Trial Protocol

„**EFF**ects of **E**xposure and **C**ognitive-behavioural **T**herapy for chronic **BACK** pain („**EFFECT-BACK** “)”

a randomized controlled psychotherapy study ("two-arm intervention study")

Study acronym:	**EFFECT-BACK**
Date:	**20.01.2022**
NCT Number:	**05294081**

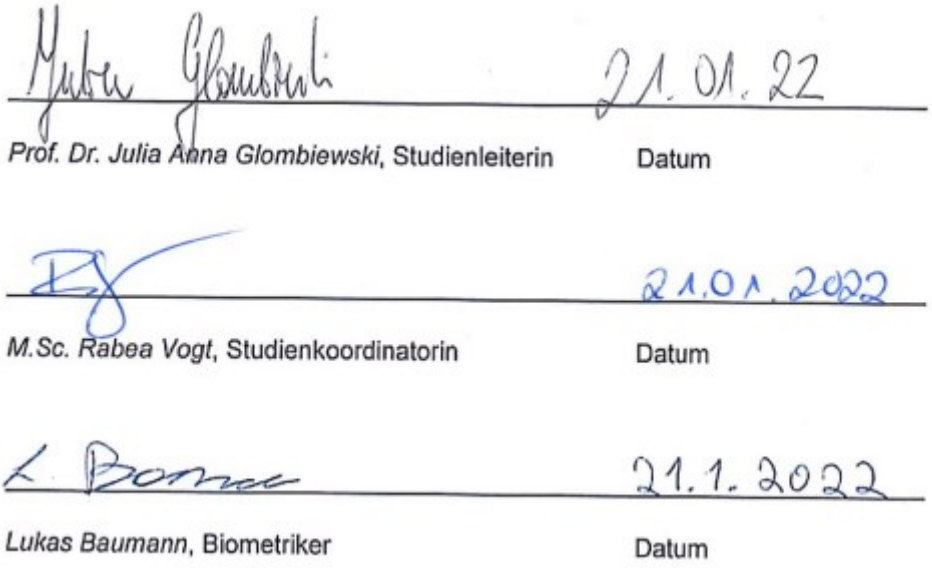
Content

1. BASIC INFORMATIONS

1.1. Involved persons, institutions and committees

Director of Studies Name: Prof. Dr. Julia Anna Glombiewski (PI) Address: University Koblenz - Landau, Fortstraße 7, 76829 Landau Phone: 06341 280 35 65 E-Mail: glombiewski@uni-landau.de	**Biometrician** Name: Lukas Baumann Address: Institute for Medical Biometry, Heidelberg University Hospital, Im Neuenheimer Feld 130.3, 69120 Heidelberg Phone.: 06221 566594 E-Mail: baumann@imbi.uni-heidelberg.de Name: Dr.sc.hum. Anja Sander Address: Institute for Medical Biometry, Heidelberg University Hospital, Im Neuenheimer Feld 130.3, 69120 Heidelberg Phone.: 06221 565859 E-Mail: sander@imbi.uni-heidelberg.de
Study coordination/project management Name: M.Sc. Rabea Vogt Address: University Koblenz - Landau, Fortstraße 7, 76829 Landau Phone: 06341 280 356 27 E-Mail: vogt@uni-landau.de	**Monitoring** Centre for Methods, Diagnostics and Evaluation, University Koblenz-Landau
	Datamanagement Name: Christina Klose Address: Institute for Medical Biometry, Heidelberg University Hospital, Im Neuenheimer Feld 130.3, 69120 Heidelberg Phone: 06221 56 5500 E-Mail: klose@imbi.uni-heidelberg.de

1.2 Signatures



Prof. Dr. Julia Anna Glombiewski, Studienleiterin — Datum

M.Sc. Rabea Vogt, Studienkoordinatorin — Datum

Lukas Baumann, Biometriker — Datum

1.3 Declaration of the local study managers

I have read this study protocol and confirm that it contains all the information regarding the Clinical Study. I affirm that I will conduct the study in accordance with the protocol and all legal requirements.

The first patient at our center will be enrolled only after all ethical and legal requirements have been met. I assure that I will obtain informed consent for study participation from all participating patients.

_____

Name and signature of local Clinical Project Manager Date

1.4 Summary

The overall aim of the present study is to compare two different psychological methods, Cognitive Behavioural Therapy (CBT) and Graduated Exposure in vivo (EXP) in the treatment of chronic low back pain with regard to effectiveness and improvement in perceived limitation.

Exploratory research will also be conducted to identify predictors of efficacy for each treatment group. This should optimize treatment options and create effective treatment offers for subgroups of pain patients.

Exposure therapy is an effective and economical form of treatment and was shown in a previous pilot study to be superior to CBT in reducing perceived limitations of movement. CBT, on the other hand, appeared to be more effective in establishing coping strategies. With the help of the current study, it should be possible to compare the effectiveness of both treatment methods and, in perspective, to identify those patient groups that benefit from exposure therapy and thus create a customized treatment program for subgroups of pain patients.

A total of 380 patients (age: ≥ 18) with chronic back pain and a sufficient degree of impairment will be included and analysed in the study. The preparation period for the study is planned to be 3 months (March to May 2022), followed by a 20-month recruitment period and the treatment phase with a subsequent 6-month follow-up phase (total period 36 months).

1.5 Synopsis

Study title	**EFF**ects of **E**xposure and **C**ognitive-behavioural **T**herapy for chronic **BACK** pain („**EFFECT-BACK**“)
Acronym	EFFECT-BACK
Director of study	Prof. Dr. Julia Anna Glombiewski
Indication/target population/disease	Patients with chronic back pain
Study design	Prospective, controlled, multicentre, open-label intervention study with two treatment arms (CBT versus EXP); parallel group design with randomized allocation; 10-week intervention phase with booster sessions and follow-up (6 months).
Aims of the clinical trial	Overall objective of the project: Improvement and expansion of the treatment offer in the treatment of patients with chronic back pain. Primary study objective: • To compare two different psychological methods (Cognitive Behavioural Therapy and Graduated Exposure in vivo) in the treatment of chronic back pain with regard to effectiveness and improvement in perceived limitation. Exploratory study objective: • To identify predictors of effectiveness for each treatment group. The variables of movement avoidance and coping will be considered.
Outcomes	Primary outcome measure: Clinically significant improvement in pain-related impairment (measured with the QPBDS) from baseline to 6-month follow-up. Secondary outcome measures: Pain intensity and experienced impairment (adapted scales of the DSF), coping (FESV), BAT-BACK (behavioural test for avoidance of movements), depressiveness (HADS), catastrophising (PCS), avoidance (PHODA), psych. flexibility (PIPS), fear of pain (PASS-20), absence from work, use of the health care system, socio-legal situation (module S, DSF).
Recruiting number	Screening: 494 randomized: 380 to be analyzed: 380
Inclusion criteria	Chronic back pain (duration > 6 months, pain most days of the week); sufficient level of limitation defined by QBPDS ≥15 (Quebec Back Pain Disability Scale, [1]); age ≥ 18; patient's written informed consent for study participation.
Exclusion criteria	Surgery on the back during the last 6 months or planned back surgery; Medical contraindications (red flags); Insufficient knowledge of German (reading and language); Pregnancy; Severe alcohol and/or drug addiction; Psychotic symptomatology; Parallel psychological treatment; Physical inability to participate in the sessions; Parallel participation in another intervention study.
Interventions/ treatment plan	10 sessions of psychotherapy: Cognitive Behavioural Therapy or Exposure Therapy. 2 booster sessions

Schedule (duration of study)	Study preparation period (months): 3 Recruitment period (months): 20 First enrolled patient to last completed patient (months): 28 Time for data cleaning and analysis (months): 5 Duration of the entire studyn(months): 36
participating (recruitment) centres	planned: n = 5 University outpatient clinic Landau University outpatient clinic Marburg University outpatient clinic Mainz University Hospital Essen University Hospital Heidelberg
Statistical methods	Statistical methods to compare the groups for the primary and secondary outcome criteria: The primary outcome criterion will be analysed using a logistic mixed regression model that includes treatment group and baseline QPBDS, HADS, BAT-BACK and PHODA fixed effects. In addition, centre-specific random intercepts are specified. Missing values are imputed. Similar regression models are used for the exploratory analysis of the secondary outcome criteria. Methods for additional analyses, such as subgroup analyses and matched analyses: For the exploratory subgroup analysis, a linear mixed regression model will test the interaction between treatment group and baseline BAT-BACK or FESV scores.
Financing	Funding for the therapies and funding for the research-linked parts of the project is provided by the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG).

1.6 List of acronyms

CLBP	Chronic Lower Back Pain
CBT	Cognitive behavioural therapy
EXP	Exposure Therapy
RCT	Randomized Controlled Study
DSMB	Data Safety Monitoring Board
GP	General Practitioner
IMBI	Institute for Medical Biometry
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
SOP	Standard Operating Procedure
RBM	Risk Based Monitoring
SAB	Scientific Advisory Board

2. BACKGROUND AND RESEARCH QUESTION

The study is a clinical multicentre study and will be conducted in the psychotherapy outpatient clinic of the University of Koblenz-Landau and 4 other recruitment centres in Mainz, Marburg, Essen and Heidelberg. Prof. Dr. Julia Anna Glombiewski will be the project leader.

2.1 Theoretical background

According to a recently published study by the Robert Koch Institute with over 62 000 participants, one in six men (17.1%) and one in four women (24.4%) in Germany reported having suffered from chronic low back pain (CLBP) in the last 12 months [2]. CLBP is a major cause of medical costs, absenteeism and disability [3]. Despite apparent advances in medical care, the prevalence of CLBP continues to rise [4].

According to current guidelines, most of the treatments commonly offered, such as injections or surgery, are ineffective; only pharmacotherapy shows small effects but carries a high risk of side effects [5].

Cognitive behavioural therapy (CBT), multidisciplinary approaches with psychological treatment components such as CBT and exercise, supported by psychological elements, improve pain and condition-related disability in the long term [6, 7]. Disappointingly, however, in most studies the effects of multidisciplinary or psychological treatment approaches are small to moderate, and in the case of multidisciplinary approaches, do not always justify the high costs of inpatient programmes [8, 9]. In outpatient care, specific psychological services in addition to pharmacotherapy and physiotherapy are rare.

EXP treatment for pain is a rarely used psychological treatment that specifically addresses the avoidance of physical activity in people with CLBP. In a previous pilot study [10] with 88 participants, we conducted for the first time a short (10 sessions) and a longer (15 sessions) outpatient EXP therapy programme and compared it with a standard 15-session CBT programme:

- EXP was more effective than CBT in reducing movement-related impairment.
- EXP-short outperformed EXP-long in efficiency after 10 sessions, meaning that individuals improved faster when offered fewer sessions.
- EXP could be safely delivered in the outpatient psychological setting, however CBT was more effective than EXP in improving coping strategies.

A specific behavioural measure, the "BAT-BACK" test, successfully identified participants who benefited from EXP in terms of reducing pain-related impairment [11]. Therefore, in the future, EXP therapy could be a customised treatment option to achieve better treatment outcomes in subgroups of CLBP patients. However, studies with more participants are needed to further

clarify whether EXP is successful and for which subgroup of patients. To the best of our knowledge, this is the first study aimed at finding out which patient group is more likely to benefit from EXP and which from CBT.

2.2 Evidence

The effectiveness of CBT-based therapies for chronic low back pain has been investigated in several randomised controlled trials (RCTs). The results indicate that the effect sizes are rather small and that there are no major differences between the different CBT-based therapies in terms of reduction of pain-related impairment [12]. All of these studies have low power due to small case numbers and do not provide the opportunity to conduct subgroup analyses.

There is limited evidence on the efficacy of EXP in CLBP [13]. About ten years ago, the first single case studies showed that EXP can reduce impairment and pain-related anxiety in this patient group and provided large effect sizes [14, 15].

Following the case studies, three RCTs published in the same year (all with N< 90), compared treatment groups with graduated EXP with a waiting list group and a group undergoing a graduated activity programme [16, 17], or with a group of patients in regular medical care [18]. These studies found some benefits of EXP, including greater reductions in pain-related anxiety and perceived harmfulness of physical activity.

The pilot study was the first to compare a CBT control group with an EXP group in a psychological setting, and the results were promising [10]. One reason for the good effects could be the involvement of international treatment experts (e.g. Jeroen de Jong, University Hospital Maastricht [18]) and researchers who conducted the previous RCTs and case studies and whose experience minimised problems in both treatment and study design.

2.3 Research question and justification of the project

We are currently facing the challenge of a widespread disease without being able to offer satisfactory treatment options. A comparison of an already established treatment method (CBT) with a still less known and used treatment method (EXP) should create starting points here. In addition, customized chronic pain treatment specifically to subgroups of pain patients could improve care [19, 20].

In addition, EXP therapy is a promising and cost-effective treatment option that could easily be incorporated into multidisciplinary programmes for inpatients or offered by outpatient psychotherapists as part of the newly established 12-hour brief psychotherapy. In order to validate the preliminary results of the pilot study and to answer open questions, a multicentre study with a larger number of participants is planned.

The study should also lead to a larger number of therapists trained in EXP therapy in different regions in Germany and to an increase in the visibility of our treatment manuals and could lead to a more frequent use of EXP for the benefit of the CLBP population. By publishing the results, we hope to raise awareness, especially among psychological psychotherapists, that brief, manualised, focused treatments may be sufficient to reduce the burden of chronic pain. The identification of predictors will help all practitioners involved in the treatment of chronic pain (e.g. GPs) to identify those patients who are more likely to benefit from EXP and those who are more likely to benefit from CBT.

3. STUDY GOALS AND HYPOTHESIS

The overall objective of the project is to improve and expand the range of treatments for patients with chronic back pain.

The scientific study objectives are:

- To compare two different psychological methods (Cognitive Behavioural Therapy and Graduated Exposure in vivo) in the treatment of chronic back pain with regard to effectiveness and improvement of perceived pain-related impairment.
- To identify predictors of effectiveness for each treatment group. We will look at the variables of movement avoidance and coping.

We expect exposure treatment (EXP) to be more successful than CBT in reducing pain-related impairment for chronic back pain. In terms of customised treatment, we expect that.

a) individuals with higher scores on the behavioural avoidance test "BAT-BACK" will be more likely to benefit from EXP than from CBT and that

b) individuals with lower scores on the Coping Test (FESV) are more likely to benefit from CBT than EXP.

3.1 Primary Outcome:

Pain-related impairment. Clinically significant improvement between baseline and 6-month follow-up survey: Quebec Back Pain Disability Scale (QBPDS, [1]):

Mandatory outcome measures in pain studies are defined in IMMPACT [22]. We define pain-related disability as the primary endpoint, which we measure using the QBPDS [1]. We focus on clinically significant improvement in impairment (using the Jacobson and Truax (JT) method) [23], as this is a more conservative and most meaningful method for patients to define a treatment outcome [24].

As in the pilot study, to define a reliable and clinically significant improvement in QBPDS [1], we will use the test-retest reliability of .92 and the pre-treatment mean from the Kopec et al. study [25] (M = 45.6, SD = 15.66).

Since there are no normative data for the QBPDS [1], we will use Jacobson and Truax's "Criterion A", a criterion that relates exclusively to clinical distribution and was already used in the pilot study. Criterion A assesses whether a person deviates by more than 2 SD from the mean of the "patient" group:

crit_A = mean (patients) - 2*stdev(patients).

Based on the pilot study, the cut-off value for criterion A for the QBPDS [1] will be 14. Thus, an improvement of 14 or more will be considered clinically significant.

3.2 Secondary Outcome:

Absolute changes at post and follow-up:

- Pain-related disability: Quebec Back Pain Disability Scale (QBPDS, [1]).
- Coping: Coping scale from the questionnaire for the assessment of pain processing (Fragebogen zur Erfassung der Schmerzverarbeitung, FESV, [26]) at post and follow-up survey
- Depressiveness: Depression scale from the Anxiety and Depression Scale (HADS, [27]) for post and follow-up assessment.
- Catastrophising: Pain Catastrophising (PCS, [28]) for post and follow-up survey
- Avoidance/fear of movement: Photo Series of Daily Activities (PHODA, [29]) for post and follow-up survey
- Fear of pain: Pain Anxiety Symptom Scale (PASS-20, [30]) for post and follow-up survey
- Behavioural test on avoidance behaviour: Behavioural Avoidance Test - Back Pain (BAT-BACK, [31]) for post and follow-up survey
- Psychological flexibility: Psychological Inflexibility in Pain Scale (PIPS, [32]) at post and follow-up.

Absolute changes and clinically significant improvement at post and follow-up:

- Pain-related disability: Pain Disability Index (PDI, [33]) at post and follow-up.
- Pain intensity and experienced impairment: adapted 11-item scales from the German Pain Questionnaire (Deutscher Schmerzfragebogen, DSF, [34]) for the post and follow-up survey.

As with the primary outcome criterion, the Jacobson and Truax (JZ) method [23] will be used. Similar to the pilot study, we will use the test-retest reliability of .91 from the study by Grönblad et al. [35] and the pre-treatment mean (M = 33.69, SD = 11.59) and normative population data (M = 6.8, SD = 11.4) from the study by Mewes et al. [36] to define a reliable and clinically significant improvement in PDI [33]. The reliable improvement criterion is set at 9.64 or more and the threshold for clinically significant change is set at 10.51 (clinical distribution criterion only, criterion "A"). The reliable improvement criterion based on both clinical distribution and normative data (criterion "C") is defined as an improvement of 20.13 or more. For the numerical pain intensity scale, an improvement of at least 1.5 points (or about 20%) is considered clinically significant [37].

Further:

- Assessment of safety/recording of adverse side effects: After every third hour of therapy, patients self-report side effects: Inventory for the Assessment of Negative Effects of Psychotherapy (INEP, [36]). In addition, the therapist fills out a checklist after every therapy session to record side effects and/or events that could influence the course of therapy.

3.3 Demography and anamnesis

- Demographic and anamnestic information: Demographic and medical history questionnaire with queries on use of the health care system and absences from work for the baseline survey, socio-legal situation (module "S" of the DSF [27]) for the baseline survey and follow-up.

4. STUDY DESIGN AND DESCRIPTION

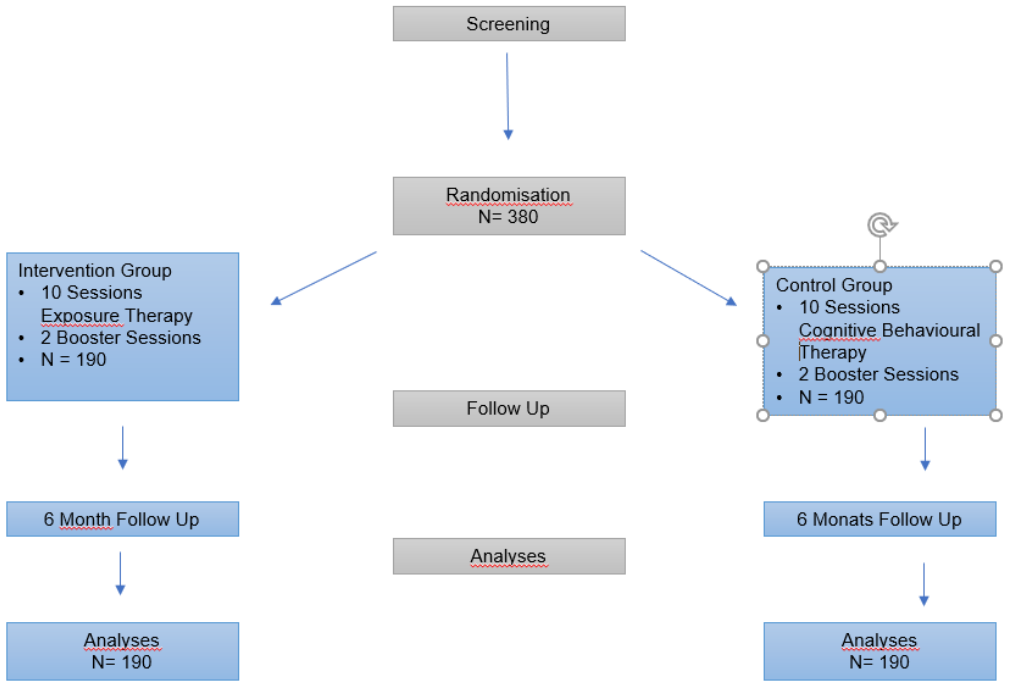


Figure 1: Study design

4.1 Study type

This is a prospective, multicentre, randomized, controlled, open-label, two-arm intervention study with a parallel group design.

4.2 Number and type of comparison groups

Two parallel groups are formed, the intervention group receives 10 sessions of EXP therapy, the control group receives 10 sessions of CBT.

4.3 Allocation

The allocation to the therapy methods is randomised. See chapter 6.1.2

4.4 Scope of the study, number of subjects and recruitment

This is a multicentre study, the study is being conducted at 5 centres throughout Germany. A total of 380 patients will be included, 190 patients per study arm.

Due to very liberal inclusion and exclusion criteria and based on the data from the pilot study, we expect that 77 % of the participants who are screened for eligibility during the preliminary examination (V2, see Figure 3 in Section 6 "Examination procedure / visit schedule") will

participate in the study. Based on the data from the pilot study [10] and data from pain research, we assume a 20% drop-out rate. The number of participants to be recruited for the whole study is adjusted for the drop-out rate of 20%. Otherwise, compliance in the pilot study was high with minimal missings in all survey instruments.

Recruitment is done through subsequent working groups:

Verantwortliche/r	Institution	Rekrutierungsziel (n)
Prof. Dr. Julia Anna Glombiewski (Dr. Jens Heider)	University Koblenz- Landau Outpatient clinic	60
Prof. Dr. Michael Witthöft	University Mainz Outpatient clinic	60
Prof. Dr. Winfried Rief (Dr. Jenny Riecke)	University Marburg Outpatient clinic	60
Prof. Dr. med. Ulrike Bingel	University Hospital Essen (Multidisciplinary Pain Centre)	100
PD Dr. med. Jens Keßler	University Hospital Heidelberg (Multidisciplinary Pain Centre)	100

Table 1: Recruitment centers

Recruitment is carried out by directly approaching patients at the respective study centre or through self-initiated enquiries by interested persons (e.g. in response to newspaper advertising, information flyers in the outpatient clinics or at GPs, etc.).

4.5 Study schedule

After approval of the study by the DFG, the first preliminary work has already begun before the actual preparation period for the study starts (3 months, planned from March 2022 to May 2022). This will be followed by a 20-month recruitment period and the treatment phase with a subsequent 6-month follow-up phase (total study period: 36 months).

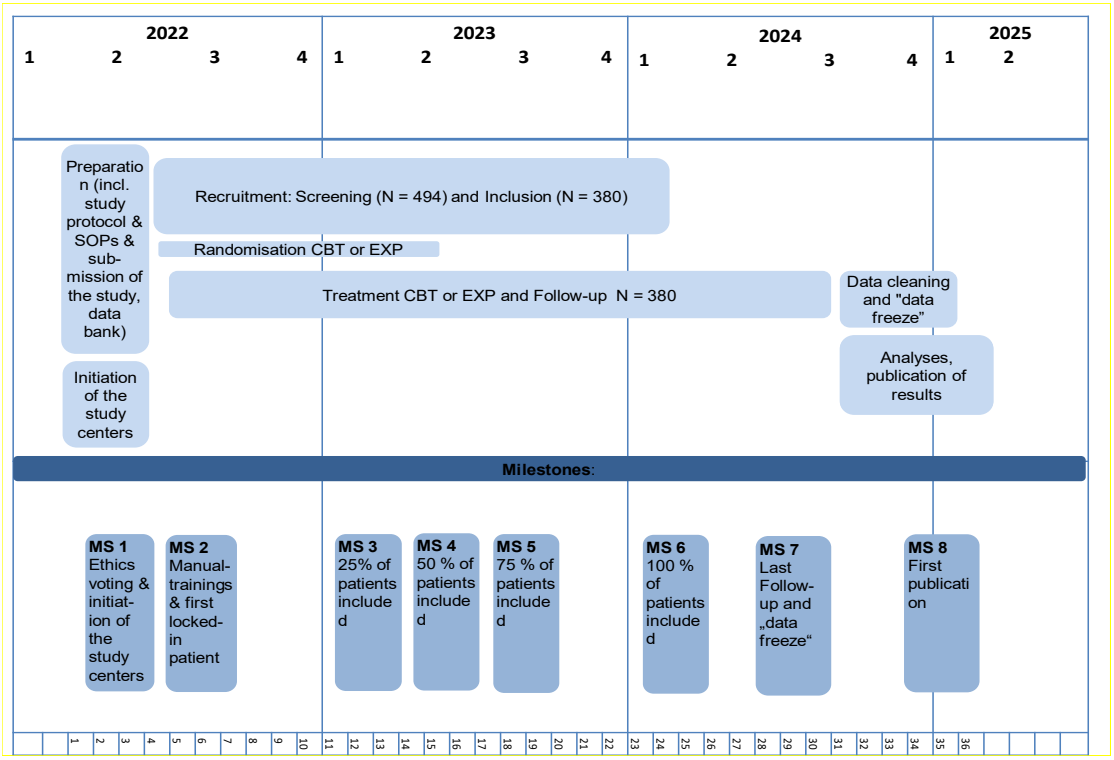


Figure 2: Course of study

After positive screening, the initial examination T0 begins, which is divided into two parts. In total, the patients come to 3 visits during the baseline survey, in which the clarification of the inclusion and exclusion criteria, detailed information about the study and the informed consent of the participants take place. In addition to the collection of demographic data and the biographical anamnesis, which includes information on age, gender, nationality, professional qualification as well as data on occupational and socio-legal situation, absenteeism and use of the health care system, a clinical interview (Mini-DIPS), a series of questionnaires and self-report scales as well as the BAT-BACK behavioural test are also carried out (see chapters 3.1 and 3.2).

Following randomised assignment to one of the treatment methods, the patients receive ten sessions of exposure therapy or cognitive-behavioural therapy of 50 minutes each in visits 5 to 14, which should usually take place weekly. Side effects are recorded after every third session. After the end of the treatment phase, the post survey T1 starts with the same surveys as at T0, with the exception of the demographic data, the Mini DIPS and the personality diagnostics (LPFS-BF and PID5BF+M). A booster session follows in visits 16 and 17. Six months after the end of treatment (visit 14), the follow-up survey T2 is carried out with the same surveys as at T1; in addition, the socio-legal situation is again queried with the module "S" of the DSF.

5. SELECTION OF PATIENTS

A total of 380 patients will be included and analysed in the study.

5.1 Inclusion criteria

The following criteria must be present to be included in the study (inclusion criteria):

- Chronic back pain (duration > 6 months, pain most days of the week).
- Sufficient level of limitation, defined via QBPDS ≥15 (Quebec Back Pain Disability Scale, [21]).
- Age ≥ 18 years
- Written informed consent of the patient to participate in the study.

5.2 Exclusion criteria

If at least one of the following points is present, participation in the study will not take place (exclusion criteria):

- Surgery on the back during the last 6 months or planned back surgery
- Medical contraindications (red flags)
- Insufficient knowledge of German (reading and speaking)
- Pregnancy
- Severe alcohol and/or drug addiction
- Psychotic symptoms
- Parallel psychological treatment
- Physical inability to attend sessions
- Parallel participation in another intervention study

6. COURSE OF STUDY

	STUDY SECTION							
	Enrolment	Randomisation and Baseline T0			Treatment	Post Treatment T1	Booster sessions	Follow Up T2
Visit	V1	V2	V3	V4	V5 - V14	V15	V16 / V17	V18
Screening	X	X						
Informed consent		X						
Inclusion and exclusion criteria		X						
Anamnesis and demographics				X				
Module „S“ DSF*		X						X
Randomisation				X				
INTERVENTION:								
CBT					X		X	
EXP					X		X	
ASSESSMENTS: *Accompanying treatments*				X	X	X	X	X
*Pain medication***				X	X	X	X	X
QBPDS		X				X		X
Mini DIPS				X				
LPFS-BF und PID5BF+M		X						
PDI			X		X	X	X	X
*DSF****			X		X	X	X	X
*FESV*****			X			X		X
HADS			X			X		X
PCS			X			X		X
PHODA			X			X		X
PASS-20			X			X		X
BAT-BACK			X			X		X
PIPS			X			X		X
WAI-SR					X (V7, V10, V13)		X	
*REV******					X (V7-V14)			
INEP					X (V7, V10, V13)		X	
Checklist on side effects					X (V7, V10, V13)		X	

Figure 3: Visit plan

* Module on the socio-legal situation, absenteeism
** including adjuvant pain medication (antidepressants)
*** Adapted scales on pain intensity and experienced impairment
**** Coping scale
***** only in EXP condition

6.1 Study Phases

6.1.1 Informed Consent

Each patient is informed about the study in writing and verbally by means of a detailed information session between a study staff member and the patient. In particular, the patients are informed about the following points:

- the scientific significance of the study and justification of the effort involved
- the duration of the study
- possible stresses and risks associated with specific study procedures
- the possibility of withdrawing from the study at any time and without the expectation of negative consequences.

The patient receives the written patient information and the information on data protection. After the information, each patient is given sufficient time and opportunity to clarify open questions and to decide on his or her participation.

Each patient signs and dates his or her consent to participate in the study in writing on the consent form. The patient's consent must also explicitly refer to the collection and processing of personal data. Therefore, patients are explicitly informed about the purpose and scope of the collection and the use of these data, especially health data.

One copy of the signed consent form (copy or 2nd original) is given to the patient, the other remains at the recruitment centre.

If interested and upon request, the study participants can be included in a mailing list and informed about the study results after publication.

6.1.2 Randomisation

Randomisation takes place after obtaining informed consent and the baseline survey. Patients are randomly assigned to the treatment conditions CBT or EXP in a 1:1 ratio via the centralised web-based tool Randomizer (www.randomizer.at). Randomisation will be stratified by centre. In order to achieve equally sized groups per stratum, randomisation will be block-wise. Block length will be determined by the study biometrician and kept confidential to prevent selection bias.

6.1.3 Treatment and Aftercare

The treatment phase lasts about 10 weeks. Depending on the therapy condition, the patients receive 10 sessions of CBT or EXP, which are followed by the post-survey.

Two therapeutic booster sessions take place one and three months after the end of therapy. The follow-up survey takes place 6 months after the end of the intervention, which corresponds to the usual follow-up period and allows to assess the longer-term impact of the intervention and the cost-effectiveness of the treatments.

Interventions

Cognitive behavioural therapy and **graduated exposure in vivo**: these two types of treatment are designed to help patients acquire better pain management strategies and thus improve well-being and quality of life. They differ in their methodology and focus (e.g. extent and type of (physical) exercises and homework), but are both intended to lead to the same goal and follow a manualised approach in the study.

- EXP for pain aims to reduce pain-related impairment by guiding patients to overcome the fear of movement and to put weight back on their bodies.

- CBT encourages patients to develop an adaptive coping style, guides attention-direction and problem-solving orientation.

The treatments are carried out by therapists with different levels of experience in treating pain patients, therefore the treatments are supervised every 2-3 sessions (teleconference-based group supervision with 4 participants and an experienced supervisor with separate supervision groups for each treatment arm).

Additional treatments

All (adjuvant) pain medication taken for at least 4 weeks before the first survey will be documented and allowed. If participants have just started a new medication, the first survey will be delayed by 4 weeks in the baseline measurements until it can be assumed that the medication is stable. Participants are asked not to change their medication until the follow-up. If a change is necessary, e.g. on the advice of the GP, this will be documented and taken into account in the analyses. Participants are asked to refrain from taking medication on demand/emergency medication (e.g. taking an additional dose of ibuprofen if the pain gets worse), as this could be a safety behaviour that contradicts the basic principle of exposure.

6.1.4 End of Study Participation

The regular end of study participation for each participant occurs with the completion of the follow-up survey (6-month catamnesis).

Premature withdrawal of a patient from the study (discontinuation criteria)

The patient may withdraw consent and discontinue treatment or participation in the study at any time and without giving reasons. Treatment discontinuation alone does not lead to study

exclusion. The data collected from the patient up to the point of withdrawal will continue to be used in the study unless the patient withdraws consent for this as well and requests that his/her data be deleted.

If a patient withdraws his or her consent and drops out of the study, participation is terminated. If possible, and if the patient is willing to provide information, an attempt should be made to find out the reason for the early termination of the study. The participant is asked to provide the reason for discontinuation, but is advised that he or she does not have to do so. It will be documented in the study documents and the eCRF that, when and, if applicable, why he or she withdrew consent.

Procedure after (early) withdrawal

Study participation is voluntary and withdrawal of consent is possible at any time without consequences. If necessary, the psychological-psychotherapeutic centres will arrange a connection to the psychotherapy outpatient clinics for (further) treatment. The medical centres provide counselling on further treatment options and information on psychotherapists in private practice.

7. RISK AND BENEFITS OF THE STUDY

7.1 Possible complications and/or risks

Psychological diagnosis and therapy for chronic pain and in general is not associated with risks, even though answering personal questions can lead to unpleasant feelings. Psychological therapy may occasionally be accompanied by stronger emotions.

There are no possible impairments or risks for the study participants. The patients will receive state-of-the-art outpatient psychotherapy and fill out introduced and standardised questionnaires. Both the control group (CBT) and the intervention group (EXP) will receive effective treatments.

There will be no special physical demands on the study participants during the study (no blood or saliva sampling, no medication or placebo administration, no invasive measurements). Within the framework of the exposure treatment, a short-term increase in pain or muscle soreness may occur due to physical stress exercises (e.g. if patients should become physically active again after a longer period of inactivity and therefore feel muscle soreness or similar). In addition, symptoms of fatigue can occur due to filling out the questionnaires.

Prof. Dr. Ulrike Bingel will be the medical supervisor of the study and will be involved in clarifying red flags of the exposure condition. In the pilot study, patient feedback was obtained

and evaluated, and side effects of both therapy conditions were recorded; based on these data, no increased risks for the participating patients are to be expected.

The study is conducted in compliance with the principles of the Declaration of Helsinki, the international principles of "good clinical practice" (ICH-GCP) and all applicable laws, e.g. the Data Protection Act. A Data Security and Monitoring Body (DSMB) will be established to ensure that imbalances between the two intervention groups are identified early.

Precautions are taken to avoid possible negative effects (see chapters 3.2 and 7.2).

In the course of therapy and diagnostics, personal and, if necessary, confidential experiences and attitudes of the study participants will be asked. All persons involved in the study are subject to confidentiality. All data will be collected and analysed pseudonymously. The study participants will be fully informed in detail from the beginning about the aims, duration and procedure of the study.

The study participants will receive feedback on the diagnoses, since this is a psychotherapy study and this is a prerequisite for a sustainable therapeutic relationship. We expect benefits for the patients and the health system, therefore the benefits of the study will outweigh the costs and potential risks.

7.2 Documentation of side effects

Possible side effects are recorded and documented by means of self-reporting by the patient after every third hour of therapy (INEP, see chapter 3.2). In addition, the therapist fills out a checklist after every third hour of therapy to record side effects and/or events that could influence the course of therapy:

- worsening of physical or psychological symptoms
- Inpatient admission to a somatic, psychiatric hospital
- Rehabilitation therapy
- Therapy interruption (> 4 weeks)
- Stressful events in the private and/or professional environment

The side effects or events are assessed by the therapist in consultation with the supervisor with regard to their severity (mild, moderate, severe) and, if necessary, countermeasures are taken in accordance with the study.

8. BIOMETRY

8.1 Research hypothesis

The primary objective of the study is to demonstrate the superiority of EXP over CBT with respect to the primary outcome criterion - clinically significant improvement in pain-related

impairment (as measured by the QPBDS) from baseline to 6-month follow-up. See Chapter 3.1 for the definition of clinically significant improvement.

The following null and alternative hypotheses will be tested:

H0: pk,CBT = pk,EXP vs. H1: pk,CBT ≠ pk,EXP

where pk,CBT and pk,EXP denote the probabilities of a clinically significant improvement in pain-related impairment in the CBT and EXP groups, respectively, conditional on the baseline QPBDS score and the baseline HADS score.

8.2 Primary Estimand

The Addendum to the ICH E9 Guideline proposes the Estimands concept as a clear and transparent definition of what should be estimated in a study (ICH, 2019). An Estimand is composed of the attributes Treatment, Population, Variable, Intercurrent Events and Summary Measure. The primary estimand, which corresponds to the primary study objective, is defined below:

Treatment: 10 sessions of manualised Cognitive Behavioural Therapy + two booster sessions vs. 10 sessions of manualised Exposure Therapy + 2 booster sessions.

Population: Defined by the inclusion and exclusion criteria.

Variable: clinically significant improvement in pain-related distress, as measured by the QBPDS, from baseline to 6-month follow-up. See chapter 3.1 for definition of clinically significant improvement.

Intercurrent Events:

- Treatment interruption or discontinuation - treatment policy strategy
- Change of treatment - treatment policy strategy
- Additional medication or treatment - treatment policy strategy
- Death - hypothetical strategy (death not related to treatment)

Summary Measure: Odds Ratio

For all secondary questions, the intercurrent events are the same as for the primary estimand. Only the attribute variable changes according to the respective endpoint.

8.3 Planning the scope of the study (caseload planning)

In our pilot study, a rate of 44% was observed in the CBT group for the primary outcome criterion [10]. The short and long EXP groups showed rates of 63.3% and 65.4% respectively. However, in the pilot study, 15% of the subjects were excluded because of low levels of pain-related anxiety. Therefore, 15% of the target population of this study could not benefit from

EXP. For this reason, we assume a conservative rate of 60% responders in the EXP condition. Using a two-sided chi-square test to detect this effect at a significance level of 0.05 and a power of 80%, 152 patients per group are required. It is expected that using a logistic mixed model that includes baseline QBPDS, HADS, BAT-BACK and PHODA scores as fixed effects and the centre as a random effect in addition to the treatment group will increase the power of the analysis. Based on comparable studies in this research area and the pilot study, we expect a drop-out rate of 20%, so that 190 patients per group (380 in total) will be randomised. The calculations were performed with PASS 14.0.8.

8.4 Definition of evaluation collectives

Full Analysis Set: The Full Analysis Set (FAS) includes all randomised patients. According to the intention-to-treat (ITT) principle, all patients are assigned to the group to which they were randomised. The FAS is the primary evaluation set for all efficacy outcome criteria.

Per Protocol Set: The Per Protocol (PP) Set includes all patients in the FAS who completed the study without serious protocol violations. Relevant protocol violations that lead to exclusion from the PP set are defined in the statistical analysis plan (SAP). Since evaluations in the PP Set cannot be interpreted causally, PP analyses play a subordinate role in the interpretation of the results and should only be seen as supplementary analyses.

Safety Set: The Safety Set includes all randomised patients who participated in at least one therapy session. The patients are assigned to the group from which they received the majority of therapy sessions.

8.5 Statistical methods

8.5.1 General Methodology

The methods of statistical analysis will be described in detail in a statistical analysis plan (SAP), which will be prepared promptly after the start of the study. All statistical analyses will be conducted using SAS v9.4 software or a later version.

Demographic and other baseline variables, as well as all other variables, will be summarised descriptively for each treatment group. Absolute and relative probabilities will be calculated for categorical variables. For continuous variables, mean, standard deviation, minimum, maximum, median and 1st and 3rd quartiles are calculated.

8.5.2 Analysis of the main objective criterion

The primary target criterion is analysed with a logistic mixed regression model. The primary outcome criterion is the dependent variable. Treatment group and baseline values of QPBDS, HADS, BAT-BACK and PHODA are considered as fixed effects. In addition, centre-specific random intercepts will be specified. The confirmatory test of the hypothesis described in

chapter 8.3.2 is carried out in the FAS by means of a z-test, which tests whether the regression coefficient for the treatment group is different from 0. This test is performed at a two-sided significance level of 5%.

Missing values for the QPBDS (from which the primary target criterion is also derived) and the HADS are imputed for each item. The predictive mean matching (PMM) method is used for this. The QPBDS (baseline and 6-month follow-up) and the HADS, BAT-BACK and PHODA (baseline) are also included in the multiple imputation model, as is the centre as a random effect.

As sensitivity analyses, a pattern mixture model is used instead of the PMM model for imputation, and best-case and worst-case scenarios for imputation of missing values are considered.

Supplementary analyses for the primary outcome criterion include analyses in which depression, assessed on the basis of a clinical structured interview (binary), is included as a covariate in the logistic mixed regression model - instead of the baseline HADS score. In addition, a model is calculated in which a change in medication (binary) is included as a covariate. It should be noted that the covariate adjustment of logistic regression models changes the parameter to be estimated ("non-collapsibility"). The probability parameters refer in each case to subgroups of patients who have the same expression of the variable to which conditionalization is applied [40]. Since the supplementary analyses conditionalize on other covariates, there is therefore a change in the true regression parameter for the treatment group.

8.5.3 Analysis of the secondary target criteria

Secondary outcomes will be analysed using appropriate mixed regression models, adjusting for baseline and HADS baseline. Centre-specific random intercepts are also specified in each model. Descriptive p-values and 95% confidence intervals are calculated for the effect of the treatment group.

8.5.4 Identification of predictive covariates

To identify subgroups of patients who particularly benefit from EXP, a linear mixed regression model is calculated in which the QBPDS score at 6-month follow-up is the dependent variable, and the treatment group, baseline QBPDS score, baseline HADS score, baseline PHODA score, baseline BAT-BACK score, baseline FESV score are the independent variables. In addition, interaction terms between the treatment group and the BAT-BACK as well as the FESV score are taken into account. Centre-specific random intercepts are also specified. To test whether the BAT-BACK or the FESV score are related to the treatment group, it is tested whether the respective interaction terms are different from 0. The mixed regression model is

also used to estimate individualised treatment effects and to estimate optimal individualised treatment rules.

9. DATA MANAGEMENT

9.1 Patient identification list and pseudonymisation

All patient-related data is recorded in pseudonymised form. The identity of the patient cannot be deduced from the pseudonym. For the patient identification number, a combination of a fixed recruitment centre number (1 = Essen, 2 = Heidelberg, 3 = Landau, 4 = Mainz, 5 = Marburg) and a consecutive centre-specific patient number is chosen.

Each trial centre maintains a coding list in which the patient identification numbers are assigned to the names of the participants. The coding list is only accessible to the local trial managers and the local study coordinator and is kept in a lockable cabinet and destroyed at the latest 2 years after the end of the study. As long as the coding list exists, participants can request the deletion or destruction of all data collected from them at any time.

In addition, the participation of the persons concerned in the study is noted in the respective patient file.

9.2 List of responsibilities

For each recruitment centre, a coding list for study staff and study officers is also filed in the study centre folder with, among other things, the name, function in the study, study-related activity and staff ID of the responsible persons. The staff ID is also composed of a combination of the defined recruitment centre number (1 = Essen, 2 = Heidelberg, 3 = Landau, 4 = Mainz, 5 = Marburg) and consecutive centre-specific number of the staff members.

9.3 Data collection

All information required by the protocol to be collected during the trial must be entered into the eCRF by the responsible personnel or designated representative. The responsible staff or designated representative should complete the eCRF sections as soon as possible after the information is collected, preferably on the same day that the participant appears for an examination, treatment or measurement procedure. Any outstanding entries must be completed immediately after the T2 follow-up appointment. An explanation should be given for any missing data. The completed eCRF must be reviewed and signed by the responsible staff member or designated representative.

9.4 Data management

The Institute of Medical Biometry (IMBI) is responsible for data management within the study. An efficient infrastructure for electronic data capture and data management will be established. The study data will be captured and managed using the REDCap (Research Electronic Data Capture [41]) system, a secure, web-based application hosted by the IMBI. Data transfer is encrypted using Secure Socket Layer (SSL) technology. The database server is protected by a firewall. The system provides an infrastructure for defining user roles and rights. Only authorised users can enter or edit data; access is restricted to the data of patients in the respective centre. All data changes are logged with a computerised time stamp in an audit trail. All data is pseudonymised. To ensure high data quality, rules for data validation are defined in a data validation plan. Completeness and plausibility of the data are checked during data entry (edit checks) and with the help of validation programmes that generate queries. A tracking system for the eCRF data is established to ensure that the data is managed in a timely manner. When no further data changes are to be made to the database, the eCRF data is locked. The data are finally downloaded and used for statistical analysis. All data management procedures are carried out according to IMBI's written standard operating procedures (SOPs), which ensure efficient and GCP-compliant (Good Clinical Practice) implementation. At the end of the study, the data are converted into different data formats (e.g. csv files) to archive them and ensure their reuse.

9.5 Study documents and their storage (archiving)

The originals of all essential study documents are retained by the study director for at least ten years after the final report has been prepared.

At each recruitment center, accrued administrative documents (e.g. ethics votes), the patient identification list, signed informed consent forms, and general study documentation (study protocol, amendments, study forms) will be retained for the above mentioned time, with the exception of the patient identification list, which will be destroyed after only 2 years. All records must be kept in a secure place and kept confidential. The patient identification list should be kept separately from the documentation records, in a lockable cabinet.

Original study patient records (e.g., medical records) or essential study documents are to be retained in accordance with the retention period applicable to recruitment centers, but no less than ten years. The recruitment center or the responsible investigator(s) must take precautions to prevent the accidental or premature destruction of these documents.

9.6 Video recording

Video recordings are planned to ensure and check the fidelity of the study and for supervision purposes. These data will be stored in encrypted form. The video recordings will be deleted after completion of the evaluation, but at the latest one year after completion of the last study treatment.

9.7 Data safety

Extensive measures are taken to protect the data, especially personal data, against access by third parties.

Within the framework of the study, personal data of the test persons (e.g. name, address, telephone number), data to answer the research question (pain burden, depressiveness, etc.) as well as video recordings for adherence control and supervision are processed.

The local therapy files and study data are stored in lockable cabinets and are only accessible to the respective treating therapists and study staff, who are subject to the legal duty of confidentiality.

In the event of withdrawal of consent to the study by the patient, no further data will be collected from the time of withdrawal. The data collected so far will continue to be used and evaluated within the study. If a patient only discontinues the study treatment, the data required for the study can continue to be collected and used.

All therapists, supervisors and study assistants are also subject to medical confidentiality. No information collected in the course of therapy will be passed on to third parties.

10. QUALITY ASSURANCE

10.1 Standard Operating Procedures

To ensure adherence to the study protocol and standardised conduct of the study in all participating centres, detailed standard operating procedures (SOP) are defined by the study management and communicated to all centres.

10.2 Control of the study process and data quality

Risk-based monitoring (RBM), which includes clinical site visits if required, is conducted by the "Centre for Methods, Diagnostics and Evaluation" at the University of Koblenz-Landau in collaboration with central (statistical) monitoring by the IMBI at the University of Heidelberg.

Monitoring will follow a study-specific monitoring manual and a risk-based approach to ensure protocol compliance, patient safety and data integrity.

The monitor will conduct and document visits prior to the start of the study. During this first site visit, the monitor will review the processes around informed consent, documentation, data analysis and administration. All subsequent visits will depend on the feedback the monitor receives regularly from the central (statistical) monitoring regarding all target criteria, including adverse events, and on feedback from the centres themselves and from the study directors, who will store all study processes on an encrypted server. Compliance with the protocol is systematically monitored through clinical supervision and evaluation of the treatment videos. Inconsistencies are reported to the monitor by the supervisor.

If one centre's data differs greatly from that of other centres or shows other inconsistencies, further site visits are planned. This also happens if unexpected or critical side effects occur, compliance with the protocol is not ensured, or dropout rates are above expectations (both compared to the pilot study), or if recruitment problems occur. The monitor is given access to all study-relevant documents by the principal investigator and other investigators. The investigators agree to cooperate fully with the monitor or other third parties.

Prof. Dr. Ulrike Bingel is the principal investigator of the study and is responsible for ensuring the safety of the EXP condition.

To check and ensure adherence to the manual, the therapy sessions will be videotaped and assessed for adherence. The assessment of treatment adherence is based on Leeuw and colleagues' method for assessing treatment delivery in clinical trials [42]. Accordingly, manual adherence is defined as the presence of at least 70 % of the essential treatment elements. Treatment contamination is defined as the presence of at least 10% of the prohibited treatment elements.

Treatment differentiation (i.e. the presence of sufficient differences between the two treatments) is considered achieved when more than 90% of the sessions have been correctly classified (as EXP or CBT). According to Leeuw and colleagues, each treatment element is assigned one of the following categories for each treatment condition:

(1) essential and specific

(2) essential but not specific

(3) compatible but not essential and not unique

(4) prohibited

Elements in category (1) are only allowed in one treatment but not in the other, otherwise the treatment may be considered "contaminated".

Manual compliance is checked at the lead study centre by the study coordinators.

10.3 Information on the monitoring programme

Independent Data Safety and Monitoring Board (DSMB): The independent DSMB will monitor the progress of the study according to the predefined milestones and make recommendations to the study management for stopping, modifying or continuing the study. The principles for the DSMB are ethical aspects and safety aspects for the patients. The task of the DSMB is to check whether the conduct of the study is still ethically justifiable, whether the safety of the patients is guaranteed and whether the conduct of the study is acceptable. To this end, the DSMB is regularly informed about compliance with the protocol, patient recruitment and observed negative side effects. It consists of a psychologist with practical and scientific experience in the field of chronic pain (Dr. Paul Nilges), a medical pain specialist (Prof. Dr. Frank Petzke) and a statistician (Prof. Dr. Oliver Christ). The DSMB will be regularly informed about all safety aspects of the study and will review the safety data. A meeting or teleconference of the board is scheduled every 6 months during the treatment phase.

Scientific Advisory Board (SAB): The Scientific Advisory Board will provide independent advice on scientific, ethical and data protection issues and the dissemination process as appropriate. It includes two world-renowned experts on chronic pain and its treatment, Prof. Dr. Steven Linton and Prof. Dr. Johan Vlaeyen.

Clinical expert advisor: Dr. Jeroen de Jong, Maastricht University Hospital, will support the exposure treatment arm of the study, e.g. by holding a workshop with Prof. Dr. Julia Glombiewski before the start of the recruitment phase, as this is less known and requires more expertise in training.

11. ETHICS AND REGULATIONS

11.1 Declaration of Helsinki and Good Clinical Practice

The study will be conducted in accordance with the ethical principles and recommendations originating in the Declaration of Helsinki and in accordance with the international guidelines on "Good Clinical Practice" (ICH-GCP), as applicable. The current version of the Declaration is observed in the conduct of the intervention, evaluation and documentation.

Legal and regulatory requirements are observed, whereby the Medicines Act and the Medical Devices Act do not apply. Due to the pilot study, in which we have thoroughly investigated the side effects, no increased risks for the participating patients are to be expected.

A Data Safety and Monitoring Board (DSMB) will be established to ensure that imbalances between the two intervention groups are detected early. We expect benefits to patients and the health system, therefore the benefits of the trial will outweigh the costs and potential risks.

The Clinical Project Manager of each recruitment centre is responsible and ensures that all people involved in the study on site are informed about the current study protocol.

11.2 Ethics committees

The study protocol is submitted with the required further documents to the responsible lead ethics committee of the study director with a request for evaluation. The study can only begin after the Ethics Committee has given its approval.

The Ethics Committees of the participating recruitment centres will receive a copy of the positive assessment of the first Ethics Committee and the documents required for granting the "second vote" in each case. Each participating trial site will receive copies of the positive evaluation of the first Ethics Committee and of its responsible Ethics Committee for the trial site folder.

11.3 Revisions of the study protocol

The study protocol must be followed. Deviations from the planned examination and treatment measures or times must be documented and justified.

Changes or additions to the study protocol can only be initiated and authorised by the study management. The lead ethics committee and the ethics committees of the participating trial centres are informed about changes to the study protocol. If necessary, their approval will be sought again. Changes requiring evaluation may not be implemented before the decision of the ethics committee.

11.4 Patient insurance

Accident-route insurance is taken out for all study participants at all centres.

11.5 Registration

The study will be registered in the following public register: **U.S. NIH ClinicalTrials.gov**

The study coordinator is responsible for the registration in the registry and the maintenance of the registry data.

11.6 Funding

Funding of the project is provided by the German Research Foundation (DFG).

11.7 Final report and publication

We will communicate the results to the IASP (International Association for the study of pain) and its German and European sections as well as to psychological societies such as the German Psychological Society. The results will be presented at national and international conferences to medical and psychological experts to improve awareness of effective pain treatments. We expect interest in the results from the German pension insurance and health insurance companies. The treatment manuals, if proven effective, will be offered to the public (Open Assess). The results of the study will be reported according to the CONSORT statement. Data sharing takes place after publication of the results (OSF repository).

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