vs. medication alone in severely depressed patients, N=124; IPT vs. CBT in Social Phobia with/without depression, N=118), we experienced no recruitment problems in primary care and specialty mental health settings. We included 29 chronically depressed patients with early onset in 14 months (42 patients were screened), and 10 more training cases before the beginning of the study. The protocol was found to be feasible (only two drop-outs in the IPT-group, no suicide attempts).

b) The trial sites have been selected according to their scientific and clinical expertise in the field of depression treatment, their experiences in conducting large-scale investigations, pre-existing collaborations with the PI-centre and the numbers of accessible patients. All participating sites have their clinical focus on the treatment and research of depression and have established structures for successful patient recruitment during the course of other studies on depression. The Tübingen site, for example, recruited in an earlier study a sample of 339 unipolar depressed patients over 3 years (at 3 sites) and diagnosed 45% chronic depression (19% dysthymia). At the Heidelberg site app. 250 patients with depression are annually seen in the psychiatric out-patient clinic (app. 50% chronic). Additionally, 200 patients with depression are treated as inpatients. Some of the sites also participated in the “Competence Network on Depression and Suicidality” funded by the BMBF.

The recruitment and intervention phases will last 30 months (see Figure 2), i.e., patients can be enrolled continuously during 18 months. In order to achieve the total number (N=450) of screened patients in that period, an average of 25 patients have to be contacted every month. Consequently, an average number of 3 screened patients are required in each of the 10 trial sites per month. See Table 1 for detailed numbers of patients at each participating site. Participating Sites will produce summary recruitment reports 3-monthly for the Coordinating Center.

Table 1: Recruiting centers & numbers of allocated subjects projected for each trial site

<table>
<thead>
<tr>
<th>#</th>
<th>Recruiting center</th>
<th>Expected no. of patients allocated for the trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>University of Leipzig, Dept. of Psychiatry</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>University of Tübingen, Dept. of Psychology and Psychology Clinic</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>EOS-Clinic for Psychotherapy, Muenster</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>University of Marburg, Psychological Outpatient Clinic</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>University Medical Center Bonn, Dept. of Psychiatry and Psychotherapy</td>
<td>24</td>
</tr>
<tr>
<td>6</td>
<td>University Medical Center Hamburg-Eppendorf and Clinic Center Eilbek, Dept. of Psychosomatic Medicine and Psychotherapy</td>
<td>16</td>
</tr>
<tr>
<td>7</td>
<td>University of Lübeck, Dept. of Psychiatry and Psychotherapy</td>
<td>36</td>
</tr>
<tr>
<td>8</td>
<td>University of Heidelberg, Dept. of Psychiatry</td>
<td>40</td>
</tr>
</tbody>
</table>
9.3 Level of significance

Will be set at $a=0.05$

9.4 Criteria for termination of the trial

See Section 4.6

9.5 Missing, unused and spurious data

The final analyses will be performed in the intention to treat (ITT) population, allocating patients to treatment groups according to the arm to which they were randomized, and using the LOCF method in case of missing outcome data at week 20. Because of the chronic nature of the disorder, spontaneous remission is unlikely to happen. During data entry missing examinations will be performed and documented (see also Section 13).

9.6 Reporting of deviations from the original statistical plan

Protocol deviations: All important deviations related to study inclusion or exclusion criteria, conduct of the trial, patient management or patient assessment will be described. Deviations will be summarized by trial site, grouped by those who entered the study even though they did not satisfy the inclusion criteria and those who developed withdrawal criteria during the study but were not withdrawn.

Deviation from the Statistical Analysis Plan: If the SAP contains any changes to the analyses outlined in the trial protocol, they will be marked as such, and reasons for amendments will be given. The SAP will be appended to the trial protocol.

9.7 Subjects included in the analysis

The trial will be analyzed according to the ITT-principle. That means, the primary analysis for comparison of the treatment groups with regard to the primary endpoint will be based on the 'full analysis set'. The full analysis set includes all randomized patients, and patients are analyzed as belonging to their randomized arm, regardless of whether they refused or discontinued therapy, or whether other protocol deviations are known. In order to preserve the ITT principle as far as possible and to minimize bias, patients randomized to one of the treatment arms who do not start with the assigned therapy, will be included in the analysis, since the decision not to start therapy might be influenced by the knowledge of the treatment assignment.
The 'per-protocol set' is a subset of the patients in the full analysis set and includes only patients for whom no serious protocol violations are known. Comparisons of the treatments in the per-protocol set will be performed for the purpose of sensitivity analysis.

## 10 Access to Source Data/Documents

In the framework of the clinical trial, quality-assurance will be guaranteed by monitoring, auditing and authorized supervision. In this case access to source data/documents will be provided. See also Sponsor declaration in the appendices of the full application.

## 11 Quality Control and Quality Assurance

The investigators grant the monitor access to patient files for verification of proper documentation of study data. The laws on data confidentiality ("Bundesdatenschutzgesetz") fully apply. Persons authorized by the Sponsor as well as the competent authorities are allowed to verify data.

During the course of the study, a well trained monitor from the University Medical Center Hamburg-Eppendorf will visit the investigators regularly, depending on enrollment rates and study progression, approximately every 6 months. The investigator will need to set aside a reasonable amount of their time and the time of the designated members of their staff who are involved in the study for monitoring visits. After initializing the study the monitor will stay in regular contact with the study centers on short notice to get information about the compliance with the study protocol requirements, consensus of the data in the CRF and the originals, dating of the randomization, the updated patient identification lists, and the archiving system. These visits and telephone calls are supposed to control the progress of the trial, realize problems early and potentially solve them. The monitor will review the case report forms of the patients in the study to make certain that the items have been completed and that the data provided are accurate and obtained in the manner specified within the protocol.

The investigators will allow the monitor to have access to all original documents which prove the data on the CRFs. The monitor signs to handle all data that are under professional secrecy or show the patient’s identity confidentially, and will use the data only for the purpose the patient gave informed consent for. No data disclosing the identity of patients should leave the study centre as a result of the monitoring procedure. The monitor, the investigators and the Sponsor will maintain confidentiality of all patient records.

In addition to the routine monitoring procedures outlined above, a further quality assurance measure will be implemented. Summaries of the regular monitoring reports and further information on the trial progress (number of patients recruited, adverse events etc.) will be translated in English and sent to the members of the DSMB for inspection each half year. Thus, as an independent committee, the DSMB performs a second-level quality assurance step similar to internal audits in clinical trials of pharmacological interventions.

Further procedures:
• Regular supervision and monitoring of adherence
• Video recording of the psychotherapy sessions
• All therapists and raters will be asked to remind patients on a continuous basis to complete the questionnaires and to check the questionnaires for appropriateness

Certification of Participating Sites

A site will be considered certified when the following have been submitted to the PIs:

1. Name of study coordinator (or, if no study coordinator is designated, name of back up investigator)
2. Date the IRB affiliated with the Participating Site has approved the CT Protocol
3. Date of contract with Coordinating Center (Contracts will include the plans for payments and data entry, and will note that the Participating Site agrees to abide by the study’s publications policies
4. Name of center supervisor for CBASP and SYSP

12 Ethics

According to law regulations the patients will be appropriately educated about the nature, the relevance, and the meaning of the planned study. Written informed consent will be obtained prior to randomization and after the study has been fully explained to the patients. Patients can withdraw at any point without any disadvantage.

The education includes the following:

1. Goals and procedure of the trial
2. Deliberate character of the participation and the right to withdraw at any point without any disadvantage and without giving reasons
3. Benefits expected due to the participation in the study
4. Offer of more detailed information
5. Explanation of treatments
6. Obligations of the participant/insurance conditions

Side effects of evidence-based psychotherapies are fortunately rather rare (Hoffmann et al., 2008). A transient worsening of symptoms at the beginning of therapy may be due to giving up avoidance behavior but is rather rare. All patients will be regularly seen by his therapist and checked for acute suicidal risk and other AE/SAE according to clinical practice guidelines. In case of high risk for suicide or other severe psychiatric events, the patient will be transferred to inpatient psychiatric treatment. Further procedures are: Continuous monitoring (video recording of therapy sessions) and supervision of therapies for adherence and for the detection of psychiatric crisis or intolerable side-effects (AE); Immediate report of SAE to the PIs and initiation of specific intervention (e.g. hospitalization) to offer best possible treatment (see 8.1 and 8.2). All therapists and supervisors will be professionally trained therapists, safeguarding confidentiality of patient information.
The study has to be approved by the Ethical Committee of the University of Freiburg and the other sites, respectively. Any subsequent protocol amendments will be submitted to the Ethical Committee of the University of Freiburg for approval. The trial will be conducted in accordance with the Guidelines for Good Clinical Practice (GCP) following the principles of the Declaration of Helsinki.

### 13 Data Handling and Record Keeping

All protocol-required information collected during the study will be entered by the investigators, or designated representative in the CRF. The investigator will maintain a list of individuals who are authorized to enter or correct data. Data on patients collected on CRFs in the course of this trial will be documented in an anonymous fashion, i.e., the patient will be identified only by a patient identification number. Throughout the trial, all findings will be documented on the CRFs by the responsible investigator or an authorized person (according to the signature form of the centers). Paper forms will be signed by either of them. They will be complete, clear, accurate, legible, and plausible. Missing examinations or data must be marked along with an explanation. Corrections will be made according to the GCP-guidelines.

The CRF data will be transferred into the data base by double entry. Procedures for transfer and transformation of data will be validated. If data are transformed during processing, this is done in a way that it is always possible to compare the original data and observations with the processed data. Patients’ data will be checked for plausibility.

For coding, the following systems will be used: International Classification of Diseases (ICD) 10 for coding the illnesses and diseases.

Throughout this study, all data will be saved on electronic files and treated confidentially. For protection of the data, methods are implemented for prevention of passing of data to unauthorized third persons. Throughout the whole data-recording and –analysis, patients will be identified only by a patient identification number - never by their full name, initials or date of birth.

The legal provisions by the respective laws will be heeded. The investigator will keep sufficient information for every patient (name, date of birth, internal clinic number, patient identification number, gender, informed consent), in order to identify the patient. According to the ICH-GCP-guidelines, these documents (Patient Identification List) will be archived for at least 10 years. By conducting this study, the investigators agree that they and their staff will maintain all information provided by patients in strict confidence. Study documents provided (protocols, CRFs and other material) will be stored appropriately to further ensure their confidentiality. It is understood that the confidential information provided to the investigator will not be disclosed to others without direct written authorization from, except to the extent necessary to obtain informed consent from the patients, who are possibly eligible and might choose to participate in this trial. Such information will not be communicated by telephone to potential or enrolled patients or to any other individual.
The evaluation of the study will be done by the Principle Investigators exclusively. Scores, CRFs and all other documents used are the property of the Sponsor and may not be used differently or passed on without permission.

14 Organizational Structure

The organizational structure of the trial includes a steering committee, whose members participate in at least quarterly conference calls, and a data safety monitoring board (DSMB).

Steering Committee

Topics for discussion and decision: e.g. set-up of inclusion of patients and recruitment procedures, set-up of data management. Data analysis, preparation of publications.

The role of the DSMB committee is to monitor the progress of the trial, adherence to protocol and treatments, and give recommendations to the steering committee of the trial for discontinuation, modification or continuation of the study. In particular the DSMB will advise on potential stopping of treatment arms. Furthermore, the DSMB will receive and monitor reports on serious adverse events (SAEs) at regular intervals.

The DSMB committee will be invited for three meetings (one day) at the PI-centre in the course of the trial. The first meeting will be scheduled at the beginning, when training of therapists has been accomplished and recruitment and treatment has started. The third meeting will be scheduled at the end of the trial to discuss data analysis, preparation of publications, etc. Three experts have been invited and have agreed to serve as members of the DSMB committee for the proposed trial (see Table 2). The members cover different fields of expertise important to the trial.

In addition, Mr. Ch.F. Reynolds had reviewed this study protocol.

Table 2 Members of the DMSB and Steering Committee

<table>
<thead>
<tr>
<th>Data Monitoring and Safety Board (DMSB)</th>
</tr>
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<tbody>
<tr>
<td>1 Prof. Ch. F. Reynolds</td>
</tr>
<tr>
<td>2 Prof. J. C. Markowitz</td>
</tr>
<tr>
<td>3 Prof. Dr. K. Wegscheider</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Steering Committee</th>
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</thead>
<tbody>
<tr>
<td>1 PI and Co-PI</td>
</tr>
<tr>
<td>2 PI of each trial site</td>
</tr>
<tr>
<td>3 Jürgen Matzat</td>
</tr>
<tr>
<td>4 Prof. Dr. R. Richter</td>
</tr>
</tbody>
</table>
15 Financing and Insurance

Financial plan: see full application.
All cooperating sites and clinical facilities have a standard public liability insurance (allgemeine Betriebshaftpflichtversicherung).

16 Publication Policy

Before recruitment and data collection starts, the trial will be registered at www.clinicaltrials.gov.

Study results will be published in accordance to the criteria of the CONSORT-Statement. At least within one year of termination of the study, a manuscript for publication will be finalized.

Any formal presentation or publication of data collected as a direct or indirect result of this trial will be considered as a joint publication by the investigators. It requires the agreement of the Coordinating Investigator and the Co-Principal Investigator. Authorship will be determined by mutual agreement.

The results of the study may be presented during scientific symposia or published in a scientific journal only after review and written approval by the Coordinating Investigator and the Co-Principal Investigator. Investigators from the participating trial sites agree not to engage in presentations based on data gathered individually or by a subgroup of centers before publication of the first main publication, unless this has been agreed otherwise by all other investigators, the Coordinating Investigator and the Co-Principal Investigator.

The Coordinating Investigator and the Co-Principal Investigator will receive copies of any intended communication, presentation or publication reasonably in advance (at least 15 working days for an abstract or material to be presented orally and 45 working days for a manuscript). This request is made so to allow to review the communications for accuracy, to verify that confidential information is not inadvertently being divulged, to allow adequate input or supplementary information that may not have been available to the investigator, and to allow establishment of co-authorship.

17 References


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18 Appendices
Protocol approval

Coordinating Investigator

Signature Date 01.07.2009

Co-Principal Investigator

Signature Date 06.07.2009

Statistician

Signature Date 06.07.2009
Summary of changes in ‘amendment #1, July 30, 2010’:

‘Amendment #1’ includes (a) the abandonment of the a priori planned interims analysis as a result of the recommendation of the Data Safety Monitoring Board (DSMB), (b) a reduction of trial sites from 10 to 8, and (c) the introduction of a ‘procedures manual’ (ProcMan) as a means to measure and enhance study quality and uniformity of procedures across trial sites. The amendment did not result in changes to the design of the study. The published study protocol already included ‘amendment #1’.
2. Original statistical analysis plan, final statistical analysis plan, summary of changes

The statistical analysis plan was conducted as described in section 9.1 of the protocol. There have been no changes to the statistical analysis plan from original to final protocol.

Section 9.1 from the final protocol reads as follows:

“Statistical analyses will be done using the program 'Statistical Analysis System' SAS or SPSS. All program scripts which run for analysis will be documented and saved. The final analyses will be performed in the intention to treat (ITT) population, allocating patients to treatment groups according to the arm to which they were randomized, and using the LOCF method in case of missing outcome data at week 20. Because of the chronic nature of the disorder, spontaneous remission is unlikely to happen. At main analysis, the null hypothesis of equal efficacy will be tested (two-sided test) using analysis of covariance (ANCOVA) controlled for pre-treatment scores and centre. Secondary analyses of the primary endpoint will include a per-protocol approach, regression controlling for additional factors, and exploratory analyses of treatment effect modifiers. To examine changes over time, the MIXED model approach to repeated measures with 2 treatments by 4 measurement points will be used: baseline, after 12 weeks, after 20 weeks (acute intervention), and after 28 further weeks of continuation treatment. Analyses of continuous secondary variables will be performed using generalized linear mixed models. For remission rates, chi-squared tests and logistic regression will be used. The analysis of time to remission and time to response will be analyzed using standard survival analysis techniques. Rates of (serious) adverse events with two-sided 95% confidence intervals will be reported separately for patients who attended at least one session of CBASP or of SYSP, respectively. Standard methods will be used to provide tabular and graphical summaries as appropriate for continuous and categorical variables. To assess generalizability, demographic and clinical characteristics will be compared between participants who are subsequently randomized and participants who are screened but not randomized. The specific eligibility and exclusionary criteria by which participants are excluded from randomization will be tabulated. Demographic and clinical characteristics will be compared among the clinical coordinating centers and between the treatment groups to identify any imbalances. Subgroup Analyses: Interaction terms between the treatment comparison and baseline factors in pre-specified participant subgroups will be used to test for differences in the treatment comparison of the primary outcome and other outcomes between different subgroups. The factors (moderators) to be considered in subgroup analyses (such as Childhood trauma, comorbidity, treatment expectation, suicidality and previous treatment), and further predictors, mediators will specified in the detailed statistical analysis plan (SAP). Before the start of the analysis the detailed SAP will be prepared by the responsible statistician. This will be completed during the 'blind review' of the data, at the latest. This blind review, i.e., a checking and assessment of the data will be performed after the end of the recruitment period, and it will be conducted ignoring treatment assignment. If the SAP contains any changes to the analyses outlined in the trial protocol, they will be marked as such, and reasons for amendments will be given. The SAP will be appended to the trial protocol. The randomization code will be broken in two steps. The participants will be identified as belonging to group “1” or “2” without revealing which is the CBASP and SYSP group. The “1” and “2” code will not be broken until the primary and secondary statistical analyses have been completed and reviewed by the investigators.”