International Deprexis Trial in Multiple Sclerosis (IDEMS) – a multicenter randomized controlled trial

Acronym: IDEMS
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Protocol

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Coordinating Center: Charité – Universitätsmedizin Berlin
NeuroCure Clinical Research Center (NCRC)
Charitéplatz 1, 10117 Berlin

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Biostatistician: Prof. Dr. Tim Friede

We hereby agree on the following protocol. We are aware of the ICH-GCP guidelines and certify the trial will be conducted according to those regulations.

Principal Investigator
Stefan M. Gold (P.I.)

Signature

3/17/2017 Berlin
Date, Place

- Confidential -

The content of the protocol is confidential and serves to inform the following peers about content and course of the trial: investigators, their employees, the ethics committee and competent authority as well as a CRO, monitor and to inform possible participants.

Abbreviations

AE	Adverse Event
CBT	cognitive behavioral therapy
ICBT	internet-based CBT
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Event
ITT	Intent to treat Population
PPP	Per protocol population
RCT	Randomized controlled trial
WLC	waitlist controls

1 Synopsis

Study Title	**International Deprexis Trial in Multiple Sclerosis (IDEMS) – a multi-center randomized controlled trial**
Type of Study	Randomized controlled trial
Coordinating Center	Charité – Universitätsmedizin Berlin NeuroCure Clinical Research Center (NCRC) Charitéplatz 1, 10117 Berlin FAX: +49 30 450 539 921
Principal Investigator	Prof. Dr. Stefan M. Gold Responsible medical investigator at coordinating center: Prof. Dr. Friedemann Paul
Hypotheses	The online program "Deprexis" is effective in reducing depressive symptoms in patients with multiple sclerosis
Rationale	Depression is the most common comorbidity of MS. However, depression remains underdiagnosed and there are no treatments with proven effectiveness from large (phase III) trials. In addition, symptoms of MS such as mobility issues, cognitive impairment and fatigue make it difficult for MS patients to travel to and attend regular psychotherapy. Effective treatment options are therefore needed. The internet-based program "Deprexis" could facilitate access to treatment and has shown promise in a small monocenter study in Germany. The current trial will evaluate the effectiveness of Deprexis in an international multicenter trial.
IMP & Treatment	a) Deprexis as stand-alone for 12 weeks b) Deprexis with added email support for 12 weeks
Control	Waitlist control
Study design	Three arm, randomized, controlled, multicenter trial
Anticipated schedule	Initiation of recruitment – February 2017 Closure of recruitment – February 2019 Closure of trial – September 2019
Number of participants	375
Target Population	Multiple sclerosis
Inclusion Criteria	- age $\geq$ 18 - neurologist-confirmed diagnosis of MS - self-reported depressive symptoms (BDI-Fastscreen $\geq$ 4) - fluent in German or English (depending on study site), - willingness to engage in self-administration of an iCBT intervention for 12 weeks and complete follow-up - ability to travel to the outpatient center for two clinical assessments (baseline and week 12) - internet access at home - informed consent by patient
Exclusion Criteria	- unwilling or unable to consent, - diagnosis of bipolar or psychosis (as determined by M.I.N.I structured interview), - substantial neurocognitive impairments such as dementia or autism - moderate or high risk of suicide (according to MINI module C) or by clinical impression

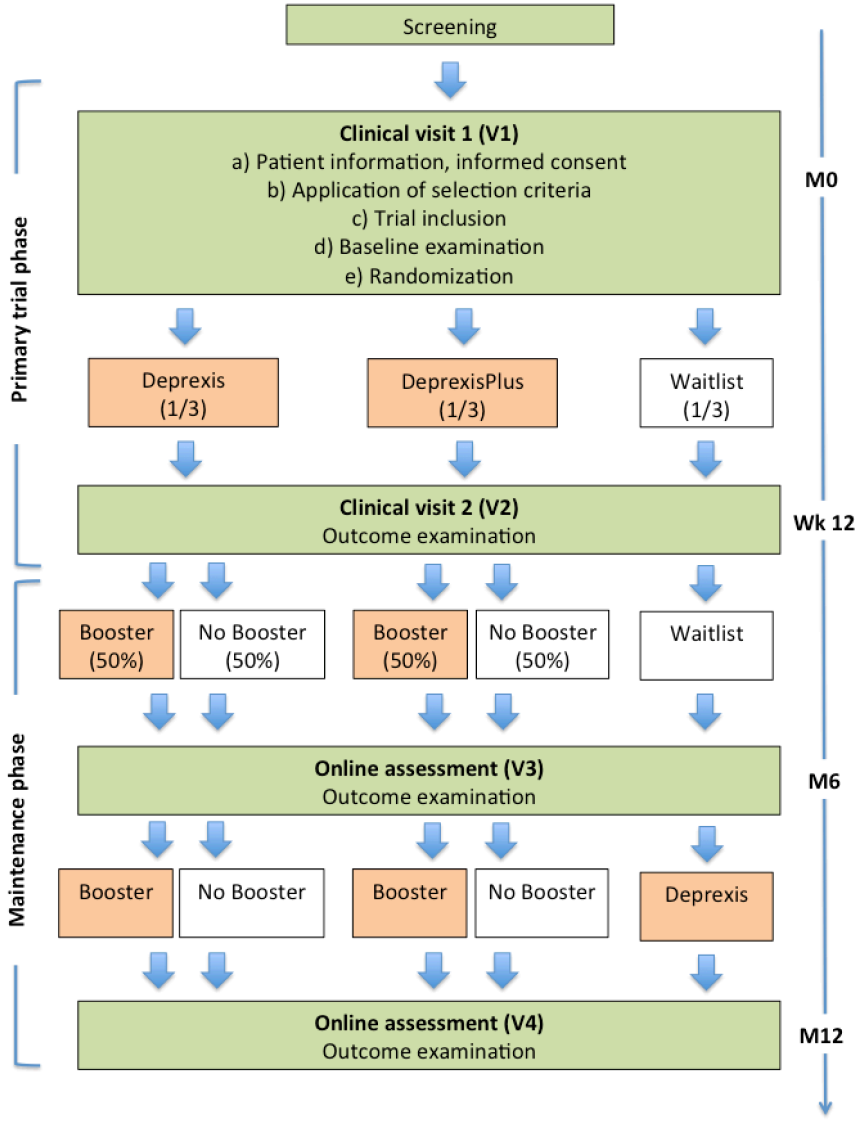
	- very severe depression that would interfere with the ability to participate in the study (based on clinical judgment by the physician at the recruitment site). Patients with very severe depression will be referred to psychiatric services for immediate treatment. - current psychotherapy/behavioral treatments for depression - started pharmacotherapy for depression within the last 2 months - MS relapse or steroid treatment in the last 4 weeks - concurrent participation in another interventional clinical trial - Refusal to saving, processing and forwarding of pseudonymized data
Visits	Clinical visits: Baseline and Week 12 Online questionnaires: Month 6 and Month 12

Endpoints	• Primary endpoint: Beck Depression Inventory - II
	• Secondary endpoints:
	  ○ WHO-QoL BREF
	  ○ Multiple Sclerosis Impact Scale, MSIS-29
	  ○ Fatigue Scale for Motor and Cognitive Functions (FSMC)
	  ○ Chalder Fatigue Scale
	  ○ Current MDD diagnosis (M.I.N.I. structured clinical interview, clinician-rating, version 5.0.0)
	  ○ Montgomery Asberg Depression Rating Scale (MADRS)
	• Safety and moderators
	  ○ Suicidal Behaviors Questionnaire-Revised
	  ○ Brief Cognitive Assessment in MS (BICAMS)

Safety	Documentation of adverse events with every visit. SOP suicidality
Criteria for Discontinuation	<u>Of Participation for an Individual:</u> Obligatory: Personal decision of the individual, potential harm (occurrence of clinically relevant suicidal ideation or at the discretion of the investigator) Possible: Retrospectively assessed exclusion criterion Severe Adverse Event (SAE) or Suspected Unexpected Serious Adverse Reaction (SUSAR) <u>Of the trial itself:</u> Change of the risk-benefit-analysis
Statistical Evaluation/Sample Size Calculation	The primary outcome change in BDI from baseline to week 12 will be will be analyzed as intention-to-treat (ITT) by means of linear mixed effect models for repeated measures adjusted for baseline measurements including all patients with at least one post-baseline measurement. A sample size of 100 patients per intervention group gives a conjunctive power (probability of rejecting both null hypotheses comparing Deprexis and DeprexisPlus to waitlist control) of 90% for a Dunnett test at the usual one-sided significance level of 2.5%. Adjusting for 20% dropout we aim to recruit 125 patients per group resulting in a total sample size of 375 patients.
Pharmacological-toxicological Evaluation	N/A
Possible Risks, Adverse Reactions, Contraindications, Procedures in case of incidents	The intervention is generally considered low risk as Deprexis has been used in numerous clinical trials without evidence for adverse events and is categorized as a “low risk” medical device according to

	its German CE®-certification. We will exclude patients with more than a low risk of suicidality. Standard operating procedures are in place to respond to occurrence of suicidal thoughts and intent in any participant.
Risk-Benefit-Analysis	Risk-benefit ratio is considered acceptable as risk is low but patients may benefit from a new online intervention tool to reduce depressive symptoms.

Course of trial (flow chart)



2 Introduction

2.1 Introduction and Background

Prevalence and impact of depression in MS

MS patients frequently experience neuropsychiatric symptoms such as depressive mood, fatigue, and cognitive impairment. Depression is common with a lifetime risk for major depressive disorder (MDD) as high as 25-50% (1) and a point prevalence of up to 25% (2). Depression is particularly frequent in younger patients (3). Depression in MS has been linked to biological as well as psychological factors and substantially impacts psychosocial function (4). Importantly, depressive symptoms correlate with decreased quality of life, absence from work, and lower social support in MS patients (5, 6). Depression is also associated with lower immunotherapy adherence rates and may thus have direct consequences for overall health outcome (7). Moreover, depression is one of the main predictors for suicidal ideation and suicide risk in patients with MS (8). If left untreated, depressive symptoms in MS rarely remit spontaneously, often become chronic (9), and may worsen over time, particularly in patients with baseline scores indicative of clinical depression (10). Despite its immediate clinical relevance, depression remains widely undiagnosed and untreated in MS patients (11).

The need to develop novel therapeutic options for depression in MS

Unfortunately, evidence for the efficacy of pharmacological or non-pharmacological interventions for MS-associated depression is scarce. Only two small placebo-controlled randomized controlled trials (RCTs) to date have evaluated the effects of pharmacotherapy with desipramine or paroxetine in MS-associated depression (12, 13). A Cochrane review (14) concluded that there was some benefit (albeit not statistically significant for most endpoints) but also a risk for adverse side effects such as nausea and headaches. One recent meta-analysis supports the efficacy of cognitive behavioral therapy (CBT) in individual or group settings (SMD -0.46, 95% CI -0.75 to -0.17, p=0.002) to reduce depressive symptoms in MS patients (15). This analysis however also found high levels of statistical heterogeneity. This means that there was substantial variance in the size of the treatment effect between the different trials that was larger than expected by chance alone, reducing the reliability of the aggregate effect size and thereby weakening the conclusions that can be drawn.

Since MS frequently causes motor impairment and decreased mobility as well as increased fatigability and cognitive problems, self-paced, remote access options for psychotherapy may be particularly useful to enhance availability of effective depression interventions such as CBT for MS patients. For example, psychotherapy delivered by phone has been shown to decrease depressive symptoms in MS patients (16, 17). Such approaches, however, still require availability of a trained psychotherapist. Guidelines for psychiatric disorders in MS published by the American Academy of Neurology in 2014 recommended the use of telephone-administered CBT with weak level of evidence (level C) and concluded that evidence for pharmacotherapy and individual and group therapies was insufficient (level U) (18). Thus, there is an urgent, unmet need to develop and rigorously test the efficacy of treatment strategies for MS-associated depression and to facilitate access to these treatments. Importantly, all RCTs for depression treatments in MS – be it pharmacological or behavioral – have been conducted in relatively small samples (range n=19 to n=127). To date, large, definitive trials (phase III) of the most promising therapeutic approaches that could inform clinical practice are completely lacking.

Preliminary Studies

Given the mobility issues and fatigability typically associated with MS as well as the limited availability of psychotherapists, self-guided, automated, internet-based interventions might be particularly useful for MS patients with a need for depression treatment, at least as an interim solution until psychotherapy becomes available. Another obvious advantage of such interventions would be that they can be broken down into smaller modules and completed at any time, therefore allowing patients with increased fatigability or deficits in cognitive domains such as processing speed or attention to proceed at their own pace. Among all available fully-automated, internet based CBT interventions, a program called “Depexis” developed by GAIA group in Hamburg/Germany is one of the most researched options (with 6 published phase II RCTs to date). In addition, a recent meta-analysis suggested that among the fully-automated programs, it is the most effective (19).

Evidence for efficacy of Deprexis

Evidence from several RCTs to date supports the efficacy of Deprexis among adults with elevated depressive symptoms when compared to waitlist control. In a first trial (20), n=396 participants were recruited from Internet forums in Germany and randomized on a 4:1 schedule to Deprexis or a waitlist control condition. In this trial, a between-group posttreatment effect size of d=0.65 (linear mixed-model analyses) was observed. However, attrition was somewhat problematic in this study (only 55% of participants completed posttreatment assessments). Another RCT with n=210 participants (21) confirmed a significant treatment effect of Deprexis, albeit with a smaller effect size (between-group difference d=0.36). Here, attrition was acceptable, with 82% completing the post-assessment. Another trial explored the program's efficacy among patients with epilepsy and elevated levels of depressive symptoms (22). In a sample of n=78 patients, the self-guided Deprexis version yielded small effects (between-group difference d=0.46). Attrition rate was in an acceptable range, with 72% completing posttreatment assessments. Finally, one recent RCT (n=163) supports the program's efficacy among adults with initially severe depression symptoms (23). Here, a posttreatment between-group effect of d=0.57 was observed. Attrition rates were acceptable, with 81% of participants completing post-assessments.

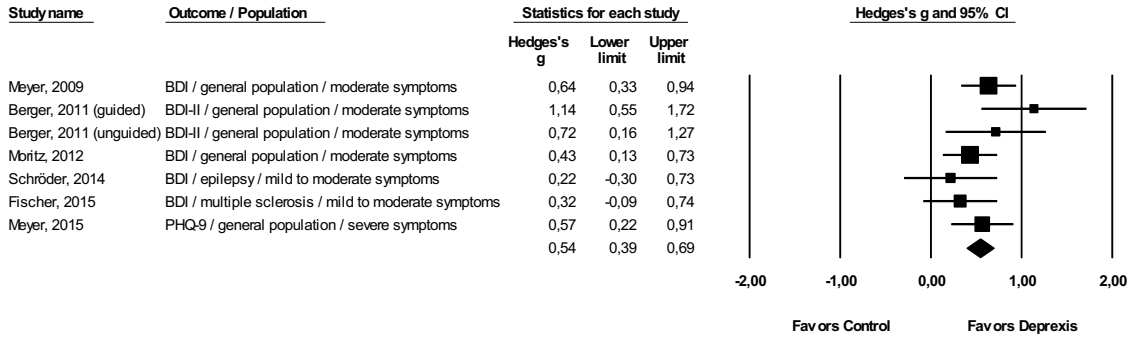


Figure 1: Meta-analytic summary of all published RCTs comparing Deprexis to a waitlist control group (forest plot). Data support efficacy of Deprexis with a medium effect size (p<.001).

The added value of therapist support: Deprexis vs DeprexisPlus

The literature on internet-based interventions strongly suggests that guided internet-based cognitive behavioral therapy (ICBT) is more effective than self-guided treatments and that various types of contact with a clinician or trained technician (like an interview or coming for assessment) tends to lead to better outcomes (24). Although Deprexis has been found to show the largest effect size of any of the fully automated programs evaluated to date, its efficacy might still be enhanced further by adding therapist contact. One small study compared the benefits of Deprexis with the same intervention complemented with weekly therapist support via e-mail (25). A waiting-list control group was also included. Seventy-six individuals meeting the diagnostic criteria of major depression or dysthymia were randomly assigned to one of the three conditions. The Beck Depression Inventory (BDI-II) was used as the primary outcome measure. Secondary outcomes included general psychopathology, interpersonal problems, and quality of life. Sixty-nine participants (91%) completed the assessment at posttreatment and 59 (78%) at 6-month follow-up. Results showed significant symptom reductions in both treatment groups compared to the waiting-list control group. At posttreatment, between-group effect sizes on the BDI-II were d=0.66 for unguided Deprexis versus waiting-list and d=1.14 for guided Deprexis versus waiting-list controls. In the comparison of the two active treatments, small-to-moderate, but not statistically significant, effects in favor of the guided condition were found on all measured dimensions. In both groups, treatment gains were maintained at 6-month follow-up. The findings provide evidence that internet-delivered treatments for depression can be effective whether support is added or not but that the efficacy of interventions such as Deprexis might be further enhanced by email therapist support.

The outcome measures, study populations, and results of all published Deprexis RCTs are summarized in Figure 1, which shows the weighted average effect size derived from reported post-treatment means and standard deviations (two effect estimates from Berger et al. (25), given that a guided and unguided program version were compared). Across these studies, Deprexis was

associated with a medium effect size, Hedges g=0.54, 95% CI: 0.39 to 0.69, p<0.001, with low and non-significant heterogeneity, I^2=14.71%.

Pilot data on US version of Deprexis

An English language version of Deprexis is currently being evaluated in a RCT at the University of Texas Austin (clinicaltrials.gov identifier NCT01818453, PI: Prof. Christopher Beevers, Dept Psychology, Director of the Institute for Mental Health Research). To date, 206 participants with an elevated level of depression are enrolled in the study. Interview based ratings of depression severity were obtained using the Hamilton Depression Rating Scale. There was a significant difference between the Hamilton score at baseline and follow-up (p<0.001). Although these data are based on an interim analysis and the control group has not been analyzed so far, these data indicate that the translated version of Deprexis is similarly effective in a US population and achieves comparable effects to the German version.

Phase II trial of Deprexis in MS

We recently conducted a phase II RCT to test the feasibility and efficacy of the fully automated, internet-based cognitive behavioral therapy (iCBT) program Deprexis to reduce depressive symptoms in MS patients (26). A total of 241 patients were screened and 96 were eligible for the trial. We randomized n=90 of the eligible patients (n=45 Deprexis, n=45 waitlist controls (WLC)) and n=71 completed the study resulting in a dropout rate of 21%. Drop-out was similar in the groups (Deprexis n=10, 22·2%; WLC n= 9, 20%). In the Deprexis group, BDI scores decreased over time, with scores slightly increasing in the WLC group (Figure 2, left panel). ANCOVA intention-to-treat analysis revealed significant treatment effects (mean difference 4·02 (CI 0.79; 7.26); p=0.015) with moderate effect size (d=0.53). Group differences were slightly larger in the mixed models, multiple imputations, and the per protocol sensitivity analyses. The fraction of patients above the cut-off for clinical depression decreased from 68% (n=24) to 54% (n=19) in the Deprexis group. In contrast, the percentage of patients above the clinical cutoff slightly increased from 67% (n=24) to 69% (n=25) in the WLC (see Figure 2, right panel). When analyzed by Cochran Chi-sq, this difference was significant (p=0.01). Based on the BDI categorical analysis, number needed to treat (NNT) was eight.

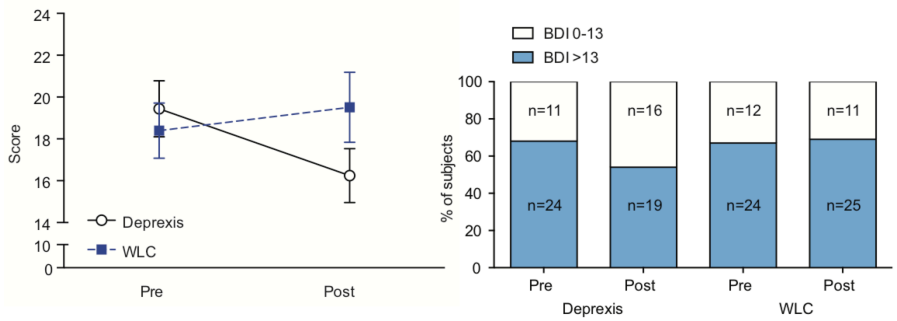


Figure 2: Phase II RCT of Deprexis to reduce depressive symptoms in MS. After the 9-week program, depression scores decrease significantly compared to the waitlist controls (WLC) with moderate effect size (p=0.015; d=0.53, left panel). The proportion of patients with clinically relevant depression (BDI>13) was also significantly reduced by the intervention compared to WLC (p=0.01). Taken from Fischer et al., *Lancet Psychiatry* (2015).

A subgroup of participants (n=34: Deprexis n=17, WLC n=17) from the online cohort volunteered to undergo additional psychodiagnostic assessment in the MS outpatient center. In this subsample, we confirmed a significant treatment effect of Deprexis on the BDI with a larger effect size (p=0.047; d=0.75). The intervention was safe with regards to adverse events monitored. Worsening of depressive symptoms from below to above the clinical cut-off (BDI > 13) occurred in n=3 patients in the WLC group and n=0 in the Deprexis group. No adverse events were noted with respect to new occurrence of suicidal ideation during the trial in either group.

2.2 Need For A Trial - Rationale

What is known:
- Substantial evidence indicates that Deprexis is effective for reducing depressive symptoms in participants without comorbid somatic disorders.
- Preliminary work supports the efficacy of Deprexis to reduce depressive symptoms in MS patients in Germany.
- The literature strongly suggests that therapist-guided internet-based interventions lead to better outcome. We have preliminary evidence that the guided version of Deprexis also leads to larger effects.

What is not known:
- Large, definitive trials that could inform clinical practice are lacking for *any* therapeutic approach in MS-associated depression (see AAN guidelines).
- The potential of added email support to enhance efficacy of iCBT in MS is unknown. It is also unknown which patients may benefit most from this added support (e.g. depending on baseline level of depression).
- It is unknown if Deprexis also works in a larger, international, and more heterogeneous MS population.
- Long-term stability of therapeutic effects and strategies to enhance it have not been explored for *any* therapeutic approach in MS-associated depression.

3 Trial Goals

3.1 Primary Endpoint

Our primary hypothesis is as follows: Deprexis is effective for reducing depressive symptoms (as measured by the Beck Depression Inventory – II) at the end of treatment (week 12).

For further details concerning the statistical evaluation please see Chapter 14.3.

3.2 Secondary Endpoints

3.2.1. Secondary endpoints
Secondary endpoints and the secondary hypotheses are listed below.

Quality of life:
- WHO-QoL BREF
- Multiple Sclerosis Impact Scale, MSIS-29

Hypothesis: Deprexis increases quality of life at the end of treatment (week 12)

Fatigue
- Fatigue Scale for Motor and Cognitive Functions (FSMC)
- Chalder Fatigue Scale

Hypothesis: Deprexis decreases fatigue at the end of treatment (week 12)

Depression
- Current diagnosis of MDD according to the M.I.N.I. structured clinical interview (clinician-based rating version 5.0.0)
- Montgomery Asberg Depression Rating Scale (MADRS)

Hypothesis: Deprexis reduces the percentage of patients with a clinical diagnosis of current MDD at the end of treatment (week 12)
Hypothesis: Deprexis reduces the severity of depression as determined by the clinician-rated MADRS at the end of treatment (week 12)

3.2.2. Moderator and safety measures

Neurological impairment

- Patient Determined Disease Steps (PDDS)
- *Expanded Disability Status Scale* (EDSS) (*in selected centers only)*

Cognitive function

- Brief Cognitive Assessment in MS (BICAMS)
- *Ancillary cognitive assessments (*in selected centers only)*
  - *Matrix Reasoning**
  - *COWAT**
  - *Animal Naming**
  - *Oral Trails**
  - *Golden Stroop**
  - *WTAR**
  - *Mini Snellen**
  - *MRR**

Suicidal ideation (safety)

- Suicidal Behaviors Questionnaire-Revised (SBQ-R)

ADDITIONAL MODERATORS *(*in selected centers only)*

- Perceived stress scale (PSS)
- Self-efficacy for managing chronic disease (SES6G)
- Berlin Social Support Scales (BSSS)
- *Experience Questionnaire**
- *Psychological vulnerability questionnaire**
- *Committed Action Questionnaire**
- *Apathy Evaluation Scale**
- *Apathy Scale**
- *Hassles and Uplifts Questionnaire**
- *Cognitive Health Questionnaire**

3.3 Design

Characteristics

Three arm, randomized, controlled, multicenter trial

Groups

- Deprexis
- DeprexisPlus
- Waitlist Control

Study organization

- Multicentric with 5 academic centers recruiting
- Total recruitment of 375 patients

3.4 Schedule

Trial Preparation

- Ethics committee and Competent Authority Approvals approx. Q4/2016
- Construction of the online study platform approx. Q3/2016
- Completion of the therapist manual approx. Q4/2016

Screening and Recruitment

- Q2/2017

Completion of Trial

- Last patient in: approx. Q2/2019
- Last patient out: approx. Q4/2019
- Completion of statistical evaluation and interpretation & presentation of final report: approx. Q2/2020

4 Patient Selection

Our target for recruitment is 375 patients (see Chapter 14.1 for sample size estimations).

4.1 Inclusion criteria

- age $\geq$ 18
- neurologist-confirmed diagnosis of MS
- self-reported depressive symptoms (BDI-Fastscreen $\geq$ 4)
- fluent in German or English (depending on study site)
- willingness to engage in self-administration of an iCBT intervention for 12 weeks and complete follow-up
- ability to travel to the outpatient center for two clinical assessments (baseline and week 12)
- internet access at home
- informed consent by patient

4.2 Exclusion criteria

- unwilling or unable to consent
- diagnosis of bipolar disorder or psychosis (as determined by M.I.N.I structured interview)
- substantial neurocognitive impairments such as dementia or autism
- moderate or high risk of suicide (according to MINI module C) or by clinical impression
- very severe depression that would interfere with the ability to participate in the study (based on clinical judgment by the physician at the recruitment site). Patients with very severe depression will be referred to psychiatric services for immediate treatment.
- current psychotherapy/behavioral treatments for depression
- started pharmacotherapy for depression within the last 2 months
- MS relapse or steroid treatment in the last 4 weeks
- concurrent participation in another interventional clinical trial
- refusal to saving, processing and forwarding of pseudonymized data

5 Treatment

5.1 Description of the treatment

In this trial, we will use Deprexis, either as a stand-alone internet-based intervention (Deprexis) or with added standardized email support by a clinical psychologist (DeprexisPlus, see below). We have recently adapted Deprexis to MS-specific needs. Content regarding psychological challenges frequently facing MS patients was incorporated into the Deprexis format and the new version was piloted in focus groups of patients. In the IDEMS trial, we will only use the MS-adapted version of Deprexis.

MS-specific Deprexis: Deprexis is an online tool based on principles of CBT. It consists of 10 sequential modules plus an introduction and a summary module. Deprexis implements the technique of simulated dialogue by giving the user multiple choice options and tailoring the subsequent content to the patient's responses. Thereby, the user's responses determine the course of each module. Depending on the user's speed, each module can be completed in less than 60 minutes. Contents are (1) psychoeducation, (2) behavioral activation, (3) cognitive modification, (4) mindfulness and acceptance, (5) interpersonal skills, (6) relaxation, physical exercise and lifestyle modification, (7) problem solving, (8) expressive writing and forgiveness, (9) positive psychology, and (10) emotion-focused interventions. The newly developed MS-Deprexis contains several MS-specific elements, the vast majority of them included in the first module: (1) The program now clarifies that it is intended specifically for MS patients; (2) several illness parameters are assessed early on in an interactive sequence, including time since diagnosis, symptom severity, and subjective impairment; (3) an interactive sequence introduces the concept that biological as well as psychosocial factors might contribute to depression in MS; (4) the psychoeducational sequence introducing a cognitive-behavioral model of depression has been modified; for example, users can now reflect on optimistic as well as pessimistic cognitive responses to having MS (e.g., "Having MS makes me appreciate every day even more" vs. "Having MS means the future is bleak and hopeless for me"); (5) the section on subjective reasons for depression has been modified; having MS is now included as a potential reason; and (6) the section in which previous research is discussed has been modified to include the results from our phase II trial in MS patients. In addition to these changes, minor changes have been made to other program modules. For example, the module on activity scheduling now acknowledges that certain activities may be inappropriate because of the MS diagnosis, and users are encouraged to select only activities that they feel safe doing. Piloting, qualitative, and quantitative assessment of the MS-specific Deprexis supported its suitability in this population.

MS-specific DeprexisPlus (guided version): This group will receive the web-based Deprexis program, in its modified version to increase suitability for MS patients, plus scheduled e-mail contact with a therapist. The manual for the e-mail support will be based on a manual developed for the IDEMS trial (see appendix). The manual aims to maximize the e-mail support's suitability for the needs and requirements of MS patients. Experiences from recent projects in which detailed clinician manuals for Deprexis support conditions have been developed will also be considered in the protocol modification (http://www.e-compared.eu/research/trials-design/). The basic structure of the e-mail support will be as follows (based on (25)): At the beginning of the treatment, a therapist will introduce herself (or himself) via e-mail, which will be integrated (secure webmail) into the online study platform. Participants will be informed that they can contact their therapist whenever they want to. Once a week, the therapist will write a short e-mail with feedback based on participants' program usage over the previous week (i.e., as in previous studies with the supported Deprexis version, the therapists will be able access information regarding which modules the participants have engaged with and for how long). This feedback will also acknowledge participants' response to a brief mood measure and to the PHQ-9 (current depression), which they are asked to complete at regular intervals as they work through the program. Progress with the relevant Deprexis related tasks and specific therapeutic techniques, or principles can be briefly discussed in the e-mails, as well as MS-specific questions or concerns. The main function of this feedback is to encourage participants' independent work with the Deprexis program and to enhance engagement. Where there is no online activity by a participant, therapists will offer their help and assistance and will ask if the participant is facing any problem with the program or with the tasks. When participants ask a question, therapists will provide an answer

within 3 days. If a therapist is on leave, participants will be notified there may be a more delay in answering questions. Two therapists with a qualification in clinical psychology will be responsible for email support in the trial (one for all patients enrolled in the German study sites and one for all patients enrolled in the US). Supervision by experienced clinical psychologists will be provided at least monthly for German-speaking and English speaking participants. To ensure consistent quality, and to be able to estimate the extra cost of guided support, all e-mail messages sent by the therapists will be saved (together with the time taken to read patient emails and respond to these) and stored in a secure file. Emails will be discussed in supervision to maintain fidelity and quality during the trial. In addition, at the end of the trial, a random 20% of emails will be rated by an independent trained assessor for treatment fidelity.

Deprexis booster: During the maintenance phase of the trial**,** Deprexis access will remain open for all patients who were randomized to either the Deprexis or the DeprexisPlus group. However, these patients will be re-randomized to receive additional booster session or just continued access to the program without any additional measures. In the booster condition, additional content (on relevant topics such as maintaining treatment gains and preventing relapses and additional modules introducing advanced CBT techniques) will be unlocked. In addition, the participants will receive weekly automated messages encouraging them to work with the program. The participants randomized to no booster will simply have continued access but not see the added content and not receive automated email reminders.

5.1.1 Known Adverse Events

In the previous monocenter trial of Deprexis in MS, we considered new occurrence of suicidal ideation or intent as well as worsening of depressive symptoms above the clinical threshold as potential adverse events. None of the enrolled participants met the predefined criterion for acute risk of suicide (response 3a or 3b on SBQ-R item 3 plus score of 5 or 6 on SBQ-R item 4) at baseline or the after the intervention. For the low threshold definition using BDI item 9, the criterion was not met by any patient in the Deprexis group (pre: n=0; post: n=0) but in one instance in the WLC group (pre: n=1; post: n=1). For SBQ-R item 4, n=2 patients met the low threshold criterion before and n=0 patients after Deprexis in the treatment group. In the WLC group, this criterion was met in n=4 at baseline and n=3 nine weeks after baseline. However, no evidence for new occurrence of suicidal ideation was seen during the trial in either of the groups using the low threshold criteria. Worsening of depressive symptoms during the trial from below to above the cut-off for “caseness” (BDI > 13) was observed in n=3 patient in the WLC but not in the Deprexis group.

5.1.2 Treatment Plan

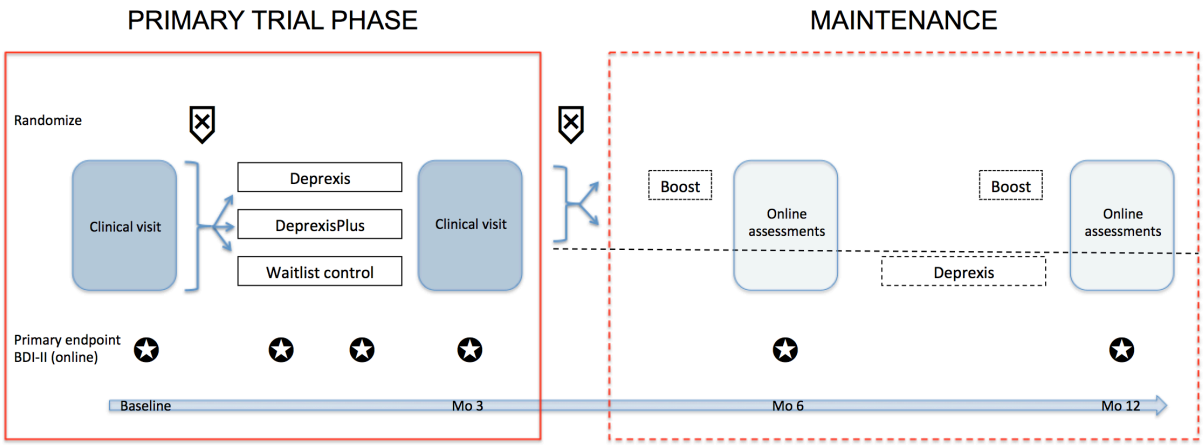


Figure 1: Trial Design Schematic and Treatment Plan.

5.1.3 Compliance

Ascertainment of compliance

We will assess time spent working with the Deprexis program by each patient as a measure of treatment adherence. The Deprexis interface tracks usage time of each participant, thereby allowing evaluation of treatment adherence. The usage log of Deprexis uses 5-minute blocks and excludes each block of inactivity so that the logged usage times is a good estimate of time spent working with the program. We will use the time spent working with the program and the number of modules completed (with at least 15 minutes spent in the module) as an indicator of treatment adherence. For DeprexisPlus, we will also collect data on number of email contacts per patients and total time spent on each email.

5.2 Emergencies

In case of emergency supposedly due to application of IMP treatment is immediately discontinued. Regulatory reporting duties apply. As we consider occurrence of suicidal ideation and intent as a potential adverse event in patients with depressive symptoms, we have developed specific SOPs for reponsing to such events (see SOP suicidality in the appendix).

6 Trial Conduction

6.1 Screening and Recruitment

Screening will happen within the participating centers.

Recruitment

- Recruitment happens as a distinct informational visit.

6.2 Informed Consent

Patients will be informed about the conduction of the trial in a personal conversation by a physician. They will receive the written patient information, and be given time to read it thoroughly and without haste. If further questions arise, the physician will answer them openly and correctly. If the patient is able to consent, but unable to sign the documents, an independent witness may sign the forms to document the orally given consent by the patient.

6.3 Prevention of simultaneous inclusion in multiple trials

Inclusion in another interventional trial is an exclusion criterion. It is the duty of the recruiting investigator to rule out current participation in another trial. Patient information will explicitly state the impossibility to partake if already participating in another trial.

6.4 Enrolment

- Recruitment of new patients at any of the study sites will be tracked in pseudonymized form by the study platform

6.5 Visits, Investigations and deviations of standard-of-care

Methodological Continuity
Same methods to measure variables and outcome parameters will be used throughout the conduction of the trial.

Time points
Treatment will be administered for 12 weeks during the primary trial phase.

Complementary Scientific Program

Several ancillary studies are planned, some of them only in selected sites:

Neuroimaging: Structural and functional (resting state and emotion regulation task) MRI studies are planned at several sites. These will be conducted only during the clinical visits (V1 and V2).

Psychological moderators and predictors of treatment response: Additional paper and pencil questionnaire to measure potential psychological moderators and treatment reponse predictors will be obtained at several sites. These will be conducted only during the clinical visits (V1 and V2).

Molecular and cellular shifts in the immune system: Obtaining blood samples for storage of serum, plasma and cryopreserved peripheral blood mononuclear cells (PBMCs) are planned at several sites. These materials will be used to explore potential immunological markers of treatment response. Blood samples will be obtained only during the clinical visits (V1 and V2).

Investigation	V1 (wk 0)	Interim (wk 4)	Interim (wk 8)	V2 (wk 12)	V3 Follow-up (M 6)	V4 Follow-up (M 12)
Check for selection criteria	X					
Informed Consent	X					
Case history	X					
Clinical Examination	X			X		
Questionnaires	X	X	X	X	X	X
Demographic data	X					
Laboratory examination						
Blood sampling (optional)	X			X		
MRI (optional)	X			X		
Incidence of AEs/SAEs		X	X	X	X	X

Blue: Clinical visits at the study site; **Black**: Online assessments

In case of a loss to follow up we contact the local registration authorities to ensure we can reach the highest amount of patients possible, even if they moved.

6.5.1 V1 (clinical visit)

Informed consent is obtained and selection criteria will be checked. If all inclusion criteria are met and all exclusion criteria are excluded baseline examination will be performed and patients will be randomized.
The following data will be collected:

- Case history and demographic data
- Clinical examination, including
  - a basic medical examination
  - a neurological examination
  - a structured clinical interview for psychiatric symptoms
  - self-report questionnaires
- *Laboratory examination (optional)*
  - *Immunology*
- *Neuroimaging (optional)*
  - *Structural MRI*
  - *Resting-state fMRI*
  - *Task fMRI*

6.5.2 V2 (clinical visit) at 12 weeks post randomization (+/- 7 days permissible)

Visits will be conducted on site at unit/neurological ward:

- Clinical examination, including
  - a basic medical examination
  - a neurological examination
  - a structured clinical interview for psychiatric symptoms
  - self-report questionnaires
- Incidence of AEs
- *Laboratory examination (optional)*
  - *Immunology*
- *Neuroimaging (optional)*
  - *Structural MRI*
  - *Resting-state fMRI*
  - *Task fMRI*

6.5.3 Follow-Up assessments – V3 and V4 (online) (+ 28 days permissible)

Follow-up assessments will be conducted online. The following data will be collected at V3 and V4:

- Self report questionnaires
- Incidence of AEs

6.5.4 Laboratory Details

No routine laboratory markers will be obtained. In some centers, ancillary scientific studies are carried out to study immunological correlates of depressive symptoms in MS and their response to treatment using serum samples and PBMCs (see above)

6.6 Duration of trial participation for the individual subject

Prerequisites of trial completion for the individual subject

- Duration of treatment: 12 weeks
- Duration of follow-up: 1 year after study inclusion

7 Risk-Benefit-Consideration

Risks, Adverse Reactions, Burden, Advantages and Disadvantages for Participants

RISKS

Risk of the treatment: The intervention is generally considered low risk as Deprexis has been used in numerous clinical trials without evidence for adverse events and is categorized as a "low risk" medical device according to its German CE®-certification. The FDA has reviewed Deprexis in July 2015 and classified it as a mobile medical application. The FDA does not intent to enforce any regulatory requirements under applicable provisions of the Federal Food Drug and Cosmetic Act, Section 513(g). A potential safety concern regarding an online intervention targeted at depression is suicidal ideation and intent.
Procedures implemented to control risk: Acute risk for suicide at baseline (as determined by the SBQ-R, see above) will lead to exclusion from the trial and patients will immediately be referred to specialists for crisis intervention. In our previous trial (26) we found no evidence for the new occurrence of suicidal thoughts during the trial or at 6-months follow-up in the Deprexis or waitlist control group. Similarly, previous trials of Deprexis (including the recent trial of patients with severe depression (23)) also showed no evidence for increased suicidal ideation and intent. However, in the proposed trial we will establish a detailed protocol for detection and response to suicide risk. During the clinical visits, all patients will be asked about suicidal ideation and intent. In addition, we will obtain information about emergency contacts (friends/family) in a standardized manner. If participants express suicidality during their clinical visit, the site PI (neurologist or experienced clinical psychologist) will be contacted immediately by the study coordinator and will explore things further with them in person. If participants appear to present an immediate danger to themselves, then standard procedures established at each site will be followed for possible commitment. Participants will be informed in the informed consent form about the possibility that confidentiality may need to be breached if they express an immediate, serious danger to themselves. Finally, the secure online study platform will include a feature where helpline numbers will be automatically displayed if response on the BDI-II indicates suicide risk at any time (item 9 = 3). In this case, an automated email alert will also be sent to the study center of the patient for a follow-up phone call by the study coordinator and the site PI (neurologist or experienced clinical psychologist).

Risk of blood sampling: Blood sampling is considered low risk. Blood drawing from a vein may cause pain from insertion of the needle, light headedness, faintness, bruising, localized bleeding which may

look and feel like a bruise, and rarely inflammation of the vein, clotting of the vein and/or infection at the needle site.
Procedures implemented to control risk: Blood sampling will be conducted according to established protocols and performed by authorized personnel (study nurse or physician).

Risk of MRI examinations: There are no specific side effects from having an MRI scan, although some patients become claustrophobic (fear of enclosed space) during the MRI scan. Because the MRI uses magnets, participants with cardiac pacemakers, certain artificial heart valves, and/or other metallic/electronic material in their bodies cannot undergo MRI imaging and will not be eligible for this study. MRI is painless and requires only that you lie in the scanning machine. The machine produces loud sounds. It is therefore essential that you wear earplugs during the MRI scan to protect your hearing. Patients with severe claustrophobia during prior MRI scans or patients with a prior allergic reaction to gadolinium should not participate in this study.
Procedures implemented to control risk: Patients will carefully be examined for potential contraindications for MRI scans and scans performed by authorized personnel under appropriate supervision of a neuroradiologist.

BURDEN

The main burden for participants in the trial is coming in for the clinical examinations (V1 and V2), completing the online questionnaires and working with the Deprexis program. Patient will be reimbursed for their time and effort.

ADVANTAGES

Participants will receive a novel online program to reduce depressive symptoms free of charge, either immediately or after waiting for 6 months (i.e. all patients will receive treatment). Participants may also benefit from a throrough clinical and psychological examination conducted at V1 and V2 by authorized personnel under the supervision of experienced clinicians.

8 Discontinuation and Ongoing Treatment

8.1 Premature discontinuation of participation for an individual subject

Reasons to discontinue participation (Criteria of discontinuation)

The following conditions are obligatory reasons to discontinue further participation in the trial according to the protocol:

- Decision of the patient
- Any further situation rendering further participation potentially harmful to the patient at the discretion of the investigator

The following conditions are possible reasons to discontinue further participation in the trial according to the protocol, and have to be reviewed as soon as possible by the principal investigator:

- Serious adverse event (SAE) and Suspected unexpected serious adverse reaction (SUSAR)
- Retrospectively assessed exclusion criterion

8.2 Premature discontinuation of the trial

A premature discontinuation of the trial may be decided if new scientific data emerging during the course of the trial changes the risk-benefit-balance significantly. If such data emerges, recruitment and treatment of currently treated patients will be paused immediately. A final decision on continuation or termination of the trial will then be made by the principal investigator.

SAEs will be assessed in detail at the second clinical visit for each patient with a specific focus on new occurrence of psychopathology and suicidal ideation and intent (based on MINI structured interview and the SBQ-R at the M3 clinical visit). There are no predefined stopping rules.

8.3 Ongoing procedures besides the protocol

After premature discontinuation of the trial

Patients will be followed up at the same time points as lined out in the regular study protocol for safety endpoints if they agree to.

After regular completion of the trial

Patients may seek advice on the study or related issues after completion of the trial, but may be then referred to structures of regular health care (GPs, neurologists, psychiatrists, outpatient clinics, etc.) in case the scope of the issue is covered by standard of care.

9 Adverse Events

The following chapter contains the definitions of and procedures to assess and grade adverse events. Furthermore, it states the chain of report for severe or unexpected events.

9.1 Definitions

Adverse Event - AE

Any untoward medical or psychological occurrence temporally associated with the use of the intervention, but not necessarily causally related.

Every AE has to be rated concerning its severity:

- Mild: The AE is transient and easily bearable for the patient.
- Moderate: The AE causes inconveniences to the patient and interferes with his or her usual activities.
- Severe: The AE causes significant disturbances for the patient‘s usual activities.
- whether criteria of an SAE are fulfilled

Every AE has to be judged in terms of causal relation to the IMP:

- no causal relation
  The event is well understood and derives from another cause.
- possible causal relation
  An event with an understandable temporal relation to IMP application, well-fitting to a known pattern of reaction to the IMP, but easily attributable to several other factors.
- probable causal relation
  An event with an understandable temporal relation to IMP application, well-fitting to a known or expected pattern of reaction to the IMP. The event resolves after cessation of IMP application and is not explicable through other known factors of the patient’s clinical condition.
- certain causal relation
  An event with an understandable temporal relation to IMP application, well-fitting to a known or expected pattern of reaction to the IMP. The event resolves after cessation of IMP application.

Documentation on MS relapse or progression and hospitalization due to MS relapse or progression should be made on the designated CRF-pages.

Serious Adverse Event - SAE

Every AE fulfilling any of the following criteria is considered an SAE:

- Suicidal ideation or intent (as measured by a score of 3 on BDI-II item 9 at any assessment, during the clinical interview at V2 or spontaneous report in a web message to the therapist or by contacting the study site)
- Hospitalization due to psychiatric disorder classified according to ICD10 or DSM5
- Lethal or life-threatening (incl. suicide or suicide attempt)

Suspected Unexpected Serious Adverse Reaction - SUSAR

SUSARs are suspected unexpected serious adverse events, causally related to the application of the intervention. The following criteria have to be fulfilled:

- Type or severity of the event are not in accordance with the available information on the intervention.
- Lethal or life-threatening (incl. suicide or suicide attempt)

9.2 Documentation of AEs and SAEs

Every AE has to be documented regardless of causal relationship. Documentation contains kind of event, start and duration, intensity and causal relationship. Related symptoms, clinical and laboratory findings should be summarized to a single AE. A sheet to document AEs is part of the CRF; furthermore, SAEs have to be separately documented on a distinct SAE sheet. If the necessary information is currently not available, follow-up reports have to be completed and transferred. In case of a lethal event, the autopsy report should ideally be included.

9.3 Chain of report for SAEs and SUSARs

Obligations and deadlines given by the authorities remain untouched. This chapter is solely for the investigator's information.

Table: Reports from Investigator to Principal Investigator		
Kind	Deadline	
AE	Upon completion of patient follow-up	Written report in CRF
SAE	Within 15 days	Written report in CRF and on separate, distinct SAE form

Kind	Deadline	Investigators
SAE	On Request	
SUSAR	Case report within 15 days	x
SUSAR (Death)	Case report within 7 days	x
Follow-Up-Report (if initially incomplete)	After 8 days	x

<u>Exceptions</u>
The following SAEs should be <u>excluded of the report chain</u> in the course of this trial:

- SAEs occurring after trial inclusion but before treatment initiation
- Events with hospitalization planned before the inclusion to the trial

<u>Principal Investigator Reporting Duties</u>

The principal investigator documents every reported SAE. The principal investigator furthermore reports every SUSAR immediately, in any case within 15 days after it became apparent, to the participating investigators. A lethal or life-threatening SUSAR is reported immediately, in any case within 7 days after it became apparent, to the participating investigators. A follow-up report within further 8 days can be transmitted if information retrieved was initially incomplete.
All data will be transformed in pseudonymized form.

9.4 Data Monitoring Committee (DMC)

The DMC is an independent committee regularly assessing safety data during the course of this study. Primary interest of the DMC is the safety of trial participants and integrity and validity of collected data. The DMC reviews frequency and severity of SAEs. It states a recommendation to the principal investigator whether to continue or discontinue trial conduction. Details on the predefined criteria are given in Chapter 12.5.3.

Members of the DMC are
Sarah Minden, M.D., Brigham and Women's Hospital, Harvard Medical School, Boston, USA
Carsten Spitzer, M.D., Asklepios Clinic Tiefenbrunn, Germany

10 Documentation

10.1 Case Report Form (CRF)

Acquired data is documented in paper CRF as well as eCRFs (IDEMS study platform). A copy of the paper CRF can be found in the appendix.

10.2 Investigator Site File (ISF)

All essential documents according to ICH GCP Chapter 8 are filed in the Investigator Site File on site.

10.3 Trial Master File (TMF)

All essential documents according to ICH GCP Chapter 8 are filed in the Trial Master File at the coordinating centre (NCRC).

11 Quality Management

11.1 Assessment of trial conduction and data quality

Indicators of quality for trial conduction are

- Adherence to recruitment rate
- Adherence to selection criteria
- Adherence to per-protocol-treatment
- Adherence to visit schedule

11.1.1 Monitoring

Internal Monitoring for German sites will be conducted by the coordinating centre / principal investigator. Every patient will be monitored for selection criteria and informed consent. Internal monitoring will also verify if appropriate SOPs were followed in case an SAE (suicidal ideation or intent) occurred. The investigator assures complete and unrestricted access to study data for the monitor. Monitoring details will be fixed in a monitoring manual.

Most of the data will be directly entered to the electronic study platform (mostly be the participant) or CRF and are thus considered source data.

11.1.2 Audits / Inspections

No internal audits are planned, but the Principal Investigator reserves the right to initiate a previously not planned audit.

11.2 Standardization and Validity

All rating scales have previously been standardized and validated.

12 Data Management

All personalized data is acquired in a pseudonymized manner. Every patient is attributed a unique ID in the course of inclusion. The investigator keeps a confident list containing full patient name and attributed ID. This list is accessible only to the local study team and monitors. Source data files are accessible to monitors, auditors and inspectors.

12.1 Data Acquisition and CRFs

Acquisition is performed using *paper Case Report Forms (CRF),* distributed by the sponsor. Additional data are acquired in the study platform.
The original is intended for the principal investigator/coordinating study center, a copy remains on the local site. Forms have to be completed with a pen, use of pencils is not permitted. Corrections have to

be done as follows: any mistake is crossed out by a single line, correct information is written next to it, dated and signed by the investigator and ideally a reason for correction is given. If missing information prohibits completion of a field, an explanation should be given.

12.2 Data Processing

For paper CRFs, the principal investigator/coordinating centre transposes data to a digital format. Data will be checked for range, validity and consistency. Implausible or missing data can be corrected in accordance with the investigator, documentation of correction is stored along with the CRFs. Validated data is stored in a database. At the end of the trial official database closure is documented. For evaluation of data we intend to use the current version of SPSS.

12.3 Creation of Pseudonym

Patients will be incrementally numbered based on date and time of inclusion. The number consists of a letter referring to the site of inclusion (B=Berlin, H=Hamburg, P=PennState, K=Kansas City, L=Los Angeles) and four patient-related digits (i.e. the first patient in Berlin will receive the code “B0001”).

12.4 Randomization

The trial will use a central, web-based randomization tool built into the study platform. Randomization will be conducted through this online system, ensuring concealed allocation. Patients will be randomized 1:1:1 to one of the three trial arms (no blocking, no stratification). To ensure concealed allocation, eligibility will be determined and all baseline assessments completed before randomization in compliance with CONSORT guidelines (extended CONSORT Statement to Randomized Trials of Non-pharmacological Treatment (27) and CONSORT Statement for eHealth (28)). Group assignment will be communicated automatically by a webmessage in the study platform. The clinicians and raters who will be conducting clinical assessments (structured interviews) will be blind to treatment assignment (single blind RCT).

Sample size estimation

A sample size of 100 patients per intervention group gives a conjunctive power (probability of rejecting both null hypotheses comparing Deprexis and DeprexisPlus to waitlist control) of 90% for a Dunnett test at the usual one-sided significance level of 2.5% assuming standardized mean differences of 0.5 for Deprexis vs. WLC and 0.8 for DeprexisPlus vs. WLC in the primary outcome change in BDI from baseline to week 12. Adjusting for 20% dropout we aim to recruit 125 patients per group resulting in a total sample size of 375 patients. The power was simulated with 10,000 replications using EAST 6.3.

12.5 Statistical Evaluation

Statistical analysis will be conducted in accordance with the following guidelines of the International Conference on Harmonization (ICH):

- ICH E3: Structure and Contents of Clinical Study Reports
- ICH E6: Good Clinical Practice (GCP). Consolidated Guideline
- ICH E9: Note for Guidance on Statistical Principles in Clinical Trials

12.5.1 Hypotheses

Primary hypothesis: All analyses will be conducted as intention-to-treat (ITT). To definitively test the effectiveness of Deprexis for reducing depressive symptoms in MS at the end of treatment, the primary outcome change in BDI from baseline to week 12 will be will be analyzed by means of linear mixed effect models for repeated measures adjusted for baseline measurements with fixed effects for intervention, center, time and baseline BDI score, and random subject effects for individual patients including all patients with at least one post-baseline measurement (29). Least squares means will be reported for the intervention groups with 95% confidence interval (CI) as well as the difference between the least squares group means with 95% CI. Deprexis vs. WLC and DepresixPlus vs. WLC will be tested by a Dunnett test controlling the familywise type I error rate at the level of 2.5%

(one-sided). *The primary hypothesis will be tested in a confirmatory manner.* In a secondary step, we will determine the added value of therapist email support Deprexis vs. DeprexisPlus at a two-sided level of 5%, if efficacy of Deprexis and DeprexisPlus for reducing depressive symptoms in MS could be demonstrated.

Secondary hypotheses: The analyses of secondary and tertiary endpoints (such as BDI-FS, QoL, cognitive function and fatigue scales) will follow the same approach as the analyses described for the primary endpoint. The proposed trial will create a large data set from n=400 MS patients and followed for 12 months that will enable us to gain valuable insight into the potential predictors, confounders, intermediates in the causal pathway, and interactions of Deprexis(Plus) treatment effects. In supporting exploratory analyses we will investigate potential moderators of treatment effects by including these and their interaction with treatment in the linear mixed effects models described above. Potential moderators include disease-modifying therapies (DMTs), level of disability at baseline (as measured by Disease Steps and patient-rated EDSS), cognitive status at baseline (as measured by BICAMS), and level of fatigue at baseline (as measured by the FSMC).

12.5.2 Evaluation of primary endpoint

Primary hypothesis is tested in a confirmatory manner:
All analyses will be conducted as intention-to-treat (ITT). The specific statistical analyses for each aim are as follows: **Aim 1:** To definitively test the effectiveness of Deprexis for reducing depressive symptoms in MS at the end of treatment, the primary outcome change in BDI from baseline to week 12 will be will be analyzed by means of linear mixed effect models for repeated measures adjusted for baseline measurements with fixed effects for intervention, center, time and baseline BDI score, and random subject effects for individual patients including all patients with at least one post-baseline measurement (29). Least squares means will be reported for the intervention groups with 95% confidence interval (CI) as well as the difference between the least squares group means with 95% CI. Deprexis vs. WLC and DepresixPlus vs. WLC will be tested by a Dunnett test controlling the familywise type I error rate at the level of 2.5% (one-sided). **Aim 2:** To determine the added value of therapist email support Deprexis vs. DeprexisPlus will be tested at a two-sided level of 5%, if efficacy of Deprexis and DeprexisPlus for reducing depressive symptoms in MS could be demonstrated. **Aim 3:** To explore the long-term stability of therapeutic effects (12 months) and the potential of a booster session to enhance maintenance, we will conduct similar linear mixed effect models for repeated measures in a two group comparison (Booster condition vs No Booster) during the extension phase (i.e. from week 12 (V2) to the end of the trial (month 12) accounting for the intervention (Deprexis or DeprexisPlus). Here, we will only include patients who had originally been randomized to either Deprexis or DeprexisPlus in primary trial phase.
Missing data: Although the mixed models described above are robust to a certain extent to missing data, sensitivity analyses will be performed as supporting analyses, if missing data are substantial and suspected to be due to dropout. Models that can account for informative dropout such as shared random effects models will be employed to explore the sensitivity of the analyses to certain dropout mechanisms (30). Standard procedures for reporting of adverse events will be used. Adverse events will be summarized as frequencies and percentages by intervention group. No interim analyses are foreseen. The ITT population as well as all other details will be defined in the Statistical Analysis Plan, which will be finalized before database lock.

12.5.3 Interim analyses by the DMC

No interim analyses are planned.

13 Reporting

13.1 Biometric Report

Statistic evaluation and writing of a report is performed by the biostatistician Prof. Dr. Tim Friede, Universitätsmedizin Göttingen, in close collaboration with the principal investigator. The content of this report is confidential.

13.2 Final Report

The final report of the trial follows the requirements of the guideline ICH E3: Structure and Contents of Clinical Study Reports. After completion of the biometric report, the prinicipal investigator writes the final report.

13.3 Publication

Results of the trial will be published regardless of the results. Any publication has to be agreed upon as determined in the Academic Collaboration Agreement in its fully executed form.

14 Ethical, juridical and administrational issues

14.1 Juridical prerequisites for trial initiation

The principal investigator and every participating investigator agree to comply to the GCP standards and national regulations.

Ethics Committee Vote

Study protocol, patient information and consenting form are presented to the Ethics Committee for evaluation at each study site. A positive vote is mandatory for trial initiation.

Patient information and Informed Consent

Patient information

Previous to trial inclusion, every patient will be informed about purpose, possible risks and benefits by the local investigator orally and in writing.

Informed Consent to Participation

Every patient consents in written form to participate in the trial. The patient has to be provided with enough time to think about the trial, ask possibly remaining questions and form a decision. Consent forms are signed and individually dated by patients and the investigator. If the patient is currently not able to write and sign, testified oral consent is acceptable. Information and consent form are made out in duplicate, one copy remains with the patient, the original with the investigator.

Insurance for Participants

All sites are responsible to ensure that they have sufficient liability insurance for conducting this study. No further participant insurance beyond the liability insurance of the participating sites has been obtained.

Privacy

Every participant will be informed about the storage, evaluation and publication of their medical data in a pseudonymized manner. Patients have the right to be informed about the saved data. Patients disagreeing cannot participate in this trial.

14.2 Storage and Access

Original study files, including CRFs, will be stored by the coordinating centre for at least 10 years after trial completion. The investigator stores every administrative documents, as well as signed consent forms, CRF copies and the general trial documentation for the same period of time.
Archiving of source data is left to the discretion of the local investigator, but has to last at least 10 years. Patient ID logs have to be archived for 15 years according to the 2001/83/EG guideline.

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