Clinical investigation plan

CIP; following ISO 14155:2020

Researching the **E**ffecti**V**eness of a ***AL****ivis*, a **DI**gital health application for **B**orderline **P**ersonality **D**isorder: a randomized controlled trial (REVALDI-BPD)

28.03.2025

version 5

Table of Contents

1. General 6
1.1 Identification of the clinical investigation plan 6
a) Title 6
b) Reference number 6
c) Version / Date 6
d) Summary of the revision history 6
e) Version/issue number and reference number 6
f) Abbreviations 7
1.2 Sponsor 8
1.3 Principal investigator, coordinating investigator and investigation site 8
a) Name, address, contact details and professional position 8
1) principal investigator 8
2) coordinating investigator 8
b) Name and address of the investigation site 8
c) Name and address of external organizations 8
1.4 Overall synopsis of the clinical investigation 9
1.5 Introduction 9
2. Identification and description of the investigational device 10
a) Summary description 10
b) Manufacturer 10
c) Name/number of the model/type, software version and accessories 10
d) Description of traceability during and after the clinical investigation 10
e) Intended purpose 10
f) Populations and indications 11
g) Description of the investigational device 11
h) Necessary training and experience needed to use the investigational device 12
i) Medical or surgical procedures involved in the use of the investigational device 12
j) References to the Investigator’s brochure (IB) and IFU. 13
3. Justification for the design of the clinical investigation 13
a) evaluation of pre-clinical testing/assessment and prior clinical investigations 13
b) Clinical data relevant to the proposed clinical investigation 13
c) Clinical development stage 13
4. Benefits and risks 13
a) Anticipated clinical benefits 13
b) Anticipated adverse device effects 14
c) Risks associated with participation in the clinical investigation 14
d) Possible interactions with concomitant medical treatments 14
e) Control or mitigation of risks. 14
f) Rationale for benefit-risk ratio 14
g) Medical justifiability 14
5. Objectives and hypotheses 15
a) Purpose, claims, effectiveness, safety 15

b) Objectives 15
c) Scientific justification and clinical relevance 15
d) Primary and secondary hypotheses 15
e) Risks and anticipated adverse device effects 16
6. Design 17
6.1 General 17
a) Description of the design type of clinical investigation to be performed 19
b) Measures against bias 20
c) Primary and secondary endpoints 20
d) Methods and timing 23
e) Equipment for assessing the clinical investigation variables 26
f) Replacement of subjects 26
g) Investigation sites 26
h) Completion of the clinical investigation 26
6.2 Investigational device and comparator 27
a) Exposure to the investigational device or comparator 27
b) Other medical devices or medication 27
c) Number of investigational devices 27
6.3 Subjects 28
a) Inclusion criteria 28
b) Exclusion criteria 28
c) Criteria and procedures for subject withdrawal or lost to follow-up 28
1) Withdrawal of a subject or stop of use 28
2) Tracing of subjects lost to follow-up 28
3) Replacement of subjects 28
d) Point of enrolment 28
e) Point of randomization 29
f) Total expected duration 29
g) Expected duration for each subject 29
h) Number of subjects 29
i) Enrolment period 29
j) Relationship of investigation population to target population 29
k) Vulnerable, pregnant, and breastfeeding population 29
6.4 Procedures 29
a) Procedures during the clinical investigation 29
b) Activities performed by sponsor representatives 30
c) Factors compromising outcome or interpretation of results 30
d) Methods for addressing these factors 30
e) Follow-up period for clinical performance, effectiveness or safety 30
f) Specific medical care provided following the clinical investigation 30
g) Recommended follow-up for the subjects 31
h) Final disposition or potential future use of samples obtained from subjects 31
6.5 Monitoring plan 31
7. Statistical design and analysis 32

a) Analysis population 32
b) Descriptive statistics of baseline data, treatments, safety data 32
c) Analytical procedures and measures of precision 32
d) Significance level and power 33
e) Sample size 33
1) Clinical data on outcome variable and effect size 33
2) Expected outcomes across treatment groups 33
3) Adjustments due to pre-planned interim analyses 33
4) Effect size and non-inferiority margin 33
5) Randomization allocation ratio 33
6) Expected drop-out rate 33
f) Procedures to be performed by user and analysis 34
g) Pass/fail criteria 34
h) Interim analysis and criteria for termination 34
i) Management of bias 34
j) Management of potential confounding factors 34
k) Multiplicity control and adjustment of error probabilities 34
l) Subgroups for analysis 34
m) Missing, unused or spurious data, including drop-outs 35
n) Exploratory analysis and sensitivity analysis 35
p) Handling potential imbalance of numbers of subjects across investigation sites 35
q) strategy for pooling data 35
r) estimand strategy 35
8. Data management 36
a) Methods for data entry and collection 36
b) CRF tracking, data review, database cleaning, and issuing/resolving data queries 36
c) Verification, validation, and securing of electronic clinical data systems 36
d) Subject privacy 36
e) Database locking and storage 36
f) Data retention 36
g) Retention period 37
h) Other aspects of clinical quality assurance 37
9. Amendments to the CIP 37
10. Deviations from clinical investigation plan 37
a) Statement - deviation from the CIP 37
b) Recording, reporting, and analysing CIP deviations 37
c) Notification requirements and time frames 37
d) Corrective/preventive actions and principal investigator disqualification criteria 37
11. Device accountability 38
a) Accountability of investigational devices 38
b) Safe return of potentially hazardous investigational devices 38
12. Statements of compliance 38
a) Statement - Declaration of Helsinki 38

b) Statement - compliance with ISO 14155:2020 and any regional or national regulations 38
c) Statement - required approval/favourable opinion from the EC/regulatory authority 38
d) Statement - requirements imposed by the EC or regulatory authority 38
e) Statement - insurance for subjects 38
f) Statement - financing/agreement between sponsor and investigation site(s)/investigator(s) 38
13. Informed consent process 39
a) Informed consent and incentives 39
b) Informed consent process - subject unable/emergency treatment 39
14. Adverse events, adverse device effects and device deficiencies 39
a) Definitions of adverse events and adverse device effects 39
b) Definition of device deficiencies 40
c) Definitions of serious adverse events and serious adverse device effects 40
d) Non-reportable adverse events 40
e) Report period of adverse events and device deficiencies 40
f) Process for reporting adverse events 41
g) Process for reporting device deficiencies 41
h) Adverse events, adverse device effects and incidence, mitigation, or treatment 41
i) Emergency contact details for serious adverse events/device effects. 41
j) Information regarding the DMC 42
15. Vulnerable population 42
16. Suspension or premature termination of the investigation 42
a) Criteria and arrangements 42
b) Criteria for access to and breaking the blinding/masking code 42
c) Subject follow-up and continued care 42
17. Publication policy 42
a) Statement - trial registration 42
b) Statement - publicly available results 42
c) Statement - conditions/timeframes for publication 42
18. Bibliography 43
19. Signatures 47

Figure 1| Flow Chart of Trial Design 19

Table 1| Chronological Sequence of the Trial 26

1. General

1.1 Identification of the clinical investigation plan

a) Title

Researching the effectiveness of *alivis*, a digital health application for Borderline Personality Disorder: a randomized controlled trial (REVALDI-BPD)

b) Reference number

This trial will be registered in an international trial registry before the start of recruitment.

c) Version / Date

version 5 / 28.03.2025

d) Summary of the revision history

version 2 (14.08.2023): changes in endpoints, control condition, in- and exclusion criteria, and associated procedures. Video instead of telephone interviews. Moreover, the description of the program was updated to reflect more clearly which therapeutic strategies are used. All changes are marked in yellow.

version 3 (18.01.2024): change of PI. Telephone instead of video interviews. Details on monitoring have been added in section 6.5. All changes are marked in green.

version 4 (18.07.2024): removal of BPD-CL als secondary endpoint; further information on alivis and the development process; updated formulation of primary and secondary hypotheses; changes control group from TAU + information material to TAU only; further information on the emergency plan for suicidal crises; change of responder criteria; updated exclusion criteria; added subgroup analyses; added information on the estimand strategy; updated information on funding. All changes are marked in pink.

version 5 (28.03.2025): updated exclusion criterion from “Plans to change treatment in the upcoming 6 months after inclusion” to “Plans to change treatment in the upcoming 3 months after inclusion”. All changes are marked in orange.

e) Version/issue number and reference number

version 5

f) Abbreviations

ACT	Acceptance and Commitment Therapy
ANCOVA	Analysis of Covariance
AQoL-8D	Assessment of Quality of Life - 8 Dimensions
BPD	Borderline Personality Disorder
BSL-23	Borderline Symptoms List-23
ClinROM	Clinician-reported outcome measure
DBT	Dialectical Behavioral Therapy
DiGA	Digital health application
DSM-V	Diagnostic and Statistical Manual of Mental Disorders
GAD-7	Generalized Anxiety Disorder Assessment
GDPR	General Data Protection Regulation
ICMJE	International Committee of Medical Journal Editors
ITT	intention to treat
MCID	minimal clinically important difference
NPS	Net Promoter Score
PHQ-9	Patient Health Questionnaire
PP	per protocol
PROM	Patient-reported outcome measure
PRRC	Person Responsible for Regulatory Compliance
QMS	Quality Management System
RCT	randomized controlled trial
SCID-5-PD	Structured Clinical Interview for DSM-5
ST	Schema Therapy
T0	Baseline
T1	primary timepoint for analysis of effectiveness; 3 months post allocation
T2	6 months post allocation
T3	12 months post allocation
TAU	Treatment as usual
WAI	Working Alliance Inventory
WSAS	Work and Social Assessment Scale

~~ZAN-BPD Zanarini Rating Scale for Borderline Personality Disorder~~

1.2 Sponsor

GAIA AG, Hans-Henny-Jahnn-Weg 53, 22085 Hamburg
PD Dr. Gitta Jacob, Antje Riepenhausen, ~~Martina Dietrich,~~ Anja Specht, Louisa Adler

- role: Patient recruitment, trial management, online-data acquisition, telephone interviews, provision of the software, examination and evaluation of reports with regard to adverse effects, data analysis

1.3 Principal investigator, coordinating investigator and investigation site

a) Name, address, contact details and professional position

1) principal investigator

Prof. Dr. med. Jan Philipp Klein

Universität zu Lübeck, Zentrum für Integrative Psychiatrie ZiP gGmbH, Ratzeburger Allee 160, 23562 Lübeck, philipp.klein@uksh.de

- role: Scientific lead and coordinator, data analysis, monitoring

2) coordinating investigator

Not applicable.

b) Name and address of the investigation site

The clinical investigation will be conducted as an online trial without a traditional physical investigation site. Study management including patient recruitment will be conducted by the sponsor.

c) Name and address of external organizations

PD Dr. med. Eva Fassbinder

Zentrum für Integrative Psychiatrie, Campus Kiel, Department of Psychiatry and Psychotherapy, Niemannsweg 147, 24105 Kiel, Germany, eva.fassbinder@gmail.com

- role: Scientific co-lead and co-coordinator, lead and supervision of data analysis

PD Dr. med. Eva Fassbinder works on a freelancer basis also for GAIA (the sponsor) as an author for the program *alivis*.

GAIA AG, Hans-Henny-Jahnn-Weg 53, 22085 Hamburg
PD Dr. Gitta Jacob, Dr. Antje Riepenhausen, ~~Martina Dietrich,~~ Anja Specht, ~~Lea Nitzpon,~~ Louisa Adler

- role: Patient recruitment, trial management, online-data acquisition,

telephone interviews, provision of the software, examination and evaluation of reports with regard to adverse effects, data analysis

1.4 Overall synopsis of the clinical investigation

This randomized controlled trial (RCT) with 470 patients diagnosed with Borderline Personality Disorder (BPD) aims to investigate the effectiveness of the unguided digital therapeutic *alivis* for patients with BPD as defined in DSM-5. Inclusion criteria are: male, female or non-binary, age 18-65 years, diagnosis of BPD (confirmed by SCID-5-PD), borderline severity score (cut-off) of ≥ 1.07 on the Borderline Symptoms List 23 (BSL-23), stable treatment (e.g., psychotherapy, medication, no treatment~~, ...~~) for at least 30 days at the time of inclusion, consent to emergency plan for suicidal crises, consent to participation, and sufficient German language skills. Exclusion criteria are: Plans to change ~~in~~ treatment (e.g., psychotherapy, medication~~, ...~~) in the upcoming 3 months after inclusion, comorbid diagnosis of substance use disorder or lifetime diagnosis of psychotic disorder, physical condition that can cause severe psychiatric symptoms, acute decompensation of mental health, BMI <15, and prior use of the digital intervention *priovi*.

Patients will be randomized and allocated to either an intervention group, in which they will receive access to *alivis* in addition to treatment as usual (TAU; n=235), or to a control group, in which they will receive access to TAU ~~and publicly available information material on BPD~~ (n=235).

The primary endpoint will be BPD symptoms with three months post-allocation (T1) being the primary timepoint for assessment of effectiveness. Six (T2) and twelve (T3) months post-allocation will be used as follow-up assessment of endpoints. Secondary endpoints will be depressive symptoms, anxiety symptoms, costs caused due to the patient's BPD, social functioning, ~~mental~~ health-related quality of life, ~~specific BPD symptoms (on the basis of all nine BPD criteria according to DSM-5),~~ and patient activation. For a visualization of the trial design, see figure 1.

1.5 Introduction

Borderline Personality Disorder (BPD) is a common, debilitating and costly mental disorder which is characterized by an instability in interpersonal relations, behavior, and emotions (1–4). Individuals with BPD experience symptoms ranging from frantic efforts to avoid abandonment and chaotic relationships, to a distorted self-image, feelings of emptiness, emotional dysregulation, dissociation, and intense anger, impulsive behaviors, self-harm, and suicidal ideation (3).

Several effective psychotherapeutic approaches for BPD exist (5,6), including dialectical behavior therapy (DBT), schema therapy (ST), and mentalization-based treatment. However, fewer than one in four BPD patients have access to psychotherapy (7). Digital health applications (DiGAs) can provide evidence-based psychotherapies that may help to reduce this treatment gap (8). DiGAs are also suitable for patients who prefer to overcome their mental health problems on their own or for those who live in areas with low access to psychiatric-psychotherapeutic care. This evidently applies to a considerable proportion of those who have a serious mental illness but do not seek treatment (9,10).

To date, a couple of digital health applications for BPD exist, which focus on tools from ST or from DBT (11,12). *alivis* is based primarily on DBT, which is the best-evaluated behavioral treatment method for BPD (5,13). DBT is a modular treatment program, and *alivis* makes use of several of these modules: for example, skills in emotion regulation, distress tolerance, antidissociative techniques, interpersonal effectiveness, and mindfulness are taught. These DBT modules are expanded in *alivis* to include modules on basic needs from ST (14,15), which has a good evidence base in BPD (13,16,17), on values work and defusion techniques from Acceptance and Commitment Therapy (ACT; 18–20) as well as on fostering self-compassion from Mindfulness Self-Compassion Therapy (MSC; 21) adapted to the needs of patients with BPD. Similar techniques have been integrated into more recent DBT protocols (22,23). The composition of the techniques used in *alivis* is thus based on the latest findings in psychotherapy research as well as on the extensive clinical expertise of the development team. Providing such a wide range of strategies enhances the chances that the patient will be able to make use of what they are offered and eventually profit from the intervention. *alivis* was developed by clinicians and researchers with long-standing expertise in the field of BPD which they have incorporated into the development of *alivis,* and with the involvement of patients suffering from BPD.

The aim of the present RCT is to examine the effectiveness of *alivis*, a self-guided digital intervention for BPD, to decrease symptom severity in BPD patients.

2. Identification and description of the investigational device

a) Summary description

Participants allocated to the intervention group will be provided with access to the program *alivis*. *alivis* is a CE-labeled, interactive online program for patients with BPD. *alivis* is organized in simulated dialogues that enable the patient to learn more about their disease and practice relevant skills and competences for managing their symptoms and improving their quality of life.

alivis is a class I medical device according to MDR 2017/745, Annex VIII, Chapter III with software safety class A according to IEC 62304.

b) Manufacturer

alivis was developed by GAIA AG, an e-health company in Hamburg, Germany, specialized on research and development of digital therapeutics.

c) Name/number of the model/type, software version and accessories

to hand in later

d) Description of traceability during and after the clinical investigation

to hand in later

e) Intended purpose

alivis is intended to provide therapeutic methods and exercises based on evidence-based psychological and psychotherapeutic therapies for patients with

BPD, to help them manage their BPD symptoms. *alivis* is intended as a self-application for patients 18 years of age or older. *alivis* is neither intended to replace treatment provided by a health care provider nor to provide information which is used to make decisions with diagnosis or therapeutic purposes.

f) Populations and indications

Patients with Borderline Personality Disorder, ICD-10: F60.31 /ICD-11: 6D10.

g) Description of the investigational device

alivis is an interactive online program for independent use by users with BPD. It focuses on recognized treatment elements from DBT, ST, ACT, and MSC.

The program *alivis* is based on proprietary software of the developing company (broca®), with access via password-protected and https-encrypted websites. The program can be used on conventional web-browsers on desktop PCs, tablets and smartphones. Users (patients randomized to the intervention group) receive access to the program for 12 months by 12-digit personal codes (vouchers), provided by the developer. Data protection and data security will be ensured by compliance with legal regulation. After initial registration and consent of general terms and conditions, users can log into the program using their email address and personal password at any time. The program is set up as an adaptive- and responsive-web-design pulling a layout template for a specific device, adapting to dimension and resolution of the display used. This results in high flexibility of usage regardless of the available hardware.

An essential element of the program is the presentation of content through simulated dialogues (so-called ‘chats’), which are performed by interaction of the user with the software acting as a virtual expert. Users navigate through the modules by reading short texts and reacting to the information by continuously choosing one or multiple predefined options of response. Based on this input, the program subsequently adjusts the content. In this process, preferences and needs of the user are matched with regard to content and style. This is a form of content tailoring that has been tried and tested over many years in other programs of the developing company and, importantly, does not involve AI-based chatbots. Brief text passages are accompanied by illustrations, audio recordings, worksheets and personalized summaries (pdf documents). Users can collect specific techniques, which they found particularly helpful, in a personalized toolbox, so that they can access them easily when they need them in their daily life. Exercises can be practiced again in a ‘practice corner’. Moreover, optional daily short text messages (SMS) are sent as reminders and to motivate and support users in their daily lives. The program also offers a symptom tracking function; that is, users are invited to complete embedded questionnaires at regular intervals in order to self-monitor changes over time. Moreover, a specific module was created to help users deal with difficult situations they encounter in their daily life. Here, the program validates the emotional struggle of the user, tries to help them clarify the situation by understanding underlying emotions, supports them to use skills they have detected as helpful while using the program, proposes new strategies (especially if the user just started the program) or reminds them to use their emergency plan in case of a suicidal crisis.

alivis covers the following therapeutic techniques and content, organized in “chats”. Length of chats can be chosen individually by the user.

- **Psychoeducation**. Psychoeducation covers a variety of issues including BPD symptoms, development and maintenance of BPD, normal and BPD-typical emotional functioning, the respective treatment strategies and how they are supposed to work etc..
- **Stress regulation and skills training**. Stress regulation with so-called crisis survival skills is a central element to DBT and is addressed in detail in specific chats, and applied to different life issues throughout the whole program. A specific emphasis in this regard is on dissociative symptoms.
- **Emotion regulation**. Emotional problems are at the core of BPD; thus emotion regulation covers both intensive psychoeducation, skills training and techniques to detect and regulate emotions in a functional way.
- **Mindfulness**. Mindfulness is another central part to most third wave therapies including DBT. It can be used both as part of stress and emotion regulation, but also as a general basis for mental health and psychological well-being.
- **Value-based activation**. To establish better value-based activation in the patients' lives, alivis discusses their personal values and how to follow them. Throughout the whole program, relations between different problems and how to solve them pursuing your values are discussed.
- **Cognitive techniques**. Cognitive techniques are mainly derived from ACT ('defusion skills') and are supposed to help patients gain a distance from overwhelming negative thoughts.
- **Social competence**. Interpersonal problems are a core problem area in BPD. Social competence includes techniques to downregulate oneself in tense social situations, healthy and assertive ways of communication in relationships, adequate ways to show own personal limits, express one's needs etc.
- **Self-compassion**. Self-invalidation, self-criticism and shame are hallmarks of BPD, thus techniques to promote self-compassion have been introduced in alivis (as in most modern BPD treatments). Psychoeducation, case examples and guided practices are provided to help users learn to be kind and understanding rather than harshly self-critical, especially when they fail, make mistakes or feel inadequate. They learn how to give themselves support and encouragement rather than being cold and judgmental when challenges and difficulty arise.

The control group will receive access to *alivis* after 12 months.

Users of *alivis* can contact the support via study email and telephone numbers or through the program itself. Support is offered in case of any questions regarding program usage and technical problems.

h) Necessary training and experience needed to use the investigational device

The application of *alivis* does not require training or any prior experience with the program.

i) Medical or surgical procedures involved in the use of the investigational device

Not applicable.

j) References to the Investigator's brochure (IB) and IFU.

Not applicable.

3. Justification for the design of the clinical investigation

a) evaluation of pre-clinical testing/assessment and prior clinical investigations

The ~~device alivis~~safety and performance of *alivis* was evaluated and confirmed ~~in pilot evaluations~~ according to the requirements applicable to the~~processes of~~ development of medical devices (IEC 62366, ISO 13485; MDR Annex I)~~ including class I medical devices~~ in a summative evaluation. This includes the verification of the functionality and content of *alivis* as well as evaluation of extensive clinical data from post-market surveillance of the technically equivalent devices *priovi* and *deprexis*. Clinical data from post-market clinical follow-up RCTs is available for the equivalent class I medical device *priovi*.

b) Clinical data relevant to the proposed clinical investigation

Several effective psychotherapeutic approaches for BPD exist (5,6). Previously published studies demonstrated initial promising effects of digital interventions for BPD (12), but so far, these digital interventions focused on isolated psychotherapeutic approaches (i.e., only ST (24) or only DBT (25)) or on psychoeducation (26). *alivis* represents modern psychotherapy for BPD by combining strategies from DBT, ST, ACT, and MSC supplemented with psychoeducation, and thus offers the patient a considerably wider spectrum of therapeutic offers than previous digital interventions for BPD. The developers of *alivis* are clinicians and researchers with long-standing expertise in the field of BPD which they have incorporated into the development of *alivis*.

c) Clinical development stage

Post-Market-Stage

Due to the CE-label of *alivis,* the trial will be a post-market clinical follow-up study in line with the existing intended purpose.

4. Benefits and risks

a) Anticipated clinical benefits

Since the intervention is designed to improve BPD symptoms, it is possible that the severity of BPD symptoms will decrease significantly for the individual study participants of the intervention group. Moreover, it is possible that study participants will experience further clinical benefits such as reduced symptoms of depression and anxiety, as well as increased~~ mental~~ health-related quality of life and ability to work.

b) Anticipated adverse device effects

When using *alivis*, it may happen that not every patient benefits from it. This circumstance can potentially lead to feelings of disappointment. Moreover, the intervention addresses topics that may evoke temporary emotional distress in rare cases~~some study participants~~. However, the program is designed in such a way that it aims at high inherent safety. First, the program addresses the user in an emphatic, affirmative manner throughout. Second, the program regularly offers emotionally stabilizing exercises for potentially disturbing topics. Whenever a potentially stressful topic is addressed, the user also has the option to skip these sections. All exercises can be interrupted or discontinued at any time.

c) Risks associated with participation in the clinical investigation

The risk for individual participants can be regarded as very low. The program itself is designed with high inherent safety. The exercises can be interrupted or discontinued at any time. If persistent emotional distress or pain occurs during or after performing the exercises, the program advises seeking medical attention.

Study procedures cover typical self-report assessments and have little potential to have a disturbing effect.

d) Possible interactions with concomitant medical treatments

The intervention is tested adjunctively to routine treatment, which provides an additional safety layer because participants can access their usual care providers if the need arises. The usual routine treatment can be continued without any changes or restrictions in both groups.

e) Control or mitigation of risks.

Potential adverse events will be recorded and analyzed throughout the trial. At each measurement timepoint, participants will be asked for the occurrence of specific adverse events, and the negative effects questionnaire (NEQ) is assessed. Moreover, users will be instructed to report adverse events via one of multiple channels (email, phone or website). All information received directly by the support team at GAIA or by the study management team will be reviewed and reports concerning safety-relevant issues will be documented and forwarded for assessment and further processing to the Person Responsible for Regulatory Compliance (PRRC). If undesirable side effects are reported, it will be clarified with the study participant whether further examinations or additional treatment is appropriate and the study participant will be motivated to make use of them.

f) Rationale for benefit-risk ratio

As described above, the risk for individual participants can be regarded as very low. Conversely, the benefit of the program is expected to be clinically meaningful. Therefore, the benefit-risk ratio is deemed to be positive.

g) Medical justifiability

This study is medically justifiable.

5. Objectives and hypotheses

a) Purpose, claims, effectiveness, safety

The digital health application *alivis* aims to narrow the gap between patients' need for effective treatment compared to the services available for patients with BPD. The aim of this RCT is to test the effectiveness of *alivis* in reducing BPD symptom severity. Moreover, intervention effects on several secondary endpoints, including depressive and anxiety symptoms, ~~mental~~ health-related quality of life, and social functioning will be examined. Testing of hypotheses will be performed in a sample of adult patients with BPD as defined in DSM-5.

b) Objectives

The primary objective of this trial is to evaluate the effectiveness of *alivis* in addition to TAU compared to TAU only.

c) Scientific justification and clinical relevance

An effect of Cohen's *d* = 0.27 has been observed for a digital intervention for BPD that is based on ST only (27). Given that *alivis* consists of a combination of DBT, ST, ACT, and MSC and that participants will be closely guided during the trial, we expect the observed effect to be slightly larger and assume an effect size of *d* = 0.30. In order to obtain a power of 0.80, at a two-sided significance level of 0.05, each group should have a sample size of 176. Outpatient RCTs for BPD have an average dropout rate of approximately 25% (28,29). To compensate for dropouts, we thus aim to include and randomize N = 470 (2 X 235) participants with an allocation ratio of 1:1.

d) Primary and secondary hypotheses

~~The primary hypothesis is that receiving *alivis* in addition to TAU leads to a better reduction of BPD symptoms measured with BSL-23 at T1 (three months after the start of the intervention), compared to receiving TAU only. Secondary hypotheses are (i) intervention group participants will exhibit a better reduction of depressive symptoms at T1, compared to those in the control group; (ii) a better reduction of anxiety symptoms, (iii) reduced costs caused due to the participant's BPD, (iv) higher social and work-related functioning, (v) greater mental health-related quality of life, (vi) fewer BPD symptoms (regarding all 9 BPD criteria) measured with the Borderline Personality Disorder Checklist (BPD-CL), and (vii) higher patient activation compared to those in the control group at three months.~~

~~In addition, exploratory moderator analyses will be used to determine whether certain baseline variables have an influence on the effectiveness of *alivis.* The following variables will be recorded a priori: currently attending psychotherapy, currently taking psychotropic medication, childhood trauma, and BPD symptom severity.~~

Let the mean treatment difference be defined as μ (= *alivis* + TAU minus TAU only).

For the primary endpoint, the following two-sided hypothesis is planned to be tested.

- BPD symptoms (BSL-23) at T1

  - H0: μ = 0 points against HA: μ ≠ 0 points

For the confirmatory secondary endpoints, the following confirmatory one-sided hypotheses are planned to be tested.

- Depressive symptoms (PHQ-9) at T1

  - H0: $\mu = 0$ points against HA: $\mu \neq 0$ points

- Anxiety symptoms (GAD-7) at T1

  - H0: $\mu = 0$ points against HA: $\mu \neq 0$ points

- Costs (self-compiled cost questionnaire) at T1

  - H0: $\mu = 0$ € against HA: $\mu \neq 0$ €

- Social functioning (WSAS) at T1

  - H0: $\mu = 0$ points against HA: $\mu \neq 0$ points

- Health-related quality of life (AQoL-8D) at T1

  - H0: $\mu = 0$ points against HA: $\mu \neq 0$ points

- Patient activation (PAM-13) at T1

  - H0: $\mu = 0$ points against HA: $\mu \neq 0$ points

Operationally, the hypotheses will be evaluated by two-sided tests at the 5% significance level. This is equivalent to using a one-sided *p*-value (nominal $\alpha = 0.025$) and a one-sided 2.5% overall significance level.

e) Risks and anticipated adverse device effects

See section 4. b-f.

6. Design

6.1 General

This study is a pragmatic, prospective RCT with two arms (30). As *alivis* already holds a CE-marking, this trial will be a post-market clinical follow-up study in line with the existing intended purpose. The trial will include a control group which receives TAU ~~in addition to publicly available information material on BPD (Links to https://borderline-info.de/ and https://www.borderline-netzwerk.info/),~~ and an intervention group which receives *alivis* in addition to TAU. The effectiveness of *alivis* will be tested by comparing the effects between both groups at three months (T1; primary hypothesis). Although participants will have access to *alivis* for 12 months in total, the relevant content of the intervention should be already covered after three months, with the remaining time mainly serving as refreshers and for stabilization (27). Therefore, we already expect effects to be present after three months.

Recruitment of patients will be conducted via online advertisement (e.g., Google Ads campaigns). Participants will be routed to a linked study website providing information about the trial and details about participation. Using a contact form on the website, participants will be able to indicate interest in participation whereupon they will receive an email with a link to LimeSurvey, a secure online survey tool. At the beginning of the survey, further information about participation will be provided and electronic informed consent will be obtained. Participants will be informed about the option to receive personal explanation and answers to further questions via telephone or email. Moreover, participants will be informed of their right to withdraw from the study at any time without negative consequences.

After electronic informed consent, participants will be asked to fill out an online demographic questionnaire followed by the set of questionnaires to collect baseline data (T0; see section 6.1.d) for further details). A likely diagnosis of BPD will be determined via the Borderline Symptom List-23 (BSL-23). Participants reaching a cut-off of ≥ 1.07 will be invited to a telephone interview which will serve to secure the diagnosis of BPD (via SCID-5-PD) and assess psychiatric comorbidities, rule out any comorbid diagnosis of substance use disorder or psychotic disorder, as well as an acute decompensation of mental health symptoms (via Mini-DIPS). Note that substance use and psychotic disorders were merely determined as exclusion criteria in face of the risk of non-adherence to complete questionnaires, but are not considered contraindications for the usage of *alivis*. In addition, consent to the emergency plan for suicidal crises will be obtained. This emergency plan requires that participants contact their physician/psychotherapist or the local emergency number in case of a suicidal crisis. The plan is established collaboratively with the participant at the end of the telephone interview. If inclusion and exclusion criteria are met, participants will be allocated to one of the two study groups by a computerized randomization procedure (for details, see section 6.1 b). Participants allocated to the intervention group will receive registration information for *alivis*, patients allocated to the control group will be notified ~~receive publicly available information material on BPD (Links to https://borderline-info.de/ and https://www.borderline-netzwerk.info/) and the information~~ that they will receive access to *alivis* in twelve months, if they wish. All of the following measurements are carried out exclusively via online questionnaires. After three months (T1; primary timepoint for evaluation of effectiveness) participants of both groups will be asked to

complete an online questionnaire. Although participants receive access to *alivis* for 12 months, we expect highest usage of the intervention during the first months, as was the case for our intervention *priovi* (27; as well as still unpublished data from a follow-up RCT). Effects of *alivis* should therefore already be seen after three months. Additionally, patients will be surveyed after six and 12 months (T2 and T3; evaluating stability of effects). As an incentive, participants will receive a 10€ voucher from www.wunschgutschein.de per assessment (T1, T2, and T3; maximum 3×10€ = 30€). All participants (from the intervention and control group) will receive this compensation if they complete the questionnaires and interview, and, in particular, the compensation in the intervention group will not depend on the actual use of *alivis*.

Contact to the participants will be established by a study director. Technical and content support for the intervention is offered via a central hotline, which is managed by a staff member who is not involved in the evaluation of the study. Participants in the intervention group will be contacted by email and/or phone if they have not redeemed their voucher for access to *alivis* 7 days after randomization. For a flow chart of the trial design, see Figure 1.

The present RCT is designed to compare *alivis* in addition to TAU with TAU only. The required initial interview to confirm diagnosis of BPD maximizes the probability that *alivis* will be tested in the appropriate intended target group.

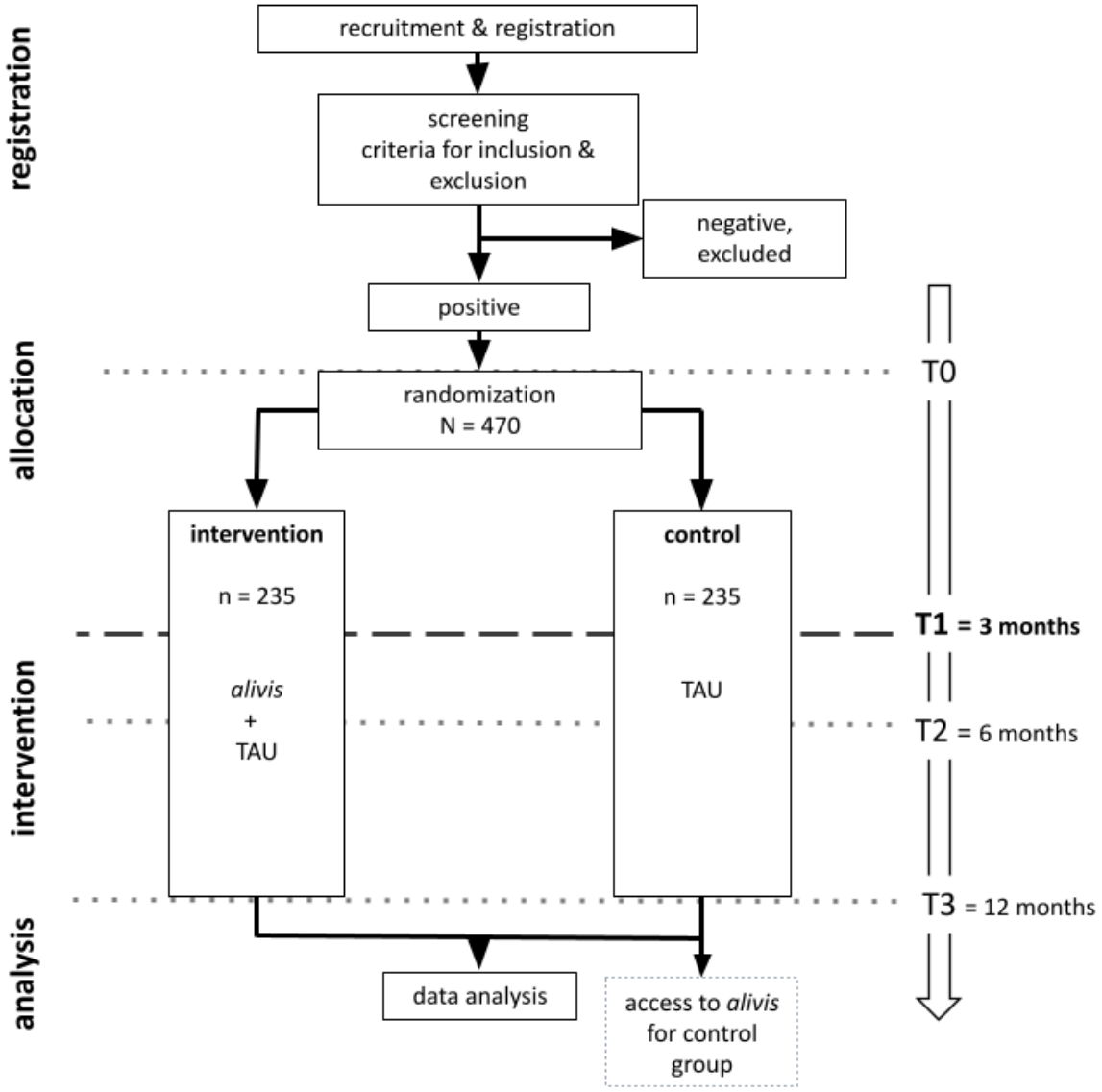

Figure 1| Flow Chart of Trial Design

The primary time point for analysis of effectiveness of the intervention will be three months after inclusion (T1). Other timepoints of data acquisition: T2 (Follow-up) = six months after inclusion, T3 (Follow-up) = 12 months after inclusion.

a) Description of the design type of clinical investigation to be performed

- prospective
- randomized (~~simple randomization;~~ 1:1, in variable blocks of 4, 8, or 16 participants each)
- two arms
- controlled (against TAU)

- online (no traditional investigation site)

b) Measures against bias

After successful screening of inclusion and exclusion criteria participants will automatically be randomized to one of two study groups (control group or intervention group) based on an algorithm.

c) Primary and secondary endpoints

Primary Endpoint: Severity of borderline symptoms at T1, assessed via the Borderline Symptoms List 23 (BSL-23).

The BSL-23 is a 23-item PROM with good psychometric properties that was validated and tested for reliability in a representative German sample (test–retest reliability r = .82, p < 0.0001; α = 0.94-0.97; high correlation of total score with general psychological burden and depression (53)) to assess the typical symptomatology and severity of BPD (54). It refers to the last week and has a range from 0 = “not at all” to 4 = “very strong”. Its single factor structure was optimized to reflect levels and changes in severity of BPD-symptomatology based on a mean score (32).

Responders will be defined by a change of borderline symptom severity on the BSL-23 total score following both conditions: (i) reaching the cut-off of 15% of the range of the scale, i.e. improvement of 0.6 points and (ii) a change of BSL-23-total score towards a less severe grade from T0 to T1. Deteriorators will be defined accordingly by both, (i) reaching a deterioration of 0.6 points and (ii) a change of BSL-23-total score towards a more severe grade from T0 to T1. Non-responders will be defined as no change of the borderline severity grade, even if a change of 0.6 points was observed.

~~The BSL-23 is a BPD-specific PROM with good psychometric properties that was optimized to reflect levels and changes in severity of BPD-symptomatology based on a mean score (31,32).~~

~~In addition to statistical significance determined by ANCOVA, which serves as the primary analysis (see section 7), a responder analysis will be performed to assess the clinical relevance of effects of *alivis* on the severity of BPD symptoms. Responders will be defined by a change of borderline symptom severity on the BSL-23 total score following both conditions: (i) reaching the psychometric criterion of a reliable change index (RCI) (33) and (ii) a change of BSL-23-total score towards a less severe grade from T0 to T1. Deteriorators will be defined accordingly by both, (i) reaching RCI and (ii) a change of BSL-23-total score towards a more severe grade from T0 to T1.~~

~~Non-responders will be defined as no change of the borderline severity grade, even if the RCI was reached.~~

Secondary Endpoints (note that the secondary endpoints are listed in priority order for the planned gatekeeping testing strategy, cf. 7.k):

Depression at T1, assessed via the Patient Health Questionnaire (PHQ-9)

The PHQ-9 is the 9-item depression module from the full PHQ with comparable sensitivity and specificity, and includes the 9 criteria upon which the diagnosis of DSM-IV depressive disorders is based. Rating will be done on a 4-point Likert scale ranging 0 = “not at all” to 3 = “nearly every day”. As a severity measure, scores range from 0 to 27 and represent: mild (<5), moderate (5-9), moderately severe (10-14), and severe depression (≥15). As a diagnostic instrument, major depression is diagnosed if 5 or more of the 9 depressive symptom criteria have been present at least “more than half the days” in the past 2 weeks, and 1 of the symptoms is depressed mood or anhedonia. “Other” depression is diagnosed if 2, 3, or 4 depressive symptoms have been present at least “more than half the days” in the past 2 weeks, and 1 of the symptoms is depressed mood or anhedonia (55). According to several studies, the German version can be considered reliable regarding psychometric standards (34–36). A reduction of 5 points will be considered as MCID (34). Responders will be defined as participants reaching this difference from T0 to T1. The proportion of responders between groups will be compared using χ^2 tests.

~~The PHQ-9 is a well-established and validated PROM in German language (34–36), to assess the 9 criteria upon which the diagnosis of DSM-IV depressive disorders is based.~~

~~A reduction of 5 points will be considered as minimal clinically important difference (MCID) (34). Responders will be defined as participants reaching this difference from T0 to T1. The proportion of responders between groups will be compared using χ^2 tests.~~

Anxiety at T1, assessed via the Generalized Anxiety Disorder Assessment (GAD-7)

This self-administered patient questionnaire is used as a screening tool and severity measure for generalized anxiety disorder (GAD) (37). Studies report good reliability, as well as criterion, construct, factorial, and procedural validity

(38,39). The GAD-7 is scored on a Likert scale ranging from 0 = “not at all” via 1 = “several days” and 2 = “more than half the days” to 3 = “nearly every day”, yielding a sum score ranging from 0-21. Scores of 5, 10, and 15 are taken as the cut-off points for mild, moderate and severe anxiety, respectively. When used as a screening tool, further evaluation is recommended when the score is 10 or greater.

~~The GAD-7 is a self-administered patient questionnaire used as a screening tool and severity measure for generalized anxiety disorder (GAD) (37). Studies report good reliability, as well as criterion, construct, factorial, and procedural validity (38,39).~~

Costs caused due to the patient’s BPD

Costs caused due to BPD will be assessed with a self-compiled instrument assessing inpatient and outpatient treatment, support from friends, family and professional services, contacts with members of the judicial authorities and public security, medication, sick leave, and physician/therapist visits during work time.

Social Functioning at T1, assessed via the Work and Social Adjustment Scale (WSAS).

The WSAS is a 5-item self-report scale to measure social functioning in regard to physical, mental and social health as well as age group referenced competence for performance. The PROM has good psychometric properties with good criterion validity, good sensitivity and strong internal consistency (α = 0.89) (40). Individual items address work, home management, social leisure, private leisure and relationships. Each item is rated on a 9-point Likert scale from 0 = “not at all impaired” to 8 = “very severely impaired”. The total score has a range of 0-40, with lower scores denoting less disability.

~~The WSAS is a scale to measure social functioning in regard to physical, mental, and social health as well as age group-referenced competence for performance. The PROM is validated for a representative German sample (40).~~

Health-Related Quality of Life at T1, assessed via the AQoL-8D score on the Assessment of Quality of Life-8 Dimensions (AQoL-8D), German version

The AQoL-8D is a health-related quality-of-life questionnaire consisting of 35 items forming eight health dimensions:

independent living, happiness, mental health, coping, relationships, self worth, pain, senses. Validation of the AQoL-8D assessing health-related quality of life showed good psychometric properties in a German patient sample, including excellent reliability (Cronbach's α = 0.96) and construct validity (strong correlation with the SF-36, r = .81) (41).

~~The AQol-8D is a self-administered questionnaire to measure quality of life in 8 dimensions (independent living, happiness, mental health, coping, relationships, self worth, pain, senses) which has demonstrated good psychometric properties in a German sample (41).~~

~~Severity of borderline symptoms at T1, assessed via the Borderline Personality Disorder Checklist (BPD-CL).~~

~~The BPD-CL is a DSM-IV based self-report instrument to assess BPD symptoms in the previous month (42). Importantly, in contrast to the BSL-23, the BPD-CL explicitly assesses all nine DSM-5 criteria.~~

Patient activation at T1, assessed via the Patient Activation Measure (PAM-13)

The PAM13 assesses patients' active participation in their medical care using 13 items (43,44). Items are answered using a Likert scale ranging from 1 = "strongly disagree" to 4 = "agree strongly", yielding a total score between 13 and 52. The German version of the PAM13, the PAM13-G, is validated and demonstrates good psychometric properties, including a good internal consistency of Cronbach's α = 0.84 (44). An improvement of 4 points on the PAM-13 is considered an MCID (56). Therefore, responders will be defined as patients who improve by at least 4 points on the PAM-13 from T0 to T2. The proportion of responders between groups will be compared using χ^2 tests.

~~The PAM-13 is a 13-item instrument assessing patients' active participation in their medical care (43). The German version of the PAM-13, the PAM-13-G, is validated and demonstrates good psychometric properties (44).~~

Exploratory Endpoints: Assessments listed in "Secondary endpoints" at T2/T3

Sociodemographic Variables:

- Age
- Gender

- Sex
- Education
- Employment Status
- Family Situation
- Language ability
- Ethnicity

Clinical Variables:

Assessed at T0 only:

- First diagnosis (date)
- Inclusion diagnosis (BPD) using the respective section of the SCID-5-PD interview (45)
- Psychiatric comorbidities (via Mini-DIPS) (46)
- Psychotherapy (past, type)

Assessed at all timepoints (T0-T3):

- Medications (name of medication, dose, frequency)
- Psychotherapy (current, type)
- Childhood trauma (via Childhood Trauma Questionnaire (CTQ; 47,48))
- Number of BPD-related hospitalizations (T0: past 12 months, T1-T2: past 3 months, T3: past 6 months)
- Number of hospitalizations due to other reasons (T0: past 12 months, T1-T2: past 3 months, T3: past 6 months)
- Number of days in sick leave (past 3 months)
- Number of days in sick pay (past 3 months)
- weight and height (current)
- Use of any other online program for BPD (T0: lifetime, T1-T2: past 3 months, T3: past 6 months; name)

Treatment satisfaction:

- Program Evaluation of the Program (NPS, Net Promoter Score) (49)
- Questionnaire on treatment satisfaction (ZUF-8; 50)
- subjective improvement of BPD symptoms and quality of life

Exploratory Variables:

- Modified version of Working Alliance Inventory WAI-I (51)

Usage monitoring (It should be noted that these data reflect only measurable engagement with *alivis* itself and do not capture how long a person has engaged with its content outside *alivis*, e.g. short text messages sent by *alivis* or PDF-materials printed from *alivis*)**:**

- Number of chats completed
- Number of days active
- Time spent in the program

Safety ~~and usage~~ monitoring:

- Negative Effects Questionnaire (NEQ; (52))
- Respective user feedback via email, telephone or contact form on the *alivis* trial website
- Suicide attempts (T0-T2: past 3 months, T3: past 6 months; main safety outcome)
- other life-threatening events (e.g., non-suicidal self-injury, drug intoxication, accidents)
- Unplanned and emergency ~~outpatient and~~ inpatient treatments (T0-T2: past 3 months, T3: past 6 months)
- Monitoring of adverse events throughout the trial (serious adverse events will be reviewed by a Safety Officer/ PRRC)
- ~~Usage~~

d) Methods and timing

~~*Severity of Borderline Symptoms*~~
~~The total score of the Borderline Symptoms List 23 (BSL-23)~~

~~The BSL-23 is a 23-item PROM with good psychometric properties that was validated and tested for reliability in a representative German sample (test–retest reliability r = .82, p < 0.0001; α = 0.94-0.97; high correlation of total score with general psychological burden and depression (53)) to assess the typical symptomatology and severity of BPD (54). It refers to the last week and has a range from 0 = "not at all" to 4 = "very strong". Its single factor structure was optimized to reflect levels and changes in severity of BPD-symptomatology based on a mean score (32).~~

~~Responders will be defined by a change of borderline symptom severity on the BSL-23 total score following both conditions: (i) reaching the psychometric criterion of a reliable change index (RCI) (33) and (ii) a change of BSL-23-total score towards a less severe grade from T0 to T1. Deteriorators will be defined accordingly by both, (i) reaching RCI and (ii) a change of BSL-23 total score towards a more severe grade from T0 to T1. Non-responders will be defined as no change of the borderline severity grade, even if the RCI was reached.~~

~~*Depression*~~
~~Total score of Patient Health Questionnaire (PHQ-9)~~

~~The PHQ-9 is the 9-item depression module from the full PHQ with comparable sensitivity and specificity, and includes the 9 criteria upon which the diagnosis of DSM-IV depressive disorders is based. Rating will be done on a 4-point Likert scale ranging 0 = "not at all" to 3 = "nearly every day". As a severity measure, scores range from 0 to 27 and represent: mild (<5), moderate (5-9), moderately severe (10-14), and severe depression (≥15). As a diagnostic instrument, major depression is diagnosed if 5 or more of the 9 depressive symptom criteria have been present at least "more than half the days" in the past 2 weeks, and 1 of the~~

~~symptoms is depressed mood or anhedonia. "Other" depression is diagnosed if 2, 3, or 4 depressive symptoms have been present at least "more than half the days" in the past 2 weeks, and 1 of the symptoms is depressed mood or anhedonia (55). According to several studies, the German version can be considered reliable regarding psychometric standards (34–36). A reduction of ≥ 5 points will be considered as MCID (34). Responders will be defined as participants reaching this difference from T0 to T1. The proportion of responders between groups will be compared using χ^2 tests.~~

~~*Anxiety*~~
~~Total score of Generalized Anxiety Disorder Assessment (GAD-7)~~

~~This self-administered patient questionnaire is used as a screening tool and severity measure for generalized anxiety disorder (GAD) (37). Studies report good reliability, as well as criterion, construct, factorial, and procedural validity (38,39). The GAD-7 is scored on a Likert scale ranging from 0 = "not at all" via 1 = "several days" and 2 = "more than half the days" to 3 = "nearly every day", yielding a sum score ranging from 0-21. Scores of 5, 10, and 15 are taken as the cut-off points for mild, moderate and severe anxiety, respectively. When used as a screening tool, further evaluation is recommended when the score is 10 or greater.~~

~~*Costs caused due to the patient's BPD*~~
~~Assessed with self-compiled questionnaire~~

~~Costs caused due to BPD will be assessed with a self-compiled instrument assessing inpatient and outpatient treatment, support from friends, family and professional services, contacts with members of the judicial authorities and public security, medication, sick leave, and physician/therapist visits during work time.~~

~~*Social Functioning*~~
~~Total score of Work and Social Adjustment Scale (WSAS) - German version~~

~~The WSAS is a 5-item self-report scale to measure social functioning in regard to physical, mental and social health as well as age group referenced competence for performance. The PROM has good psychometric properties with good criterion validity, good sensitivity and strong internal consistency (α = 0.89) (40). Individual items address work, home management, social leisure, private leisure and relationships. Each item is rated on a 9-point Likert scale from 0 = "not at all impaired" to 8 = "very severely impaired". The total score has a range of 0-40, with lower scores denoting less disability.~~

~~*Health-Related Quality of Life*~~
~~Total score of the AQoL-8D - German version~~

~~The AQoL-8D is a health related quality of life questionnaire consisting of 35 items forming eight health dimensions: independent living, happiness, mental health, coping, relationships, self worth, pain, senses. Validation of the AQoL-8D assessing health-related quality of life showed good psychometric properties in a German patient sample, including excellent reliability (Cronbach's α = 0.96) and construct validity (strong correlation with the SF-36, r = .81) (41).~~

~~*Severity of Borderline Symptoms*~~
~~Total score of the Borderline Personality Disorder Checklist (BPD-CL)~~

~~The BPD-CL is a DSM-IV/5 based self-report instrument to assess BPD symptoms in the previous month (42). It consists of 47 items that can be grouped according to the DSM-IV/5 criteria and that are rated on a 5-point Likert scale from 1 ("not at all") to 5 ("extremely").The original Dutch version of the BPD-CL has been validated in BPD patients and shows very good psychometric properties (Chronbach's α = 0.92). A validation of the German version is currently in press.~~

~~*Patient Activation*~~
~~Total score of the Patient Activation Measure (PAM-13)~~

~~The PAM13 assesses patients' active participation in their medical care using 13 items (43,44). Items are answered using a Likert scale ranging from 1 = "strongly disagree" to 4 = "agree strongly", yielding a total score between 13 and 52. The German version of the PAM13, the PAM13-G, is validated and demonstrates good psychometric properties, including a good internal consistency of Cronbach's α = 0.84 (44). An improvement of 4 points on the PAM-13 is considered an MCID (56). Therefore, responders will be defined as patients who improve by at least 4 points on the PAM-13 from T0 to T2. The proportion of responders between groups will be compared using χ^2 tests.~~

Table 1| Chronological Sequence of the Trial

	Recruitment	Allocation	Post Allocation	Follow-up
Timepoint	T0		T1	T2, T3
Screening				
Test of Inclusion Criteria	x			
Test of Exclusion Criteria	x			
Sociodemographic Variables	x			
Clinical Variables	x		x	x
Consent	x			
Randomization		x		
Intervention				
Intervention group: *alivis* + TAU Control group: TAU~~+ publicly available information material on BPD~~		♦	♦	♦
Endpoints				
BPD symptom severity (BSL-23)	x		x	x
Depression (PHQ-9)	x		x	x
General Anxiety (GAD-7)	x		x	x
Costs questionnaire	x		x	x
Social Functioning (WSAS)	x		x	x

Health-Related Quality of life (AQoL-8D)	x	x	x
~~BPD symptom severity (BPD-CL)~~	~~x~~	~~x~~	~~x~~
Patient activation (PAM-13)	x	x	x
Clinical Course	x	x	x
Net Promoter Score (NPS)*		x	x
Subjective improvement		x	x
Usage of the Program*		x	x
Exploratory Variables	x	x	x
Adverse Events (incl. NEQ)		x	x

T0: Before start of Intervention (baseline), T1: 3 months post allocation, Follow-up: T2: 6 months post allocation, T3 = 12 months post allocation. Black diamonds indicate access to *alivis*. *only assessed in the intervention group.

The primary time point for collecting data on the effectiveness of the intervention will be 3 months post allocation (T1). Six months post allocation (T2) and 12 months post allocation (T3) will be other time points for data collection, which will be treated as follow-ups to test the stability of effects. A first analysis is planned after the last patient completes T1. The complete data set will be open for analysis after the last patient completes T3. Participants will receive a 10€ voucher from www.wunschgutschein.de as an incentive for participating in T1, T2 and T3 each (max. 30€). All participants (from the intervention and control group) will receive this compensation if they complete the follow-up questionnaires, and, in particular, the compensation in the intervention group will not depend on the actual use of *alivis*. Details of data collection and analysis are summarized in Figure 1 and Table 1. The expected total duration of the study for each participant is 14 months (1 month pre-assessment, 12 months intervention phase, up to 1 month reminders for the last assessment). The expected total duration of the entire study including recruitment is estimated at 24 months.

e) Equipment for assessing the clinical investigation variables

Equipment is limited to online surveys of participants using a German provider for surveys including clinical trials, LimeSurvey. PROMs are listed under 6.1 c-d.

f) Replacement of subjects

Not applicable.

g) Investigation sites

The study is designed as an online trial; there will be no traditional physical investigation site(s). See 1.4 b and 6.1 e.

h) Completion of the clinical investigation

Data acquisition of the trial will be completed 12 to 13 months after the last patient in (up to one month buffer for reminders to complete T3). Complete analyses of the dataset will denote completion of the investigation.

6.2 Investigational device and comparator

a) Exposure to the investigational device or comparator

Participants allocated to the intervention group will be provided with access to the program *alivis*, which is to be used additionally to the care provided by their attending practitioner. The program can be used on conventional web-browsers on desktop PCs, tablets and smartphones. Users (patients randomized to the intervention group) receive access to the program for 12 months by 12-digit personal codes (vouchers), provided by the developer. After initial registration and consent to the general terms and conditions, users can log into the program using their email address and personal password at any time. The program is set up as an adaptive- and responsive-web-design pulling a layout template for a specific device, adapting to dimension and resolution of the display used. This results in high flexibility of usage regardless of the available hardware.

An essential element of the program is the presentation of content through simulated dialogues, which are performed by interaction of the user with the software acting as a virtual expert. Users navigate through the modules by reading short texts and reacting to the information by continuously choosing one or multiple predefined options of response. Based on this input, the program subsequently adjusts the content. In this process, preferences and needs of the user are matched with regard to content and style. Brief text passages are accompanied by illustrations, audio recordings, worksheets and personalized summaries (pdf documents). Chats are presented in consecutive order and build on previous content. Moreover, optional daily short text messages (SMS) are sent as reminders aimed to motivate and support users in their daily lives. The program also offers a symptom tracking function; that is, users are invited to complete embedded questionnaires at regular intervals in order to self-monitor changes over time. Text and graphical feedback are provided automatically after users complete the questionnaires embedded in the program. Exercises that the user experiences as useful can be saved in a toolbox and practiced again in a ‘practice corner’. A crisis module specifically aims at supporting users during difficult situations in daily life.

alivis is provided in addition to the care provided by the participants’ attending practitioner (TAU). This may comprise any kind of treatment prescribed or recommended by a healthcare professional, including (but not limited to) pharmacotherapy, rehabilitation, psychotherapy, etc., as well as no treatment at all.

Participants in the control condition receive access to only TAU. After 12 months (T3), they have the option to receive access to *alivis*.

b) Other medical devices or medication

Not applicable.

c) Number of investigational devices

No additional investigational device (in addition to *alivis*) will be used in this trial.

6.3 Subjects

a) Inclusion criteria

- male, female, non-binary
- age 18-65
- diagnosis of BPD (telephone interview via SCID-5-PD (45))
- borderline severity score (cut-off) of ≥ 1.07 on the BSL-23
- Stable treatment (e.g., psychotherapy, medication, no treatment~~,…~~) for at least 30 days at the time of inclusion
- consent to emergency plan for suicidal crises
- consent to participation
- sufficient knowledge of the German language

b) Exclusion criteria

- Plans to change ~~in~~ treatment (e.g., psychotherapy, medication~~,…~~) in the upcoming 3 months after inclusion
- Comorbid diagnosis of substance use disorder
- Lifetime diagnosis of psychotic disorder like schizophrenia or schizoaffective disorder (except non-transitory paranoid ideas that can be concomitant with BPS and in which the ability to test reality is mostly preserved)
- Diagnosis of a physical condition that can cause serious psychiatric symptoms
- Acute decompensation of mental health symptoms, e.g. acute manic state or acute suicidality
- BMI <15
- current pychiatric day-care or inpatient treatment
- Prior use of *priovi*

c) Criteria and procedures for subject withdrawal or lost to follow-up

1) Withdrawal of a subject or stop of use

Participants will be informed of their right to withdraw from the study at any time without negative consequences. Test subjects will not be included in the clinical trial (not randomized) if it was not possible to ascertain baseline variables (T0). There is no provision for withdrawal of follow-up examinations.

2) Tracing of subjects lost to follow-up

At prespecified points in the course of the study, participants whose response to a survey is still outstanding will be reminded by email and/or phone.

Subsequent replacement of test subjects who evade follow-up examinations is not intended. Missing data points will be imputed by applying multiple imputation (cf. section 7. m). Possible reasons for being lost to follow-up include but are not limited to no further need for a treatment (known as “good enough effect” (57,58)), lack of positive effects of the treatment, or loss of interest among control group participants.

3) Replacement of subjects

Following standards for RCTs there will be no replacement of participants.

d) Point of enrolment

With randomization and allocation to a study group the participants are enrolled in the trial.

e) Point of randomization

After informed consent is obtained, patients interested in participation will be asked to fill in an online demographic questionnaire followed by a set of questionnaires to collect baseline data (T0). After initial data acquisition and screening for inclusion criteria, patients will be asked to take part in an initial telephone interview to conduct and determine the diagnosis of BPD, rule out any primary diagnosis of substance use disorder or psychotic disorder or acute decompensation of mental health, and to obtain consent to the emergency plan for suicidal crises. In case of a positive screening process regarding inclusion and exclusion criteria, participants will be allocated to a study group by randomization procedure. For further information regarding point of time see Table 1.

f) Total expected duration

Expected total duration of the entire study including recruitment is estimated as 24 months.

g) Expected duration for each subject

Expected total duration of the study for each participant will be up to 14 months (up to 1 month pre-assessment, 12 months intervention and follow-up phase, up to 1 month reminders for the last assessment).

h) Number of subjects

N = 470

i) Enrolment period

The enrollment period is estimated as ten months.

j) Relationship of investigation population to target population

The pragmatic RCT design, which evaluates the intervention in a setting in which it is also to be used, and the small number of exclusion criteria ensure that the test population largely corresponds to the target population of *alivis*. In addition, the required initial clinical interview contributes to the fact that *alivis* is only tested in the intended target group.

k) Vulnerable, pregnant, and breastfeeding population

Pregnancy or breastfeeding are no contraindications for the use of *alivis*.

6.4 Procedures

a) Procedures during the clinical investigation

Clinical investigation-related procedures will be:

Screening of inclusion/exclusion criteria and assessment of baseline data via online survey and telephone calls using the above itemized PROMs for baseline measurement of primary and secondary endpoints, respectively (6.1 c)-d)). The baseline assessment will be completed via an online survey on LimeSurvey. Specifically, secondary endpoints and sociodemographic / clinical variables will be assessed, and a likely diagnosis of BPD will be determined via the BSL-23.

Participants reaching a cut-off of ≥ 1.07, are at least 18 years old, do not have any physical condition that can cause severe psychiatric symptoms, have not used the digital intervention *priovi* before, and have sufficient knowledge of the German language will be invited to schedule an appointment for a telephone call. A telephone interview will then serve to secure the diagnosis of BPD (via SCID-5-PD) and assess psychiatric comorbidities, rule out any comorbid diagnosis of substance use disorder or psychotic disorder, as well as an acute decompensation of mental health symptoms (via Mini-DIPS), and obtain consent to the emergency plan for suicidal crises.

All primary and secondary endpoints will be part of the data assessment after 3, 6 and 12 months as well, assessed via an online survey, see Table 1 for details.

During the study period, the study team may contact participants to remind them of outstanding surveys or to ensure correct technical function of *alivis*, as appropriate.

b) Activities performed by sponsor representatives

- Coordination and trial management, online-data acquisition and telephone interviews
- Provision of the software
- Development, programming and testing of the survey instruments
- Development of work instructions for the implementation of the measures carried out in Figure 1 (including training and monitoring of employees)
- Planning and implementation of patient recruitment
- Regular follow-up meetings (preferably virtual) to monitor project progress
- Examination and evaluation of reports of possible adverse effects
- Data analysis

c) Factors compromising outcome or interpretation of results

The outcome of the study may be influenced by a number of confounding factors (e.g., age, gender, therapy, etc.). Randomization of participants to the intervention or control group ensures approximately equal distribution in both groups, so that any differences between groups can be attributed to the intervention. Potential differences in baseline values in the outcome variables of interest will be controlled for by including them as covariates in analyses of covariance (ANCOVA).

d) Methods for addressing these factors

See section 6.4 c.

e) Follow-up period for clinical performance, effectiveness or safety

The follow-up periods of three months (primary timepoint for assessment of effectiveness), six months and 12 months (for stability of effects) have been shown to be valid and relevant periods for treatment of BPD-patients with unguided internet-based self-management interventions (25,27).

f) Specific medical care provided following the clinical investigation

Not applicable. Participants have access to routine care by the attending health care professionals over the course of the study.

g) Recommended follow-up for the subjects

Not applicable.

h) Final disposition or potential future use of samples obtained from subjects

Not applicable.

6.5 Monitoring plan

Documented monitoring visits will be conducted before, during (twice) and after the trial (close-out visit) by the sponsor to ensure adherence to the study protocol. The following items will be monitored during the audits: (i) presence of approval by ethical review board, (ii) qualification of investigators, (iii) current status of recruitment and participant flow, (iv) adherence to study protocol (e.g., presence of informed consent, correct application of inclusion and exclusion criteria, allocation to correct intervention, usage of intervention) and (v) correctness of data entries and consistency with the source documents.

7. Statistical design and analysis

All analyses and imputation procedures will be performed using standard statistical software such as *R* (59) or *SPSS*.

a) Analysis population

In line with recommendations of the CONSORT eHealth statement, we will conduct both intention-to-treat (ITT) and per-protocol (PP) analyses (60–62). For PP-analyses, the dataset will be filtered based on the variable “usage time”. Individuals in the intervention group who did not use *alivis* for at least 4 times on 4 different days will be excluded from the PP dataset. Additionally, we will exclude participants from both groups who reported using other digital health interventions for BPD for the relevant follow-up period.

b) Descriptive statistics of baseline data, treatments, safety data

Descriptive statistics will include mean value and standard deviation (or median, min, max and quartiles as appropriate) for continuous data and absolute numbers and percentages for categorical data. These will be presented separately for the intervention and control group at baseline.

c) Analytical procedures and measures of precision

The Principal Investigator will receive access to all data prior to analysis and will remain blinded to group assignment until the end of the analysis of the primary outcome and main safety outcome (suicide attempts).

Analysis of effectiveness of the intervention in addition to TAU vs. TAU will be performed by ANCOVA of the primary endpoint and all secondary endpoints (tested in sequential order in a gatekeeping testing strategy, see section 7. k), in which the posttreatment scores at T1 will be compared between treatment groups (intervention group vs. control group), using the baseline scores of the respective outcome as a covariate. Treatment effects, i.e., the difference in posttreatment scores, will be reported on the original scale, along with the 95%-CI. In addition, Cohen’s d (calculated as between-group difference divided by the pooled standard deviation) will be used as a standardized effect size to quantify differences in posttreatment outcomes. Tests of prolonged treatment effects at T2 and T3 will be performed analogously with baseline as covariate. The ITT analyses will comprise all randomized participants, with imputed outcome values as described in section 7. m.

Analysis of binary or count outcomes (such as medication or number of hospitalizations) will be conducted based on non-responder imputed data in the form of χ^2-tests and Poisson regression, as appropriate, to examine between-group effects at T1, and analogously for T2 and T3.

The primary analysis will be performed as an ITT analysis with multiple imputation under ‘missing at random’ (MAR) assumption. In addition, a conservative sensitivity analysis based on reference-based multiple imputation (J2R imputation) will be calculated (63).

An exploratory PP analysis will be conducted (61,62). For PP analyses, the dataset will be filtered based on the variable “usage time”. Individuals in the intervention group who did not use *alivis* for at least 4 times on 4 different days will be excluded

from the PP dataset (62). Additionally, we will exclude participants from both groups who reported using other digital health interventions (e.g., DiGAs, apps, online programs) for BPD for the relevant follow-up period.

Measures of accuracy will be *p*-value [significance level (α) < 0.05] and the corresponding 95% confidence interval.

Moreover, responder analyses will be conducted. Unless a specific MCID is specified for an endpoint in section 6.1d), responders will be defined by reaching the cut-off of 15% of the range of the scale (64). ~~the reliable change index (RCI; 33) will be used to identify responders to treatment in patients with complete observations. The RCI is calculated as the ratio of the difference between pre- and post-scores of an individual participant (numerator) and the standard error of measurement of the difference (denominator). RCI scores larger than 1.96 indicate that it is unlikely that the posttest score is not reflecting real change (p < .05), thus indicating that the participant is a responder (33).~~ If a specific MCID is specified for an endpoint, responder analyses will instead be based on that value. Responders will then be defined as participants reaching this difference from T0 to T1. Additionally, exploratory responder analyses will be conducted for each endpoint, where response is defined as 50% improvement since baseline. The proportion of responders between groups will be compared using χ^2 tests. Moreover, the odds ratio will be reported.

d) Significance level and power

significance level (α) = 0.05 (two-sided)
power = 0.80

e) Sample size

1) Clinical data on outcome variable and effect size

An effect of Cohen's *d* = 0.27 has been observed for a digital intervention for BPD that is based on ST only (27). Given that *alivis* consists of a combination of DBT, ST, ACT, and MSC and that participants will be closely guided during the trial, we expect the observed effect to be slightly larger and assume an effect size of *d* = 0.30. In order to obtain a power of 0.80, at a two-sided significance level of 0.05, each group should have a sample size of 176. Outpatient RCTs for BPD have an average dropout rate of approximately 25% (28,29). To compensate for dropouts, we thus aim to include and randomize N = 470 (2 X 235) participants with an allocation ratio of 1:1.

2) Expected outcomes across treatment groups

See 5. d.

3) Adjustments due to pre-planned interim analyses

An interim analysis is planned after three months (T1; primary time point). There will be no adjustments.

4) Effect size and non-inferiority margin

See 7. e 1).

5) Randomization allocation ratio

1:1, in variable blocks of 4, 8, or 16 participants each~~no block randomization, no stratification~~

6) Expected drop-out rate

25% (28,29).

f) Procedures to be performed by user and analysis

Not applicable.

g) Pass/fail criteria

Not applicable.

h) Interim analysis and criteria for termination

Dataset will be open for interim analysis after the last patient completed T1. Results of the interim analysis will have no consequences for further study conduct.

i) Management of bias

Accompanying clinical variables of the participants are recorded at baseline, post-treatment (T1) and follow-up (T2, T3). It is conceivable that differences in e.g., the concomitant therapy in both groups in the course of the study could influence the study result. The observation period is chosen so that both the intended and unexpected effects of the program can be assessed with validity.

j) Management of potential confounding factors

The result of the study could be influenced by a number of confounders (e.g., age, gender, therapy, etc.). By randomizing the participants to the intervention or control group, roughly equal distribution in both groups can be assured, so that possible differences between groups can be attributed to the intervention. Additionally, potential differences in baseline values in the outcome variables of interest will be controlled for by including them as covariates in ANCOVA.

k) Multiplicity control and adjustment of error probabilities

No adjustment of the significance level α of 0.05 (two-sided) given that a gatekeeping testing strategy will be applied as suggested by the FDA (65). The secondary endpoints (listed in section 6.1.c) are listed in priority order for that approach.

l) Subgroups for analysis

The following subgroup analyses are planned:

a) effectiveness of *alivis* depending on sex (male, female, intersex);
b) effectiveness of *alivis* depending on gender (male, female, diverse);
c) effectiveness of *alivis* in patients with concomitant psychotherapy at baseline compared to those without;
d) Effectiveness of *alivis* in patients who take psychotropic medication (ATC codes N05, N06) at baseline compared to those who do not;
e) Effectiveness of *alivis* in patients with changes in treatment (i.e., psychotherapy or regular psychotropic medication) between baseline and T1 vs. patients without changes in treatment;
f) Effectiveness of *alivis* in patients with previous diagnosis of BPD vs. in patients who were initially diagnosed with BPD as part of the study.

Results of these subgroup analyses will be visualized as a table and forest plot.

m) Missing, unused or spurious data, including drop-outs

In the ITT analysis, missing data points will be imputed using the respective variable values at baseline as well as group membership and other sociodemographic and clinical variables (~~such as~~ age, sex, education, employment, family status, psychotherapy at baseline, psychotherapy ever). The ITT analysis will be implemented following a computationally efficient implementation for bootstrapped maximum likelihood multiple imputation (67,68) by von Hippel and Bartlett (2021) using the *R* packages *bootImpute* (68) and *mice* (69). In detail, 1,000 bootstrap samples of the incomplete dataset will be generated for each outcome variable and then the relevant outcome variable will be imputed twice with the *mice* package with default settings (i.e., using predictive mean matching with a pool of 5 candidate values) as recommended.

n) Exploratory analysis and sensitivity analysis

Exploratory moderator analyses will determine the influence of certain baseline variables on the effectiveness of *alivis.* The following variables will be established a priori: currently attending psychotherapy, BPD symptoms (BSL-23), and patient activation (PAM-13).

Reference-based sensitivity analysis (‘jump to reference’ (63,68,70)) will be applied following procedures for the ITT-analysis, using an implementation for the *R* programming environment. Assumptions about the structure of missing data points will be tested in advance.o) Reporting of deviation(s) from original statistical analysis plan

If there are deviations from the original statistical planning, this deviation will be stated in the study register, study report and the publication as well.

p) Handling potential imbalance of numbers of subjects across investigation sites

Not applicable.

q) Strategy for pooling data

Not applicable.

r) Estimand strategy

The treatment policy estimand will be used to handle any potential intercurrent events. In this study, intercurrent events are defined as the initiation or discontinuation of psychotherapeutic or psychotropic treatment and the discontinuation of *alivis* usage for any reason in the intervention group. The treatment policy estimand evaluates the treatment effect for all randomized patients, irrespective of their use of *alivis* or specific elements of TAU.

The following estimand strategy attributes are defined:

- Handling of intercurrent events: intercurrent events are ignored and shown in the definition of the treatment
- Treatment: *alivis* + TAU + intercurrent events vs. TAU + intercurrent events

- Population: defined by inclusion and exclusion criteria; see sections 6.3a) and 6.3b)
- Variable: primary and secondary endpoints; see section 6.1c)
- Population-level summary: mean difference

8. Data management

a) Methods for data entry and collection

Data is collected using the online-survey provider LimeSurvey. The survey software is programmed in such a way that every possible answer (valid answer ranges) is predefined. There is a daily backup of the data. The data will be stored in pseudonymized form after the study has been completed. Personal data will be deleted after the purposes of the study according to the General Data Protection Regulation (GDPR).

b) CRF tracking, data review, database cleaning, and issuing/resolving data queries

See section 8. a.

c) Verification, validation, and securing of electronic clinical data systems

The development and the operation of the programs of the sponsor including *alivis* are secured according to an ISO 13485 and TÜV-Rheinland certified quality management system (QMS). This includes the verification, validation and backup of the sponsor's electronic data systems as well as supplier evaluation and the validation of the survey software.

d) Subject privacy

The names and contact information of participants will be shared only with the study manager. Separation of compromised information will be ensured through the procedure described in detail in section 6.1 b. All personnel will be instructed to keep patient information confidential. Presentation of data in lectures, seminars, and publications will be based solely on the summarized data (anonymized). Electronic trial data is later stored under a pseudonym, i.e., only in conjunction with the participant ID, without the possibility of tracing back to personal information. All data is stored in password-protected directories on secure servers that comply with the requirements of the GDPR.

Subjects are informed that anonymized data may be shared with researchers not involved in the current study who submit a relevant research proposal, in order to comply with the principles of open science.

e) Database locking and storage

The electronic storage of research data is pseudonymized i.e., only linked to a participant ID. All recordings are stored in encrypted files and on secure servers of the GDPR-compliant provider LimeSurvey and the sponsor. Personal data will only be stored for the purposes of the study and will be deleted upon completion of the clinical trial or expiry of the intended purpose, respectively.

f) Data retention

The electronic storage of research data will be pseudonymized for the purpose of the investigation. All recordings are stored in encrypted files and on secure servers of the survey provider LimeSurvey and GAIA AG. With completion of the clinical investigation and expiration of the purpose of data handling, all data will be anonymized and stored on servers of GAIA AG for 10 years.

g) Retention period

See section 8. f.

h) Other aspects of clinical quality assurance

See section 6.1 b.

9. Amendments to the CIP

Changes or additions to the CIP require the approval of the principal investigator and the sponsor. Consideration must be given to whether the change(s) in question are subject to the requirement to obtain a positive evaluation by the responsible ethics committee prior to implementation. In any case, the responsible ethics committee must be informed about minor changes (such as a name change) and, if necessary, an amendment must be requested. Depending on the nature of the change(s), it must also be decided whether relevant documents such as the patient information must be adapted accordingly. The study registry will be updated accordingly.

10. Deviations from clinical investigation plan

a) Statement - deviation from the CIP

It is hereby declared that the examiner performing the test is not permitted to deviate from the test plan during the course, analysis and publication of the data.

b) Recording, reporting, and analysing CIP deviations

Significant protocol deviations that have occurred unintentionally in the course of the clinical trial and at the same time a) represent a significant reduction in data quality and / or b) negatively affect the rights, safety and health of the included patient, will be reported to the ethics committee promptly after the protocol deviation becomes known.

c) Notification requirements and time frames

The following information must be communicated to the ethics committee:

- What was the type of the protocol violation?
- When did the protocol violation occur?
- Who was affected?
- What was / is being done to limit the damage incurred or to avoid repeated deviations of the same kind in the future?

d) Corrective/preventive actions and principal investigator disqualification criteria

The CIP is the decisive basis for carrying out the clinical trial. All employees involved in the study are bound by the protocol. This also applies to the principal investigator.

11. Device accountability

a) Accountability of investigational devices

Not applicable (this study represents a post marketing clinical follow up study in which *alivis* is tested in line with the existing Intended Purpose).

b) Safe return of potentially hazardous investigational devices

Not applicable.

12. Statements of compliance

a) Statement - Declaration of Helsinki

This clinical trial complies with the ethical principles of the Helsinki Declaration (WMA DECLARATION OF HELSINKI - ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS).

b) Statement - compliance with ISO 14155:2020 and any regional or national regulations

Compliance with ISO 14155:2020, the international standard and all regional or national regulations is hereby declared for the clinical trial presented.

c) Statement - required approval/favourable opinion from the EC/regulatory authority

It is hereby declared that the clinical investigation will not begin until the required approval/favourable opinion from the EC and regulatory authority have been obtained.

d) Statement - requirements imposed by the EC or regulatory authority

It is hereby declared that any additional requirements imposed by the EC or regulatory authority will be followed.

e) Statement - insurance for subjects

There is no test subject insurance. The participants are informed in the information sheet (“Probandeninformation”) that there is no test subject insurance for the study and that they are using the intervention program at their own risk.

f) Statement - financing/agreement between sponsor and investigation site(s)/investigator(s)

~~The PI will apply for funding at the Else Kröner-Fresnius-Stiftung, which has funded clinical studies in patients with BPD already in the past. In the case of a negative decision, alternative ways for funding may be considered. If no alternative funding can be obtained, t~~The study described will be financed exclusively from the participating institutions' own funds.

13. Informed consent process

a) Informed consent and incentives

Recruitment of patients will be conducted via online advertising like Google-Ads campaign, and optionally offline recruitment via Flyer, health insurance providers and advertisement in print media. Participants will be routed to a linked study website providing information about the trial and details about participation. Using a contact form on the website, participants can indicate interest in participation whereupon they receive an email with a link to LimeSurvey, a secure online survey tool. At the beginning of the survey, further information about participation will be provided and electronic informed consent will be obtained. Participants will be informed about the option to receive personal explanation and answers to further questions via telephone or email. Moreover, participants will be informed of their right to withdraw from the study at any time without negative consequences. After informed consent is obtained, participants will be asked to fill in an online demographic questionnaire followed by a set of questionnaires to collect baseline data (T0) and screen for inclusion criteria. After informed consent and initial data acquisition, a telephone interview is conducted to determine the diagnosis of BPD and rule out any primary diagnosis of substance use disorder or psychotic disorder or an acute decompensation of mental health. These diagnoses were determined as exclusion criteria in face of the risk of non-adherence to complete the questionnaires. However, they are not considered contraindications for the usage of *alivis*. In addition, consent to the emergency plan for suicidal crises is obtained.

Participants will be provided with a 10€ voucher for www.wunschgutschein.de as incentive for participation at T1, T2, and T3 (max. 30€). All participants (from the intervention and control group) will receive this compensation if they complete the follow-up questionnaires, and, in particular, the compensation in the intervention group will not depend on the actual use of *alivis*.

b) Informed consent process - subject unable/emergency treatment

Not applicable.

14. Adverse events, adverse device effects and device deficiencies

a) Definitions of adverse events and adverse device effects

Adverse events (operationalized via unplanned and emergency outpatient and inpatient treatments or suicide (attempts), as well as negative side-effects of the treatment (NEQ)) are queried at all measurement times. In addition, the intervention group has the option of sending information to the program operator using the contact form or email. In addition, participants can report adverse events directly to the study team by email, telephone, and via the contact form on the *alivis* trial website. The study manager brings together and monitors data from all of the channels described.

b) Definition of device deficiencies

Since *alivis* is a web-based application, of which only the current version is available, there are no product defects in terms of identity (there is only one software version that is shown in the program), quality (no physical product) or durability. GAIA as the manufacturer of *alivis* guarantees program availability averaging 99.5% per year. A lower average availability represents a product defect. Further product defects represent: malfunction, usage errors, missing or misleading information.

c) Definitions of serious adverse events and serious adverse device effects

A serious adverse event is any unwanted event that occurs which - directly or indirectly - has led, could have led or could lead to the death or serious deterioration of the state of health of a test person, a user or another person and was caused by the medical device or in which a causal relationship is at least likely.

d) Non-reportable adverse events

The adverse events listed in the instructions for use in the chapter "Nebenwirkungen": disappointment, distress, dissatisfaction, problems performing certain exercises, temporary worsening of symptoms when performing exercises or reflecting on your own situation. These are expected adverse events related to cognitive behavioral therapy and / or lifestyle changes.

Upon contact with the study team, these adverse events are recorded, assessed and considered as part of the risk management. Additionally, the NEQ is systematically assessed at each measurement time point. If the study reveals an unexpected frequency with one or more of these undesirable effects, trend reporting is carried out (§88 MDR).

e) Report period of adverse events and device deficiencies

GAIA reports every serious adverse event immediately after a causal relationship or a possible causal relationship has been established between the incident and *alivis*, but no later than 15 days after GAIA has become aware of the incident. There are two exceptions to this:

1. In the event of a serious hazard to public health, notification is made immediately, but no later than two days after GAIA has become aware of this hazard.

2. In the event of death or an unforeseen serious deterioration in the state of health of a person, notification is made immediately after GAIA has established a causal link between the product and the serious incident or as soon as GAIA suspects such a connection, but no later than ten days after becoming aware of received the serious incident.

If necessary, in order to ensure a speedy report, GAIA can first transmit a preliminary report and this can then be followed by the full report. In the event of uncertainty as to whether the incident should be reported after GAIA has received knowledge of a possibly reportable event, GAIA will nevertheless submit a report within the prescribed period mentioned above.

f) Process for reporting adverse events

The reporting or notification of adverse events is carried out to the BfArM using the forms provided for this purpose.

g) Process for reporting device deficiencies

Product defects are recorded, assessed and documented in accordance with the “Feedback & Complaint Handling” procedural instruction explained in more detail under sub-item h).

h) Adverse events, adverse device effects and incidence, mitigation, or treatment

When using the product, it may happen that not every patient benefits from the product. This circumstance can potentially lead to feelings of disappointment. It is also possible that the use of the program is perceived as stressful and that dealing with the program’s content feels uncomfortable. Not every exercise or recommendation is equally suitable for every patient, which can also lead to disappointment or even aggravate symptoms.

If undesirable side effects are reported, it will be clarified with the study participant whether further examinations or additional treatment is appropriate and the study participant will be motivated to make use of them. For the handling of undesirable events that are reported via the program support, a procedural instruction is available (Quality Procedure 'Feedback & Complaint Handling'). This regulates procedures for dealing with questions, feedback and undesirable events in a timely and content-wise manner, and is used in this research project. Regardless of the method of contact (phone, email, contact form in the program), messages from study participants are collected and processed centrally.

i) Emergency contact details for serious adverse events/device effects.

Information on side effects and emergency contacts is provided in the instructions for use:

[…] Es ist möglich, dass nicht jeder Patient von der Programmnutzung profitiert, was unter Umständen Gefühle der Enttäuschung auslösen könnte. Wenn die Beschäftigung mit dem Programm für Sie zu belastend ist, sollten Sie eine Pause machen, die Programmnutzung aussetzen und mit Ihrem Arzt/Psychotherapeuten darüber sprechen. Nicht jede Übung oder

jede Empfehlung ist für jeden Patienten gleichermaßen geeignet. Wenn Ihnen eine Übung oder Empfehlung Schwierigkeiten bereitet, sich unangenehm anfühlt oder Beschwerden verursacht/verstärkt, führen Sie diese nicht weiter aus. Wenden Sie sich bei Bedarf an Ihren Arzt/Psychotherapeuten. Sollten im Zusammenhang mit der Nutzung von *alivis* Nebenwirkungen auftreten, melden Sie diese unverzüglich Ihrem Arzt oder Psychotherapeuten oder wenden Sie sich per E-Mail an alivis@broca.io. Weitere Kontaktmöglichkeiten finden Sie im Impressum von *alivis* unter dem Menüpunkt „Hilfe“.

Bei Notfällen (z.B. Krisen, Suizidgefahr, Verschlechterung Ihres Gesundheitszustandes) kontaktieren Sie umgehend Ihren behandelnden Arzt/Psychotherapeuten oder wählen Sie bitte die für Ihr Land geltenden Notfallnummern von Feuerwehr oder Polizei.
Hier ein Beispiel: Deutschland: • Notruf allgemein: 112 • Notruf Rettungsdienst: 112 • Polizei: 110 • Seelsorge: 0800 111 0 111, 0800 111 0 222
Falls Sie unter den angegebenen Telefonnummern niemanden erreichen oder keine Hilfe erfahren, prüfen Sie bitte, ob sich die Telefonnummern geändert haben könnten. […]

Furthermore, in the course of obtaining the declaration of consent, the participants are informed that they can contact the study team via email and telephone.

j) Information regarding the DMC

Not applicable.

15. Vulnerable population

Not applicable.

16. Suspension or premature termination of the investigation

a) Criteria and arrangements

If, during the clinical trial, an unacceptable risk, including a serious health hazard, is suspected, or if directed to do so by the European Commission or regulatory authorities, the sponsor will suspend the trial while the risk is being assessed. The sponsor will terminate the trial if the existence of an unacceptable risk that cannot be reduced is confirmed.

b) Criteria for access to and breaking the blinding/masking code

not applicable.

c) Subject follow-up and continued care

There are no special requirements for the follow-up examination of the test subjects because, as before, they receive the usual medical care and the risk of adverse effects from the intervention *alivis* or the information documents that participants in the control group receive is very small.

17. Publication policy

a) Statement - trial registration

The study will be registered in an international trial registry with details of the specific primary and secondary endpoints and further details regarding the trial design.

b) Statement - publicly available results

The results of the clinical trial are planned to be published in a peer-reviewed journal.

c) Statement - conditions/timeframes for publication

After completing the data collection and subsequent analysis of the data set, the results of the clinical trial are planned to be published in a peer-reviewed journal regardless of whether the null hypothesis is refuted. The authorship is shared between those involved in the study according to the current guidelines of the International Committee of Medical Journal Editors (ICMJE). The data will be published in an aggregated, anonymized form.

18. Bibliography

1. ten Have M, Verheul R, Kaasenbrood A, van Dorsselaer S, Tuithof M, Kleinjan M, u. a. Prevalence rates of borderline personality disorder symptoms: a study based on the Netherlands Mental Health Survey and Incidence Study-2. BMC Psychiatry. 2016;16(1):249.
2. Wagner T, Assmann N, Köhne S, Schaich A, Alvarez-Fischer D, Borgwardt S, u. a. The societal cost of treatment-seeking patients with borderline personality disorder in Germany. Eur Arch Psychiatry Clin Neurosci. 2022;272(4):741–52.
3. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders [Internet]. Fifth Edition. American Psychiatric Association; 2013 [zitiert 15. Januar 2021]. Verfügbar unter: https://psychiatryonline.org/doi/book/10.1176/appi.books.9780890425596
4. Volkert J, Gablonski TC, Rabung S. Prevalence of personality disorders in the general adult population in Western countries: systematic review and meta-analysis. Br J Psychiatry. 2018;213(6):709–15.
5. Storebø OJ, Stoffers-Winterling JM, Völlm BA, Kongerslev MT, Mattivi JT, Jørgensen MS, u. a. Psychological therapies for people with borderline personality disorder. Cochrane Database Syst Rev. 4. Mai 2020;5:CD012955.
6. Stoffers-Winterling JM, Storebø OJ, Kongerslev MT, Faltinsen E, Todorovac A, Jørgensen MS, u. a. Psychotherapies for borderline personality disorder: a focused systematic review and meta-analysis. Br J Psychiatry. 2022;1–15.
7. Iliakis EA, Sonley AKI, Ilagan GS, Choi-Kain LW. Treatment of borderline personality disorder: is supply adequate to meet public health needs? Psychiatr Serv. 2019;70(9):772–81.
8. Fassbinder E, Hauer A, Schaich A, Schweiger U, Jacob GA, Arntz A. Integration of e-health tools into face-to-face psychotherapy for borderline personality disorder: a chance to close the gap between demand and supply? J Clin Psychol. 2015;71(8):764–77.
9. Kessler RC, Berglund PA, Bruce ML, Koch JR, Laska EM, Leaf PJ, u. a. The prevalence and correlates of untreated serious mental illness. Health Serv Res. Dezember

2001;36(6 Pt 1):987–1007.
10. Andrade LH, Alonso J, Mneimneh Z, Wells JE, Al-Hamzawi A, Borges G, u. a. Barriers to mental health treatment: results from the WHO World Mental Health surveys. Psychol Med. April 2014;44(6):1303–17.
11. Ilagan GS, Iliakis EA, Wilks CR, Vahia IV, Choi-Kain LW. Smartphone applications targeting borderline personality disorder symptoms: a systematic review and meta-analysis. Borderline Personal Disord Emot Dysregulation. Dezember 2020;7(1):12.
12. Hudon A, Gaudreau-Ménard C, Bouchard-Boivin M, Godin F, Cailhol L. The Use of Computer-Driven Technologies in the Treatment of Borderline Personality Disorder: A Systematic Review. J Clin Med. Januar 2022;11(13):3685.
13. Setkowski K, Palantza C, Ballegooijen W van, Gilissen R, Oud M, Cristea IA, u. a. Which psychotherapy is most effective and acceptable in the treatment of adults with a (sub)clinical borderline personality disorder? A systematic review and network meta-analysis. Psychol Med. Juni 2023;53(8):3261–80.
14. Arntz A, Genderen H van. Schema Therapy for Borderline Personality Disorder. John Wiley & Sons; 2020. 292 S.
15. Faßbinder E, Schweiger U, Jacob G. Therapie-Tools Schematherapie [Internet]. 2016 [zitiert 12. Juli 2023]. Verfügbar unter: https://sfbs.tu-dortmund.de/handle/sfbs/3158
16. Arntz A, Jacob GA, Lee CW, Brand-de Wilde OM, Fassbinder E, Harper RP, u. a. Effectiveness of predominantly group schema therapy and combined individual and group schema therapy for borderline personality disorder: a randomized clinical trial. JAMA Psychiatry. 2022;79(4):287–99.
17. Giesen-Bloo J, van Dyck R, Spinhoven P, van Tilburg W, Dirksen C, van Asselt T, u. a. Outpatient psychotherapy for borderline personality disorder: randomized trial of schema-focused therapy vs transference-focused psychotherapy. Arch Gen Psychiatry. 1. Juni 2006;63(6):649–58.
18. Hayes SC, Strosahl KD, Wilson KG. Acceptance and commitment therapy. Guilford press New York; 1999.
19. Morgan TA, Aljabari R. Using Acceptance and Commitment Therapy in the Treatment of Borderline Personality Disorder: Rationale, Preliminary Evidence, and Future Directions. Curr Treat Options Psychiatry. 1. Dezember 2019;6(4):271–83.
20. Ona PEZ. Acceptance and Commitment Therapy for Borderline Personality Disorder: A Flexible Treatment Plan for Clients with Emotion Dysregulation. New Harbinger Publications; 2020. 329 S.
21. Neff KD. Self-compassion: Theory, method, research, and intervention. Annu Rev Psychol. 2022;74.
22. Bohus M, Kleindienst N, Hahn C, Müller-Engelmann M, Ludäscher P, Steil R, u. a. Dialectical Behavior Therapy for Posttraumatic Stress Disorder (DBT-PTSD) Compared With Cognitive Processing Therapy (CPT) in Complex Presentations of PTSD in Women Survivors of Childhood Abuse: A Randomized Clinical Trial. JAMA Psychiatry. 1. Dezember 2020;77(12):1235–45.
23. Kleindienst N, Steil R, Priebe K, Müller-Engelmann M, Biermann M, Fydrich T, u. a. Treating adults with a dual diagnosis of borderline personality disorder and posttraumatic stress disorder related to childhood abuse: Results from a randomized clinical trial. J Consult Clin Psychol. 1. November 2021;89(11):925–36.
24. Jacob GA, Hauer A, Köhne S, Assmann N, Schaich A, Schweiger U, u. a. A Schema Therapy–Based eHealth Program for Patients with Borderline Personality Disorder (priovi): Naturalistic Single-Arm Observational Study. JMIR Ment Health. 17. Dezember 2018;5(4):e10983.
25. Rizvi SL, Hughes CD, Thomas MC. The DBT Coach mobile application as an adjunct to treatment for suicidal and self-injuring individuals with borderline personality disorder: A preliminary evaluation and challenges to client utilization. Psychol Serv. 2016;13(4):380–8.
26. Zanarini MC, Conkey LC, Temes CM, Fitzmaurice GM. Randomized Controlled Trial of Web-Based Psychoeducation for Women With Borderline Personality Disorder. J Clin

Psychiatry. 11. Juli 2017;78(3):16065.
27. Klein JP, Hauer-von Mauschwitz A, Berger T, Fassbinder E, Mayer J, Borgwardt S, u. a. Effectiveness and safety of the adjunctive use of an internet-based self-management intervention for borderline personality disorder in addition to care as usual: results from a randomised controlled trial. BMJ Open. 2021;11(9):e047771.
28. Iliakis EA, Ilagan GS, Choi-Kain LW. Dropout rates from psychotherapy trials for borderline personality disorder: A meta-analysis. Personal Disord Theory Res Treat. 2021;12:193–206.
29. Arntz A, Mensink K, Cox WR, Verhoef REJ, Emmerik AAP van, Rameckers SA, u. a. Dropout from psychological treatment for borderline personality disorder: a multilevel survival meta-analysis. Psychol Med. Februar 2023;53(3):668–86.
30. Sox HC, Lewis RJ. Pragmatic Trials: Practical Answers to “Real World” Questions. JAMA. 20. September 2016;316(11):1205–6.
31. Bohus M, Kleindienst N, Limberger MF, Stieglitz RD, Domsalla M, Chapman AL, u. a. The Short Version of the Borderline Symptom List (BSL-23): Development and Initial Data on Psychometric Properties. Psychopathology. 2009;42(1):32–9.
32. Kleindienst N, Jungkunz M, Bohus M. A proposed severity classification of borderline symptoms using the borderline symptom list (BSL-23). Borderline Personal Disord Emot Dysregulation. 2020;7:11.
33. Jacobson NS, Truax P. Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. J Consult Clin Psychol. 1991;59(1):12–9.
34. Löwe B, Unützer J, Callahan CM, Perkins AJ, Kroenke K. Monitoring depression treatment outcomes with the Patient Health Questionnaire-9. Med Care. 2004;42(12):1194–201.
35. Löwe B, Kroenke K, Herzog W, Gräfe K. Measuring depression outcome with a brief self-report instrument: sensitivity to change of the Patient Health Questionnaire (PHQ-9). J Affect Disord. 2004;81(1):61–6.
36. Martin A, Rief W, Klaiberg A, Braehler E. Validity of the Brief Patient Health Questionnaire Mood Scale (PHQ-9) in the general population. Gen Hosp Psychiatry. 2006;28(1):71–7.
37. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med. 2006;166(10):1092–7.
38. Kertz S, Bigda-Peyton J, Bjorgvinsson T. Validity of the Generalized Anxiety Disorder-7 Scale in an acute psychiatric sample. Clin Psychol Psychother. 2013;20(5):456–64.
39. Löwe B, Decker O, Müller S, Brähler E, Schellberg D, Herzog W, u. a. Validation and Standardization of the Generalized Anxiety Disorder Screener (GAD-7) in the General Population. Med Care. 2008;46(3):266–74.
40. Heissel A, Bollmann J, Kangas M, Abdulla K, Rapp M, Sanchez A. Validation of the German version of the work and social adjustment scale in a sample of depressed patients. BMC Health Serv Res. 21. Juni 2021;21(1):593.
41. Richardson J, Khan MA, Iezzi A, Maxwell A. Cross-national comparison of twelve quality of life instruments. MIC Paper 7. Germany. Research Paper 85. Melb Cent Health Econ Monash Univ [Internet]. 2013; Verfügbar unter: https://www.aqol.com.au/papers/researchpaper85.pdf
42. Bloo J, Arntz A, Schouten E. The Borderline Personality Disorder Checklist: Psychometric evaluation and factorial structure in clinical and nonclinical samples. Ann Psychol. 2017;20(2):311–36.
43. Hibbard JH, Mahoney ER, Stockard J, Tusler M. Development and Testing of a Short Form of the Patient Activation Measure. Health Serv Res. 2005;40(6p1):1918–30.
44. Brenk-Franz K, Hibbard JH, Herrmann WJ, Freund T, Szecsenyi J, Djalali S, u. a. Validation of the German Version of the Patient Activation Measure 13 (PAM13-D) in an International Multicentre Study of Primary Care Patients. PLOS ONE. 2013;8(9):e74786.
45. SCID-5-PD : strukturiertes klinisches Interview für DSM-5 Persönlichkeitsstörungen : deutsche Bearbeitung des Structured clinical interview for DSM-5® - personality disorders von Michael B. First, Janet B.W. Wiliams, Lorna Smith Benjamin, Robert L.

Spitzer : Manual - Deutsche Digitale Bibliothek [Internet]. [zitiert 20. Oktober 2021]. Verfügbar unter: http://www.deutsche-digitale-bibliothek.de/item/FILAMEI2SMDJF5BSJYPFIKLNWDIZ7R32
46. Margraf J, Cwik JC, Pflug V, Schneider S. Strukturierte klinische Interviews zur Erfassung psychischer Störungen über die Lebensspanne. Z Für Klin Psychol Psychother. Juli 2017;46(3):176–86.
47. Bernstein D, Fink L. Manual for the childhood trauma questionnaire. N Y Psychol Corp. 1998;
48. Wingenfeld K, Spitzer C, Mensebach C, Grabe HJ, Hill A, Gast U, u. a. Die deutsche Version des Childhood Trauma Questionnaire (CTQ): Erste Befunde zu den psychometrischen Kennwerten. PPmP - Psychother · Psychosom · Med Psychol. 3. März 2010;442–50.
49. Keiningham T, Aksoy L, Cooil B, Andreassen T, Williams L. A holistic examination of Net Promoter. J Database Mark Cust Strategy Manag. 2008;15:79–90.
50. Schmidt J, Lamprecht F, Wittmann WW. Zufriedenheit mit der stationären Versorgung. Entwicklung eines Fragebogens und erste Validitätsuntersuchungen. Psychother Psychosom Med Psychol. 1989;39(7):248–55.
51. Gómez Penedo JM, Berger T, Grosse Holtforth M, Krieger T, Schröder J, Hohagen F, u. a. The Working Alliance Inventory for guided Internet interventions (WAI-I). J Clin Psychol. 25. Juni 2019;
52. Rozental A, Kottorp A, Forsström D, Månsson K, Boettcher J, Andersson G, u. a. The Negative Effects Questionnaire: psychometric properties of an instrument for assessing negative effects in psychological treatments. Behav Cogn Psychother. September 2019;47(05):559–72.
53. Wolf M, Limberger MF, Kleindienst N, Stieglitz RD, Domsalla M, Philipsen A, u. a. Kurzversion der Borderline-Symptom-Liste (BSL-23): Entwicklung und Überprüfung der psychometrischen Eigenschaften. PPmP - Psychother · Psychosom · Med Psychol. August 2009;59(08):321–4.
54. Bohus M, Kleindienst N, Limberger MF, Stieglitz RD, Domsalla M, Chapman AL, u. a. The short version of the Borderline Symptom List (BSL-23): development and initial data on psychometric properties. Psychopathology. 2009;42(1):32–9.
55. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001;16(9):606–13.
56. Anderson JK, Wallace LM. Evaluation of uptake and effect on patient-reported outcomes of a clinician and patient co-led chronic musculoskeletal pain self-management programme provided by the UK National Health Service. Br J Pain. Mai 2018;12(2):104–12.
57. Owen J, Adelson J, Budge S, Wampold B, Kopta M, Minami T, u. a. Trajectories of Change in Psychotherapy. J Clin Psychol. 2015;71(9):817–27.
58. Baldwin SA, Berkeljon A, Atkins DC, Olsen JA, Nielsen SL. Rates of change in naturalistic psychotherapy: contrasting dose-effect and good-enough level models of change. J Consult Clin Psychol. 2009;77(2):203–11.
59. R Core Team. R: A language and environment for statistical computing [Internet]. Vienna, Austria; 2022. Verfügbar unter: https://cran.r-project.org/
60. Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMJ. 23. März 2010;340(mar23 1):c332–c332.
61. Eysenbach G, CONSORT-EHEALTH Group. CONSORT-EHEALTH: improving and standardizing evaluation reports of Web-based and mobile health interventions. J Med Internet Res. 2011;13(4):e126.
62. Ranganathan P, Pramesh CS, Aggarwal R. Common pitfalls in statistical analysis: Intention-to-treat versus per-protocol analysis. Perspect Clin Res. 2016;7(3):144–6.
63. Cro S, Morris TP, Kenward MG, Carpenter JR. Reference-based sensitivity analysis via multiple imputation for longitudinal trials with protocol deviation. Stata J.

2016;16(2):443–63.
64. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, Herausgeber. Allgemeine Methoden: Version 7.0. 7.0. Köln: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG); 2023.
65. Multiple Endpoints in Clinical Trials Guidance for Industry [Internet]. Center for Drug Evaluation and Research Center for Biologics Evaluation and Research; 2017 [zitiert 10. Juni 2022]. Verfügbar unter: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/multiple-endpoints-clinical-trials-guidance-industry
66. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. J R Stat Soc Ser B Methodol. 1995;57(1):289–300.
67. Schomaker M, Heumann C. Bootstrap inference when using multiple imputation. Stat Med. 2018;37(14):2252–66.
68. von Hippel PT, Bartlett JW. Maximum likelihood multiple imputation: Faster imputations and consistent standard errors without posterior draws. Stat Sci. 2021;36(3):400–20.
69. van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. J Stat Softw. 2011;045(i03).
70. Carpenter JR, Roger JH, Kenward MG. Analysis of Longitudinal Trials with Protocol Deviation: A Framework for Relevant, Accessible Assumptions, and Inference via Multiple Imputation. J Biopharm Stat. 2013;23(6):1352–71.