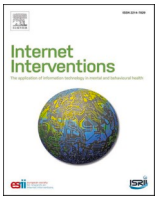
Internet Interventions 30 (2022) 100584

Contents lists available at ScienceDirect

Internet Interventions

journal homepage: www.elsevier.com/locate/invent



Evaluation of an online-based self-help intervention for patients with panic disorder – Study protocol for a randomized controlled trial

ARTICLE INFO

Keywords
Panic disorder
Agoraphobia with panic disorder
Online self-help
RCT

ABSTRACT

Background: Panic disorder is a debilitating mental disorder that can lead to functional impairments, low quality of life, and increased risk of developing comorbid mental disorders. There is now evidence for the efficacy of both guided and unguided online interventions for panic disorders. To establish the usefulness of such interventions with high ecological validity, we want to evaluate the efficacy of an online self-help program for panic disorder with and without comorbid agoraphobia.

Methods/design: Patients ($N = 156$) diagnosed with panic disorder with or without comorbid agoraphobia between 18 and 65 years with internet access, and sufficient German language skills will be recruited for this study. The intervention group (IG; $N = 78$) will receive access to the 12-week self-help online program *Selfapy*. The waitlist control group (CG; $N = 78$) will receive no intervention in the context of the study. Both groups will be allowed to access further health care services (e.g., inpatient treatment), reflecting current routine care in Germany. Outcome measures will be assessed at baseline (T1), 6 weeks (T2), and 12 weeks (T3) after the start of the intervention. The primary outcomes will be panic symptoms and quality of life at T3. Secondary outcomes include depression, work capacity, therapy-related expenses and burdens, health literacy, and side effects. We expect substantial improvements in the intervention group. We aim to evaluate the therapeutic effects and the cost-efficacy of Selfapy and its benefits for the German healthcare system.

Discussion: Online interventions may proof to be a cost-effective supplement to the healthcare system that can substantially reduce waiting periods for treatment.

Trial registration
drks.de Identifier: DRKS00023800 (registered on 06th July 2021) https://www.drks.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00023800

1. Background

Panic disorders are common and distressing anxiety disorders that substantially impact individuals and society (Murray et al., 2012; Whiteford et al., 2013). They are characterized by panic attacks accompanied by physical symptoms such as breathing problems or palpitations and psychological symptoms such as problematic cognitions and the constant fear of further panic attacks (Taylor, 2006). Panic disorders are associated with functional impairments, low quality of life, and increased risk of developing other mental disorders (Candilis et al., 1999; Lecrubier, 1998). Between 35 and 65 % of individuals with panic disorder meet the diagnostic criteria for agoraphobia (Wittchen et al., 2010). Agoraphobia is characterized by avoidance of situations and places where escaping might be difficult or embarrassing, and help might not be available in case of a panic attack. The 12-month prevalence of panic disorder with or without agoraphobia is 2 % (Jacobi et al., 2014).

Pharmacotherapy and cognitive behavioral therapy (CBT) are effective treatments for panic disorder, and the National Institute for Clinical Excellence (National Institute for Clinical Excellence, 2011) recommends CBT as the primary intervention for panic disorder with or without comorbid agoraphobia. Following the technological trend, technology-based treatment alternatives have been increasingly developed over the past years, targeting problems in existing treatments such as limited access and low acceptance. Most of these alternatives are based on CBT, as it is ideally suited for online intervention delivery due to its highly structured, directive, and standardized nature as well as its focus on psychoeducation and homework (Berger et al., 2011). Internet-based cognitive-behavioral therapy (iCBT) offers easier access for those who reject traditional forms of therapy due to stigma or other reasons (Thomas et al., 2015). A systematic review and meta-analysis including 27 studies on iCBT for panic disorder was conducted by Stech et al. (2019). Compared to inactive control groups, iCBT programs were shown to be significantly more effective and had high effect sizes for reducing symptoms of both panic disorder ($g = 1.16$) and agoraphobia ($g = 0.91$). Equal outcomes were found when compared to traditional face-to-face CBT. In over 12 studies on panic disorder and seven on agoraphobia, the effects found were stable until follow-up. Furthermore,

https://doi.org/10.1016/j.invent.2022.100584
Received 26 July 2022; Received in revised form 4 November 2022; Accepted 8 November 2022
Available online 9 November 2022
2214-7829/© 2022 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

iCBT demonstrates an additional, symptom-reducing effect when applied concurrently to classical CBT (Berger et al., 2017; Schröder et al., 2017).

While most of the literature addresses guided forms of iCBT with therapeutic support, unguided, self-directed iCBT programs also show large effect sizes for treating panic disorder (e.g., d = 0.70–1.06; Ciuca et al., 2018). Studies found no significant differences in panic disorder symptom reduction, completion rates, and satisfaction between guided and unguided iCBT (Ciuca et al., 2018; Fogliati et al., 2016). Additionally, neither frequency of a supportive attendant (Klein et al., 2009; Oromendia et al., 2016) nor the experience or training of the support person (Johnston et al., 2011) seem to have a significant influence on panic disorder symptom reduction. However, iCBT and especially unguided iCBT typically have high dropout rates and low adherence (Karyotaki et al., 2015), so it is essential to promote adherence and minimize dropout rates (e.g., via motivational content). Of particular note is the benefit of iCBT to the health care system, as it is a cost-effective treatment alternative (Andrews et al., 2018; Bergström et al., 2010). Also, iCBT can help to bridge the waiting periods for face-to-face psychotherapy, which on average lasted for five months in Germany (BPtK, 2018) and has increased since the beginning of the corona pandemic (BPtK, 2021).

In summary, more research is needed to assess the effectiveness of iCBT in clinical practice, because RCT studies tend to suffer from a lack of ecological validity (Seligman, 1995). In our case, a RCT efficacy study would 1) have unrealistic exclusion criteria regarding comorbidities, 2) have an active control group which does not reflect the waiting period in Germany, 3) not allow additional help for any study group. Therefore, we will choose only essential exclusion criteria, including as many patients as possible. Also, we decided to use a waitlist control group and to allow both study groups to seek additional help.

To address this, this study aims to evaluate the effectiveness of the online self-help program *Selfapy* for patients with panic disorders with high ecological validity. Since *Selfapy* is not offered in a primary care setting and most patients are recruited via online ads, we want to increase ecological validity by doing the same. Further, we will choose only essential exclusion criteria, including as many patients as possible, and we decide to use a waitlist control group to address the average waiting period of >5 months in Germany (BPtK, 2021). As online interventions have shown promising success, we want to assess if an implementation in the German healthcare system is effective in terms of symptom improvement, in reducing the burden on the healthcare system, and in cost reduction. For this purpose, we will conduct a randomized controlled trial comparing the self-help intervention with a waitlist control group.

1.1. Hypotheses

The main objective of this trial is to determine the efficacy of the 12-week Selfapy course for patients with panic disorder with or without comorbid agoraphobia compared to a waiting control group. Additional outcome data will be collected six weeks after the baseline assessment. However, our confirmatory hypotheses will evaluate a positive healthcare effect and will therefore focus on the 12-week outcomes. The following two hypotheses refer to our primary outcomes:

1. Panic and agoraphobia symptomatology (PAS; Bandelow, 1997) decreases significantly stronger with the use of the Selfapy program for panic disorder after 12 weeks than in a waitlist control group.
2. Perceived quality of life (WHO-5; Topp et al., 2015) increases significantly stronger after 12 weeks of using the Selfapy course for panic disorder than in a waitlist control group.

The following secondary outcomes will only be analyzed in case of confirmation for at least one primary outcome. Also, they will be tested using Bonferroni-Holm adjustment:

1. Self-reported difficulties in daily life (WSAS; Mundt et al., 2002) decrease significantly stronger by using the Selfapy course for panic disorder with or without agoraphobia after 12 weeks than in a waitlist control group.
2. Using the Selfapy course for panic disorder and agoraphobia, there is a significantly better recovery of working ability (iPCQ; Bouwmans et al., 2013) after 12 weeks than in a waitlist control group.
3. Self-assessed health literacy (MHLS; O'Connor and Casey, 2015) improves significantly stronger with the use of the Selfapy course for panic disorder and agoraphobia after 12 weeks than in a waitlist control group.
4. The extent of therapy-related efforts and burdens of patients and their relatives (CSSRI; Chisholm et al., 2000) is reduced significantly after using the Selfapy course for panic disorder and agoraphobia than in a waitlist control group after 12 weeks.

Our exploratory hypotheses do not address the target symptoms and are therefore not adjusted for alpha-accumulation:

1. Self-rated anxiety symptoms (BAI; Beck et al., 1988a) decrease significantly stronger with the use of the Selfapy course for panic disorder and agoraphobia after 12 weeks than in a waitlist control group.
2. Self-rated depressive symptoms (PHQ-9; Kroenke et al., 2001) decrease significantly stronger with the use of the Selfapy course for panic disorder and agoraphobia after 12 weeks than in a waitlist control group.
3. The use of the Selfapy course for panic disorder and agoraphobia does not lead to any side effects compared to a waitlist control group after 12 weeks (NEQ; Rozental et al., 2016).

2. Methods

2.1. Participants

Participants are recruited through newsletters, social media advertising, and information brochures. Interested individuals can register for participation online and will be contacted by the study center to schedule a diagnostic appointment after passing a screening questionnaire. All patients receive a compensation of 30€ after completing the study questionnaires.

Video calls will be conducted with all subjects, during which eligibility will be evaluated based on a diagnostic interview (DIPS-OA; Margraf et al., 2017). Trained interviewers with at least a master's degree (or equivalent) in psychology focusing on clinical psychology will conduct all interviews. The interviewers are trained at the Justus Liebig University in Giessen. Furthermore, there is close supervision on questions of diagnostics as well as inclusion and exclusion criteria with a licensed psychotherapist (CBT).

Eligible subjects are those who 1) are between 18 and 65 years of age, 2) have sufficient knowledge of the German language, 3) have uninterrupted internet access, 4) provide electronic informed consent to participate in the study, and 5) currently meet the DSM-5 diagnostic criteria of panic disorder (ICD 10: F41.0) or agoraphobia with panic disorder (ICD 10: F40.01).

Subjects will be excluded if they do not fulfill any of the inclusion criteria or meet any of the following exclusion criteria: 1) past or current diagnosis of bipolar disorder, 2) past or current diagnosis of psychotic disorder, 3) current diagnosis of substance dependence, 4) current diagnosis of a severe major depressive episode, 5) acute suicidality. A primary diagnosis of a disorder other than a panic disorder with or without comorbid agoraphobia is not an exclusion criterion, as we want to achieve higher ecological validity. However, substance dependence, bipolar disorder, or psychotic disorders are exclusion criteria because they conflict with the implementation of the program and they need to be excluded due to regulatory standards. Subjects who do not meet our

inclusion criteria due to severity of illness are encouraged to seek other forms of professional help. Adequate language skills will be determined during the diagnostic interview.

Participants are asked about suicidality with an item of PHQ-9 at all measurement time points (T1, T2, and T3). For safety reasons, subjects will be contacted if they report suicidality, and an emergency plan is drawn up with them. Nevertheless, the subject's data will not be transmitted to the police or other authorities. If subjects endorse suicidality, they will be excluded from further data collection, and only the assessments up to the occurrence of suicidality will be used for data analysis.

The study center at the University of Giessen is responsible for storing and analyzing patient data. Besides the initial interview, all data are collected via the online platform Sosci survey (https://www.soscisurvey.de) that uses SSL-encoding to protect the data. Written informed consent is obtained from all participants before participation, and the clinical protocol is approved by the ethics committee of the faculty of behavioral and empirical cultural science at the study center at Heidelberg University (Ethics Committee-No. AZ Prüß 2021 1/1). The trial is registered at the German Clinical Trials Register (DRKS register No. DRKS00023800) and follows the ethical principles of the Declaration of Helsinki.

2.2. Study design

A two-armed randomized controlled trial is conducted to test the efficacy of the minimally guided[1] online program *Selfapy* for panic disorder. Fig. 1 shows the schematic course of the study for patients in the intervention group (IG) and control group (CG). After a structured diagnostic interview (DIPS-OA, Margraf et al., 2017), in which the inclusion and exclusion criteria are clarified, eligible patients are asked to complete the baseline questionnaire. Subsequently, they are randomly assigned to the IG or CG. Patients in the IG can use Selfapy immediately after randomization, while the CG can only access Selfapy after a waiting period of 12 weeks. Interim and final evaluations will occur 6 (T2) and 12 (T3) weeks after the baseline survey.

Participants are advised to spend at least 15 to 20 min per day on the program. If a module is not finished for four weeks, this will be counted as a dropout for an additional sensitivity analysis, but will still be included in the ITT analysis. Patients in the control group will not receive any treatment or support from the researchers during the first 12 weeks after the initial survey. However, they are free to seek any other healthcare services they desire, including pharmacological and psychological treatments. All concurrent therapies will repeatedly be measured using self-reports.

2.3. Measures

Table 1 provides an overview of the measures used, described in more detail below.

2.4. Diagnostic Interview for Mental Disorders (DIPS-OA)

The Diagnostic Interview in Mental Disorders (DIPS; Margraf et al., 2017) is used to classify mental disorders and record inclusion and exclusion criteria. The person conducting the interview is part of the evaluation team (Professorship of Psychotherapy Research, Giessen University) and independent of Selfapy.

[1] The online course is completed independently by the participant. However, as part of the patient safety concept, a psychologist monitors the participant's progress to support the patient and respond to adverse events such as suicidality. The participants can ask a psychologist questions about the correct application via an integrated messaging function. The psychologists are asked to refrain from active communication with the exception of adverse events.

2.5. Primary outcomes

2.5.1. Panic symptomatology (PAS)

The Panic and Agoraphobia Scale (PAS; Bandelow, 1997) is used to assess the severity of symptoms in patients with panic disorder with or without agoraphobia. The PAS consists of 13 items assigned to five superordinate scales rated on a 5-point Likert scale. The internal consistency of the self-report version of the PAS is $\alpha = 0.86$.

2.5.2. Quality of life (WHO-5)

The questionnaire used to assess well-being is the World Health Organization-Five Well-Being Test (WHO-5; Topp et al., 2015). The WHO-5 consists of 5 items rated on a 6-point Likert scale and has an internal consistency of $\alpha = 0.92$.

2.6. Secondary outcomes

2.6.1. Coping with functional impairments (WSAS)

The Work and Social Adjustment Scale (WSAS; Lutz et al., 2019; Mundt et al., 2002) consists of 5 items, for which the true score is to be given a number between 0 and 8. The WSAS is used to assess the degree of functional impairment in various domains. The WSAS is used in comparable studies, such as Gräfe et al. (2020). The internal consistency of the WSAS ranges from $\alpha = 0.70$ to $\alpha = 0.94$ (Mundt et al., 2002).

2.6.2. Work capability (iPCQ)

Work capacity and productivity are assessed via he iMTA Productivity Cost Questionnaire (*i*PCQ; Bouwmans et al., 2013). The iPCQ asks about long-term (>2 weeks) and short-term (<2 weeks) absences from work. In addition, the iPCQ includes three questions on productivity losses as a result of illness-related work efficiency limitations. The iPCQ was validated by Friedli et al. (2018).

2.6.3. Health literacy (MHLS)

The Mental Health Literacy Scale (MHLS; O'Connor and Casey, 2015) assesses health literacy and consists of 20 items. The first 15 items are rated on a 4-point Likert scale, and the remaining items are rated on a 5-point Likert scale. The internal consistency of the overall scale is $\alpha = 0.87$. The MHLS has previously only been validated in English and was translated to German for this study with the involvement of a native-bilingual collaborator in a translation-back-translation process.

2.6.4. Therapy-related expenses and burdens for patients and their relatives (CSSRI)

Therapy-related effort is captured using the Client Sociodemographic and Services Receipt Interview (CSSRI; Chisholm et al., 2000). The CSSRI asks participants to report the actual service utilization (e.g., contact with health care providers, number of therapy sessions, amount of contact with psychotherapists and psychiatrists).

2.7. Additional outcomes/assessments

2.7.1. Anxiety symptomatology (BAI)

The Beck Anxiety Inventory (BAI; Beck et al., 1988b) is used to assess the severity of anxiety in adults and adolescents. It consists of 21 descriptive statements to be rated on a 4-point scale. The internal consistency of the BAI is $\alpha = 0.90$ in clinical samples. The German version used in our study was validated by Margraf and Ehlers (2007).

2.7.2. Depression symptomatology (PHQ-9)

The Patient Health Questionnaire-9 (PHQ-9; Kroenke et al., 2001) is used to assess the presence and severity of depressive symptoms. The PHQ-9 consists of 9 items rated on a 4-point Likert scale and has an internal consistency of $\alpha = 0.89$.

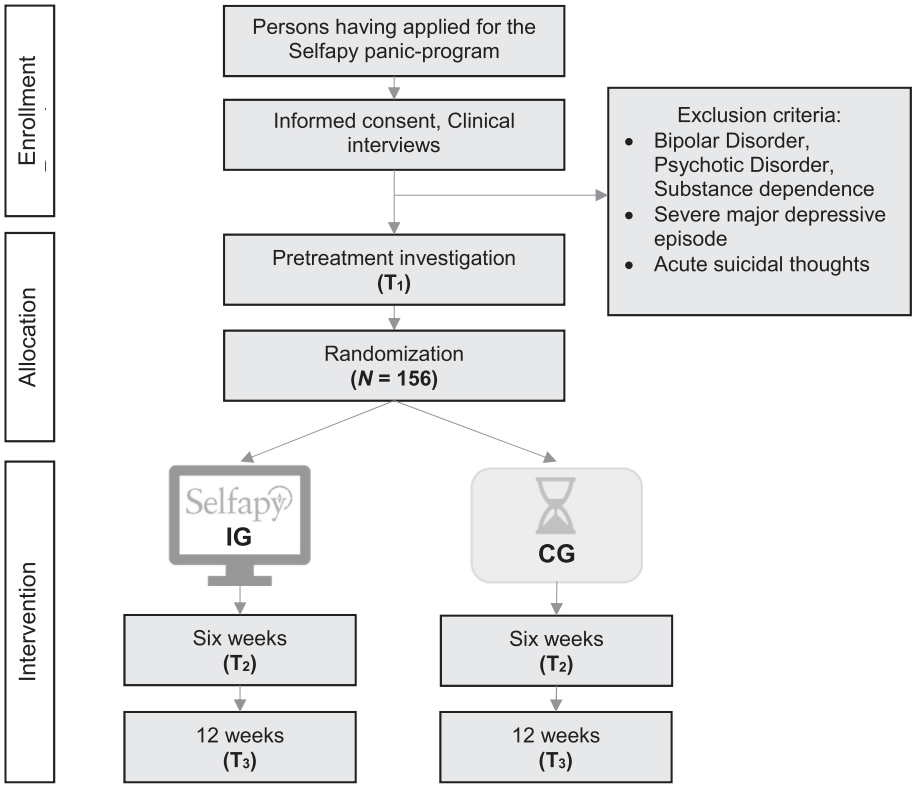


Fig. 1. CONSORT Flow diagram of the study design for intervention (IG) and control (CG) groups.

Table 1
Survey instruments at the respective measurement times.

Measurement time	Measuring instrument
Pretreatment measures (T1)	1. **Video interview**: Diagnostic Interview in Mental Disorders - Open Access (DIPS-OA). 2. **Primary outcomes** (self-assessed via online questionnaire) o Panic and Agoraphobia Scale (PAS) o Quality of life (WHO-5) 3. **Secondary outcomes** (self-assessed via online questionnaire) o Coping with difficulties in everyday life due to illness (WSAS) o Work Capability (iPCQ) o Health Literacy (MHLS). o Reduction of therapy-related expenses and burdens for patients and their relatives (CSSRI) 4. **Additional questionnaires** o Demographic questionnaire (BADO) o Anxiety symptomatology (BAI) o Depressive symptoms (PHQ-9)
Intermediate measurement, six weeks after T1 (T2)	See T1 except for video interview - **Further surveys** o Negative effects (NEQ) o BADO short version
Posttreatment measures, 12 weeks after T1 (T3)	See T2

Abbreviations. BADO = Basic Documentation; BAI = Beck Anxiety Inventory; CSSRI = Client Sociodemographic and Service Receipt Inventory; DIPS-OA = Diagnostic Interview in Mental Disorders-Open Access; iPCQ = Productivity Cost Questionnaire; MHLS = Mental Health Literacy Scale; NEQ = Negative Effects Questionnaire; PAS = Panic and Agoraphobia Scale; PHQ-9 = Patient Health Questionnaire 9; WHO-5 = World Health Organization-Five Well-Being Test; WSAS = Work and Social Adjustment Scale.

2.7.3. Negative effects (NEQ)

The Negative Effects Questionnaire (NEQ; Rozental et al., 2016) is used to capture possible adverse effects of the intervention. It consists of 32 items rated on a 4-point Likert scale and has an internal consistency of $\alpha = 0.95$.

2.7.4. Adherence

The adherence of the IG is recorded via the log files of the online platform Selfapy. The number of modules that have been finished is recorded.

2.8. Intervention

Selfapy is an internet-based intervention for treating panic disorder with or without agoraphobia (https://www.selfapy.de). The program employs evidence-based methods and exercises based on Cognitive Behavioral Therapy and elements of Mindfulness-Based Therapy (e.g., Justen-Horsten and Paschen, 2016; Lang et al., 2018; Zwick and

Table 2
Exemplary overview of modules and content of the panic disorder program.

Module	Content
Your start	In the first module, users can describe their problems and set personal goals.
First findings	This module focuses on psychoeducation. The users learn to recognize and understand the background of their problems. In addition, the users begin keeping an anxiety log to identify triggers and patterns regarding their panic and anxiety.
Anxiety Management	Here, the users learn about the fear reaction and the physical symptoms during a panic attack. In addition, users are given techniques to reduce anxiety in the specific case of a panic attack.
Your life	In this module, the users look back at the origin and development of their panic disorder. In addition, the user's self-efficacy is strengthened through various exercises.
Automatic thoughts	This module deals with the automatic thoughts behind the user's anxiety disorder. With the help of various exercises, the user learns to question his negative beliefs and replace them with more realistic ones.
The first exposure	In this module, the user is introduced to the topic of exposure. He learns how exposure works and why it is helpful in anxiety disorders. He also receives information about how he can expose himself and what there is to consider.
The second exposure	Also, in this module, the user further devotes himself to the exposure and how to do it.
Optional areas of specialization	
Mindfulness	A mindful approach to life can have a supportive effect to better deal with one's problems. With the help of formal and informal mindfulness exercises, the user learns how to integrate a mindful approach to oneself into everyday life.
Acceptance	This module teaches the user how to deal with their anxiety and panic differently through acceptance and commitment therapy exercises.
Social environment	This module deals with the effects of the social environment on one's own life. Through social networks and communication exercises, the user can optimize his social support and strengthen his skills in this area.
Problem solving training	In this module, problem solving skills are trained. Users learn to perceive a concrete problem, grasp reaction possibilities, and implement an action to change the situation.
Your anti-panic package	In the final module, users take stock of the completed course. They summarize which contents were beneficial and where they can still improve their anxiety disorder. At the end of the program, the user has an anti-panic package employed when problems arise again or relapses have already set in.

Hautzinger, 2017). The online course consists of a core course, which includes six mandatory modules, and a subsequent set of six optional specialization areas that are individually selectable (see Table 2). The program can be used via desktop browsers as well as on mobile devices. The online course is divided into different lessons, covering specific topics, such as *exposure*, *mindfulness*, or *problem-solving training,* and includes informative texts, videos, audio, and interactive exercises. Table 2 provides an overview of the core course and possible specialization areas and gives a brief overview of their contents. The course relies on empirically tested methods (Kaczkurkin and Foa, 2015; Kim et al., 2016) and has been tested in an unpublished cohort study before. Altogether, 316 Selfapy users were asked to fill out a questionnaire before and after the course. In an intent-to-treat analysis, significant improvements were found for general anxiety, specific anxiety and wellbeing with moderate to large effect sizes.

2.9. Randomization and blinding

Subjects meeting the inclusion criteria will be randomly assigned to one of two groups: (a) immediate access to the Selfapy panic course (intervention group; IG), (b) access to the Selfapy panic course after a waiting period of 12 weeks (control group; CG).

Randomization takes place after the baseline questionnaire by a member of the psychology department who is not involved in the project, using a computer-assisted procedure. Random assignment is made only if participants fulfill the inclusion criteria for the study. Before that, it is unknown which group the person will be assigned to if included (Allocation Sequence Concealment). Participants will be assigned to one of the two groups in a non-stratified 1:1 ratio. Subjects will be informed of the outcome of the random assignment via email. Participants are told that the waiting time will be randomly varied between zero and 12 weeks. Thus, patients in the CG will not know that the sample is divided into two groups, with one group starting the intervention immediately while the other group has to wait 12 weeks until receiving therapy access. The diagnostic interviewers will be blind to the group membership of the participants. After completing data collection, the statistical analysis of the outcomes is also performed in a blinded manner.

2.10. Power and sample size

The between-group effect size estimate is based on recent meta-analytic evidence for effect sizes in unguided online psychological interventions for anxiety disorders ($d = 0.45$; e.g., McCall et al., 2021). This effect size will be used as the basis for sample size design. For the planned mixed model with two measurement time points with a general correlation structure (Lu et al., 2008), a directed hypothesis, a group allocation of 1:1, a power of 0.80, and an alpha level of 0.025 after Bonferroni-Holm correction, a total of 156 patients* (78 per group) are needed. The sample size was calculated using the R tool *longpower* (Donohue, 2021). For the secondary outcomes, this sample size yields a power of 1-beta = 0.67.

2.11. Statistical analyses

For the statistical analyses, all patients who were randomly assigned to the two conditions and completed the initial survey (T1) will be included in an intention-to-treat (ITT) analysis. All available data will be used for this purpose. Missing values in the data will be replaced by multiple imputations ("Multivariate Imputation by Chained Equations"; MICE; with $n = 5$ imputations) based on the CG, using the variables *age* and *gender* as predictors in addition to the measurement-repeated stress indicators. Moreover, last-observation-carried-forward (LOCF), baseline-observation-carried-forward (BOCF), a reference-based-multiple imputation (jump-to-reference approach; Carpenter et al., 2013), and completer sensitivity analyses are performed.

The confirmatory analysis of the primary outcomes consists of calculating a mixed model with two measurement times and a general correlation structure (Lu et al., 2008). A random effect for the subjects is calculated (random intercept) and three fixed effects (group assignment, time, and the group by time interaction) are added. The two measurement time points are nested within subjects. The primary outcomes will be evaluated using a Bonferroni-Holm correction for alpha error inflation (Bortz and Schuster, 2016). Secondary confirmatory outcomes will only be analyzed in case of hypothesis confirming results in the primary analysis and the same mixed model with a random intercept for the subjects will be applied. Again, a Bonferroni-Holm correction will be employed (Bortz and Schuster, 2016).

Independent *t*-tests and $\chi 2$ tests are used to estimate differences between groups in pretreatment sample characteristics. In addition to the

ITT sample, a *per-protocol* sample sensitivity analysis is defined for exploratory analyses, including all patients in the IG who completed at least four of the modules.

There are different approaches to calculating effect sizes for mixed modeling data in the literature (Hedges, 2007). Hedges (2007) and Westfall et al. (2014) propose an effect size based on Cohen's *d*, which is similarly used for power analysis (Lu et al., 2008):

$$delta = \frac{fixed\ effect}{\sqrt{\sigma^2_{res} + \sigma^2_{intercept}}}$$

To assess the magnitude of the treatment effects, the fixed interaction effect of time and group assignment is divided by the root of the summed variances of the random effects. Effect sizes can be roughly interpreted according to Cohen's *d*: Effect sizes of 0.2 are considered small, 0.5 moderate, and 0.8 large (Cohen, 1988). Differences in response rates and additional healthcare service utilization are examined with *t*-tests and χ^2 tests.

All data analyses are performed without knowing the respective group membership (blinded data analysis). The evaluator does not know which expression of the group variable indicates membership of the IG and which indicates membership of the CG. In the appendix, an example R code is added for the analyses of the outcomes. Further, we will create an OSF repository after completing the trial with the raw data concerning the primary and secondary hypotheses and the respective code.

3. Discussion

The present study tests the effectiveness of the minimally guided online program Selfapy for patients with panic disorder with and without comorbid agoraphobia. The study was designed to strike a balance between a high degree of internal validity (e.g., randomization, standardized diagnostic procedure, etc.), allowing to attribute observed group differences to the intervention with sufficient certainty and a high external validity (e.g., allowing participants to utilize additional health care services), allowing to evaluate the effects in an ecologically valid context. In particular, no study-specific measures were taken to increase adherence to the intervention in order to gain a representative impression of how patients may make use of the software if it was part of routine clinical practice. Further, we refrained from choosing an active control group instead of a wait-list control condition, even though this design allows only limited conclusions regarding the specificity of the effects found. We did so in an attempt to assess the incremental effect of Selfapy for panic disorder patients compared to the current situation in the German health care system. Patients who want to undergo outpatient psychotherapy in Germany have to wait for an average of 20 weeks to start treatment (BPtK., 2018). One of the main advantages of an internet intervention like the one investigated in the presented study is its availability. If implemented in routine clinical care patients can make use of these interventions without delay. One could argue that the waiting period in the control group with 12 weeks is too short given the average waiting time of 20 weeks. Still we decided to restrict the waiting time in the control group to 12 weeks for several reasons. First, due to ethical reasons we wanted to hold this time period as short as possible. Withholding a likely helpful intervention should only be done as long as necessary. Again, we want to highlight, that patients in the control group as well as in the intervention group were allowed to seek additional treatments and help if they thought necessary. No patient was asked to refrain from any other mental health services. Second, 12 weeks is the time the intervention takes when completed in the recommended schedule. Therefore, fixing the control group to the same measurement schedule as the intervention allows us to evaluate the effects of having access to selfapy for panic disorders compared to not having access to this intervention.

Due to current technological progress, the implementation of online interventions may be an important addition to the German healthcare system. It may reduce barriers to treatment provision and complement current clinical care. Therefore, we aim to assess this online intervention regarding its impact on symptom reduction, wellbeing, work capability, and other measures of disease burden.

Ethics approval and consent to participate

This study was approved by the Ethics committee of the University of Heidelberg (Ethics Committee-No. AZ Prüß 2021 1/1) in accordance with the Declaration of Helsinki. Informed consent was given by all participants.

Consent for publication

Not applicable.

Funding

The study is funded by Selfapy GmbH. The Professorship for Psychotherapy Research at the Justus Liebig University in Giessen was asked by Selfapy to independently evaluate its product to be assessed to the best of our knowledge and follow good scientific practice standards. The funders have no authority over the study design, collection, management, analysis, interpretation of data, writing of the report, and the decision to publish the findings.

CRediT authorship contribution statement

JR, JQ, LR, and CL wrote the manuscript. LP, CT, SH, SB, and DR read the manuscript and provided critical feedback. All authors were included in the planning phase of the study.

Declaration of competing interest

A commercial organization (Selfapy GmbH) funded the study. The authors declare no competing interests and evaluate the intervention independently of the interest of the funder.

Availability of data and materials

The datasets generated during the upcoming study will be available in the OSF repository, [https://osf.io/xmj28/?view_only=60e98c32ce7c4830a439d35b1082913a].

Acknowledgments

Not applicable.

Appendix A. Example Code for the analyses in R.

```
library(mlmi)
library(bootImpute)
library(lme4)
library(tidyverse)
library(plyr)
library(mice)
library(broom.mixed)
library(miceadds)
library(zoo)
library(merTools)
library(Amelia)

#df is the Outcome-dataframe with the variables ID (id), dummy-#variable for the treatment (trt) and three measurements with the #according time points (y0, y1, y2), age (age), and sex (sex)
```

```
set.seed(1234)

# MICE-Imputation ---

# Imputation building on control group
ignore_vector <- df$trt
ignore_vector <- as.logical(ignore_vector)

#MICE-Imputation, 5 imputations
imp_mice <- mice(data = df, m = 5, ignore = ignore_vector)

#transform mids-object in a list
imp.data <- as.list(1:5)
for(i in 1:5){
imp.data[[i]] <- complete(imp_mice, action=i) }

#transform into long-format
imp.data_long <- lapply(imp.data, pivot_longer, cols = 3:5, names_to = "time", values_to = "value")

#Model calculation for each list element
model_mice <- lmerModList(value ~ trt*time + (1|id), data = imp.data_long)

#Random and Fixed Effects
modelRandEffStats(model_mice)
modelFixedEff(model_mice)

# LOCF-imputation ----
#Transform into long format
df_long<- pivot_longer(df, cols = 3:5, names_to = "time", values_to = "value")
df_long_locf <- df_long
df_long_locf$value <- na.locf(df_long$value) #LOCF-Imputation

#model calculation
mod.locf <- lmer(value ~ trt*time + (1|id), df_long_locf)

summary(mod.locf) # Random and Fixed effects

#BOCF-imputation ----
df_bocf <- df
df_bocf$y1 <- ifelse(is.na(df$y1), df$y0, df$y1) #BOCF für y1
df_bocf$y2 <- ifelse(is.na(df$y2), df$y0, df$y2) #BOCF für y2

#transform into long-format
df_long_bocf<- pivot_longer(df_bocf, cols = 3:5, names_to = "time", values_to = "value")

mod.bocf <- lmer(value ~ trt*time + (1|id), df_long_bocf)
summary(mod.bocf) # Random and Fixed effects

#Multiple imputations according to J2R-approach
j_to_r.wide <- bootImpute(df, refBasedCts, nBoot=500, nImp=2,
outcomeVarStem="y", nVisits=2, trtVar="trt",
baselineVars="y0", type="J2R", M=2)

# Transform into long format
j_to_r.long <- lapply(j_to_r.wide, pivot_longer, cols = 3:5, names_to = "time", values_to = "value")

#Model calculation
model_jtor <- lmerModList(value ~ trt*time + (1|id), data = j_to_r.long)

#Random Effects:
modelRandEffStats(model_jtor)

#Fixed Effects:
modelFixedEff(model_jtor)
```

References

Andrews, G., Basu, A., Cuijpers, P., Craske, M.G., McEvoy, P., English, C.L., Newby, J.M., 2018. Computer therapy for the anxiety and depression disorders is effective, acceptable and practical health care: an updated meta-analysis. J. Anxiety Disord. 55, 70–78. https://doi.org/10.1016/j.janxdis.2018.01.001.

Bandelow, B., 1997. Panic and Agoraphobia Scale: (PAS). Hogrefe, Göttingen.

Beck, A.T., Epstein, N., Brown, G., Steer, R.A., 1988. An inventory for measuring clinical anxiety: psychometric properties. J. Consult. Clin. Psychol. 56 (6), 893–897.

Beck, A.T., Epstein, N., Brown, G., Steer, R.A., 1988. An inventory for measuring clinical anxiety: psychometric properties. J. Consult. Clin. Psychol. 56 (6), 893–897. https://doi.org/10.1037/0022-006x.56.6.893.

Berger, T., Caspar, F., Richardson, R., Kneubühler, B., Sutter, D., Andersson, G., 2011. Internet-based treatment of social phobia: a randomized controlled trial comparing unguided with two types of guided self-help. Behav. Res. Ther. 49 (3), 158–169. https://doi.org/10.1016/j.brat.2010.12.007.

Berger, T., Urech, A., Krieger, T., Stolz, T., Schulz, A., Vincent, A., Moser, C.T., Moritz, S., Meyer, B., 2017. Effects of a transdiagnostic unguided internet intervention ('velibra') for anxiety disorders in primary care: results of a randomized controlled trial. Psychol. Med. 47 (1), 67–80. https://doi.org/10.1017/S0033291716002270.

Bergström, J., Andersson, G., Ljótsson, B., Rück, C., Andréewitch, S., Karlsson, A., Carlbring, P., Andersson, E., Lindefors, N., 2010. Internet-versus group-administered cognitive behaviour therapy for panic disorder in a psychiatric setting: a randomised trial. BMC Psychiatry 10 (1), 54. https://doi.org/10.1186/1471-244X-10-54.

Bortz, Jürgen, Schuster, Christof, 2016. Statistik für Human- und Sozialwissenschaftler. Extras online. Limitierte Sonderausgabe, 7., vollständig überarbeitete und erweiterte Auflage. Online verfügbar unter. Springer (Springer-Lehrbuch), Berlin, Heidelberg. http://www.springer.com/.

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

BPtK, 2018. Wartezeit für psychisch kranke Menschen weiterhin zu lang: BPtK zum G-BA-Gutachten zur Bedarfsplanung [Press release]. Berlin. October 15.

BPtK, 2021. BPtK-Auswertung: Monatelange Wartezeiten bei Psychotherapeut*innen: Corona-Pandemie verschärft das Defizit an Behandlungsplätzen [Press release]. Berlin. March 29.

Candilis, Philip J., Mclean, Renee, Y.S., Otto, Michael W., Manfro, Gisele Gus, Worthington III, John J., Penava, Susan J., Marzol, Patricia C., Pollack, Mark, 1999. Quality of life in patients with panic disorder. J. Nerv. Ment. Dis. 187 (7), 429. https://journals.lww.com/jonmd/fulltext/1999/07000/quality_of_life_in_patients_with_panic_disorder.6.aspx.

Carpenter, J.R., Roger, J.H., Kenward, M.G., 2013. Analysis of longitudinal trials with protocol deviation: a framework for relevant, accessible assumptions, and inference via multiple imputation. J. Biopharm. Stat. 23 (6), 1352–1371. https://doi.org/10.1080/10543406.2013.834911.

Chisholm, D., Knapp, M.R.J., Knudsen, H.C., Amaddeo, F., Gaite, L.U.I.S., Van Wijngaarden, B.O.B., EPSILON Study Group, 2000. Client socio-demographic and service receipt inventory-European version: development of an instrument for international research: EPSILON Study 5. Br. J. Psychiatry 177 (S39), 28–33.

Ciuca, A.M., Berger, T., Crişan, L.G., Miclea, M., 2018. Internet-based treatment for panic disorder: a three-arm randomized controlled trial comparing guided (via real-time video sessions) with unguided self-help treatment and a waitlist control. PAXPD study results. J. Anxiety Disord. 56, 43–55. https://doi.org/10.1016/j.janxdis.2018.03.009.

Cohen, J., 1988. Statistical Power Analysis for the Behavioral Sciences. Lawrence Earlbam Associates, Hillsdale, NJ.

Donohue, M.C., 2021. longpower: Power and Sample Size Calculations for Longitudinal Data. R Package Version 1.0.23.

Fogliati, V.J., Dear, B.F., Staples, L.G., Terides, M.D., Sheehan, J., Johnston, L., Kayrouz, R., Dear, R., McEvoy, P.M., Titov, N., 2016. Disorder-specific versus transdiagnostic and clinician-guided versus self-guided internet-delivered treatment for panic disorder and comorbid disorders: a randomized controlled trial. J. Anxiety Disord. 39, 88–102. https://doi.org/10.1016/j.janxdis.2016.03.005.

Friedli, T., Villiger, P.M., Gantschnig, B.E., 2018. Workability for persons with chronic diseases. A systematic review of validity and utility of assessments in German language/valid and feasible German-language assessments to assess workability in persons with chronic diseases-a systematic review. Int. J. Health Prof. 5 (1), 72–90.

Gräfe, V., Moritz, S., Greiner, W., 2020. Health economic evaluation of an internet intervention for depression (deprexis), a randomized controlled trial. Heal. Econ. Rev. 10 (1), 1–11.

Hedges, L.V., 2007. Effect sizes in cluster-randomized designs. J. Educ. Behav. Stat. 32 (4), 341–370. https://doi.org/10.3102/1076998606298043.

Jacobi, F., Höfler, M., Strehle, J., Mack, S., Gerschler, A., Scholl, L., Busch, M.A., Maske, U., Hapke, U., Gaebel, W., Maier, W., Wagner, M., Zielasek, J., Wittchen, H.-U., 2014. Psychische Störungen in der Allgemeinbevölkerung : studie zur gesundheit erwachsener in deutschland und ihr zusatzmodul psychische gesundheit (DEGS1-MH) [Mental disorders in the general population : study on the health of adults in Germany and the additional module mental health (DEGS1-MH)]. Nervenarzt 85 (1), 77–87. https://doi.org/10.1007/s00115-013-3961-y.

Johnston, L., Titov, N., Andrews, G., Spence, J., Dear, B.F., 2011. A RCT of a trans-diagnostic internet-delivered treatment for three anxiety disorders: examination of support roles and disorder-specific outcomes. PLoS ONE 6 (11), e28079. https://doi.org/10.1371/journal.pone.0028079.

Justen-Horsten, A., Paschen, H., 2016. Online-Interventionen in Therapie und Beratung: Ein Praxisleitfaden : mit E-Book inside (1. Auflage). Beltz.

Kaczkurkin, Antonia N., Foa, Edna B., 2015. Cognitive-behavioral therapy for anxiety disorders: an update on the empirical evidence. In: Dialogues in Clinical Neuroscience, 17 (3), pp. 337–346. https://doi.org/10.31887/DCNS.2015.17.3/akaczkurkin. S.

Karyotaki, E., Kleiboer, A., Smit, F., Turner, D.T., Pastor, A.M., Andersson, G., Berger, T., Botella, C., Breton, J.M., Carlbring, P., Christensen, H., de Graaf, E., Griffiths, K., Donker, T., Farrer, L., Huibers, M.J.H., Lenndin, J., Mackinnon, A., Meyer, B., Cuijpers, P., 2015. Predictors of treatment dropout in self-guided web-based interventions for depression: an 'individual patient data' meta-analysis. Psychol. Med. 45 (13), 2717–2726. https://doi.org/10.1017/S0033291715000665.

Kim, Min Kuk, Lee, Kang Soo, Kim, Borah, Choi, Tai Kiu, Lee, Sang-Hyuk, 2016. Impact of mindfulness-based cognitive therapy on intolerance of uncertainty in patients with panic disorder. Psychiatry Investig. 13 (2), 196–202. https://doi.org/10.4306/pi.2016.13.2.196. S.

Klein, B., Austin, D., Pier, C., Kiropoulos, L., Shandley, K., Mitchell, J., Gilson, K., Ciechomski, L., 2009. Internet-based treatment for panic disorder: does frequency of therapist contact make a difference? Cogn. Behav. Ther. 38 (2), 100–113. https://doi.org/10.1080/16506070802561132.

Kroenke, K., Spitzer, R.L., Williams, J.B., 2001. The PHQ-9: validity of a brief depression severity measure. J. Gen. Intern. Med. 16 (9), 606–613. https://doi.org/10.1046/j.1525-1497.2001.016009606.x.

Lang, T., Helbig-Lang, S., Westphal, D., Gloster, A.T., Wittchen, H.-U., 2018. Expositionsbasierte Therapie der Panikstörung mit Agoraphobie: Ein Behandlungsmanual (2., aktualisierte Auflage). In: Therapeutische Praxis. Hogrefe. https://doi.org/10.1026/02867-000. https://elibrary.hogrefe.com/book/10.1026/02867-000.

Lecrubier, Y., 1998. The impact of comorbidity on the treatment of panic disorder. J. Clin. Psychiatry 59 (8), 11–14. https://www.psychiatrist.com/wp-content/uploads/2021/02/14008_impact-comorbidity-treatment-panic-disorder.pdf.

Lu, K., Luo, X., Chen, P.-Y., 2008. Sample size estimation for repeated measures analysis in randomized clinical trials with missing data. Int. J. Biostat. 4 (1).

Lutz, W., Neu, R., Rubel, J.A., 2019. Evaluation and Effect Measurement in Psychotherapy. Hogrefe, Göttingen.

Margraf, J., Ehlers, A., 2007. Beck Anxiety Inventory German Version (BAI). Hans Huber, Bern.

Margraf, J., Cwik, J.C., Suppiger, A., Schneider, S., 2017. DIPS Open Access: Diagnostic Interview for Mental Disorders. [DIPS Open Access: Diagnostic Interview for Mental Disorders.]. Mental Health Research and Treament Center, Ruhr- Universität Bochum. https://doi.org/10.13154/rub.100.89.

McCall, H.C., Hadjistavropoulos, H.D., Sundström, C.R.F., 2021. Exploring the role of persuasive design in unguided internet-delivered cognitive behavioral therapy for depression and anxiety among adults: systematic review, meta-analysis, and meta-regression. J. Med. Internet Res. 23 (4), e26939 https://doi.org/10.2196/26939.

Mundt, J.C., Marks, I.M., Shear, M.K., Greist, J.H., 2002. The work and social adjustment scale: a simple measure of impairment in functioning. Br. J. Psychiatry J. Ment. Sci. 180, 461–464. https://doi.org/10.1192/bjp.180.5.461.

Murray, C.J.L., Vos, T., Lozano, R., Naghavi, M., Flaxman, A.D., Michaud, C., Ezzati, M., Shibuya, K., Salomon, J.A., Abdalla, S., Aboyans, V., Abraham, J., Ackerman, I., Aggarwal, R., Ahn, S.Y., Ali, M.K., AlMazroa, M.A., Alvarado, M., Anderson, H.R., Lopez, A.D., 2012. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of DiseaseStudy2010. Lancet 380 (9859), 2197–2223. https://doi.org/10.1016/S0140-6736(12)61689-4.

National Institute for Clinical Excellence, 2011. Clinical guidelines 123. Retrieved from. https://www.nice.org.uk/guidance/cg123/.

O'Connor, M., Casey, L., 2015. The mental health literacy scale (MHLS): a new scale-based measure of mental health literacy. Psychiatry Res. 229 (1–2), 511–516. https://doi.org/10.1016/j.psychres.2015.05.064.

Oromendia, P., Orrego, J., Bonillo, A., Molinuevo, B., 2016. Internet-based self-help treatment for panic disorder: a randomized controlled trial comparing mandatory versus optional complementary psychological support. Cogn. Behav. Ther. 45 (4), 270–286. https://doi.org/10.1080/16506073.2016.1163615.

Rozental, A., Kottorp, A., Boettcher, J., Andersson, G., Calbring, P., 2016. Negative effects of psychological treatments: an exploratory factor analysis of the negative effects questionnaire for monitoring and reporting adverse and unwanted events. PLoS One 11 (6), e0157503. https://doi.org/10.1371/journal.pone.0157503.

Schröder, J., Jelinek, L., Moritz, S., 2017. A randomized controlled trial of a trans-diagnostic internet intervention for individuals with panic and phobias - one size fits all. J. Behav. Ther. Exp. Psychiatry 54, 17–24. https://doi.org/10.1016/j.jbtep.2016.05.002.

Seligman, M.E.P., 1995. The effectiveness of psychotherapy: the consumer reports study. Am. Psychol. 50 (12), 965–974. https://doi.org/10.1037/0003-066X.50.12.965.

Stech, E.P., Lim, J., Upton, E.L., Newby, J.M., 2019. Internet-delivered cognitive behavioral therapy for panic disorder with or without agoraphobia: a systematic review and meta-analysis. Cogn. Behav. Ther. 1–24 https://doi.org/10.1080/16506073.2019.1628808.

Taylor, C.B., 2006. Panic disorder. BMJ [Br. Med. J.] 332 (7547), 951–955. https://doi.org/10.1136/bmj.332.7547.951.

Thomas, N., McLeod, B., Jones, N., Abbott, J.-A., 2015. Developing internet interventions to target the individual impact of stigma in health conditions. Internet Interv. 2 (3), 351–358. https://doi.org/10.1016/j.invent.2015.01.003.

Topp, C.W., Østergaard, S.D., Søndergaard, S., Bech, P., 2015. The WHO-5 well-being index: a systematic review of the literature. Psychother. Psychosom. 84 (3), 167–176. https://doi.org/10.1159/000376585.

Westfall, J., Kenny, D.A., Judd, C.M., 2014. Statistical power and optimal design in experiments in which samples of participants respond to samples of stimuli. J. Exp. Psychol. Gen. 143 (5), 2020–2045. https://doi.org/10.1037/xge0000014.

Whiteford, H.A., Degenhardt, L., Rehm, J., Baxter, A.J., Ferrari, A.J., Erskine, H.E., Charlson, F.J., Norman, R.E., Flaxman, A.D., Johns, N., Burstein, R., Murray, C.J., Vos, T., 2013. Global burden of disease attributable to mental and substance use disorders: findings from the global burden of disease study 2010. Lancet 382 (9904), 1575–1586. https://doi.org/10.1016/S0140-6736(13)61611-6.

Wittchen, H.-U., Gloster, A.T., Beesdo-Baum, K., Fava, G.A., Craske, M.G., 2010. Agoraphobia: a review of the diagnostic classificatory position and criteria. Depress. Anxiety 27 (2), 113–133. https://doi.org/10.1002/da.20646.

Zwick, J., Hautzinger, M., 2017. Panik und Agoraphobie: Kognitiv-verhaltenstherapeutisches Manual : mit E-Book inside und Arbeitsmaterial (1. Auflage). Beltz. http://sub-hh.ciando.com/book/?bok_id=2254200.

J. Rubel[a,*], J. Quest[a], L. Pruessner[b], C. Timm[b], S. Hartmann[b], S. Barnow[b], L. Rittmeyer[a], D. Rosenbaum[c], C. Lalk[a]

[a] *Professorship for Psychotherapy Research, Department 06 - Psychology and Sport, Justus Liebig University Giessen, Germany*

[b] *Department of Psychology, Heidelberg University, Germany*

[c] *Department of Psychiatry and Psychotherapy, University Hospital of Tuebingen, Tuebingen, Germany*

[*] Corresponding author at: Professorship for Psychotherapy Research, Department of Psychology, Justus Liebig University Giessen, Otto-Behaghel-Strasse 10, House F, 35394 Giessen, Germany.
E-mail address: julian.rubel@psychol.uni-giessen.de (J. Rubel).