Clinical Investigation Plan (CIP)

for clinical trial (pilot study) EL-P01DEP

Pilot study to evaluate a digital health application for the blended treatment of unipolar depression and anxiety disorder in adults

Pilotstudie zur Evaluation einer digitalen Gesundheitsanwendung zur verzahnten Behandlung der unipolaren Depression und Angststörung bei Erwachsenen

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Sponsor:
n/a (study analogous to MPG §23b)

Source of Material Support &
Manufacturer of the investigational device:
Elona Health GmbH
Schirmerstraße 61
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Non-disclosure statement

It is understood and agreed to that the below-identified disclosure of confidential information may provide certain information that is and must be kept confidential. To ensure the protection of such information, and to preserve any confidentiality necessary under patent and/or trade secret laws, it is agreed that:

1. For the purposes of this Agreement »Confidential Information« shall mean such technical and/or commercial information, including but not limited to any documents, drawings, sketches or designs, materials or samples disclosed by Elona Health GmbH to the other party, and which at the time of its disclosure is identified as being confidential.
2. The other party undertakes to treat as confidential all and any Confidential Information of Elona Health GmbH and agree not to disclose the same to any third party except with the prior written consent of Elona Health GmbH.
3. The restrictions on the use and disclosure of Confidential Information shall not apply to any information which is:
    a. proven to have been known to the receiving party prior to the time of its receipt pursuant to this Agreement; or
    b. in the public domain at the time of disclosure to the receiving party or thereafter enters the public domain without breach of the terms of this Agreement; or
    c. lawfully acquired by the receiving party from an independent source having a bona fide right to disclose the same; or
    d. independently developed by an employee of the receiving party who has not had access to any of the Confidential Information of the other party.
4. All Confidential Information supplied pursuant to this Agreement shall remain the property of Elona Health GmbH and no rights, including but not limited to the right to apply for industrial property rights, are granted to the other party in the same. The Parties agree that any Confidential Information is made available "as is" and that no warranties are given or liabilities of any kind are assumed with respect to the quality of such Confidential Information, including, but not limited, to its fitness for the purpose, non-infringement of third party rights, accuracy, completeness or its correctness.
5. Any sample or material which may be supplied by Elona Health GmbH to the other party shall be treated as confidential according to section 2 to 4 of this Agreement and shall be used only for purposes of evaluation or testing or any other purpose as specified by the supplying party.
6. This Agreement shall come into force on the date of the last revision of this document and shall thereafter be valid for 24 months. The obligation of confidentiality hereunder shall continue to be valid for a period of 10 years after the end of the term of this Agreement.
7. Ancillary agreements, amendments, additions hereto must be made in writing.
8. This Agreement is subject to and governed by the laws of the Federal Republic of Germany.
9. If any provision of this Agreement is determined to be illegal or in conflict with the applicable law, the validity of the remaining provisions shall not be affected. The ineffective provision shall be replaced by an effective provision that is economically equivalent. The same shall apply in case of a gap.

Investigator statement

Study product name	Elona v1.1.0 (Elona)
Sponsor	n/a (study analogous to MPG §23b)
Manufacturer	Elona Health GmbH Schirmerstraße 61 40211 Düsseldorf
Clinical Investigation Plan Identifier	EL-P01DEP-CIP
Version Number/Date	Version 2.2 (15.12.2021)

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I agree to comply with the Declaration of Helsinki, the Clinical Investigation Plan, Good Clinical Practice (ISO 14155:2020) and to national and local laws, regulations, standards, and requirements. I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation and conduct of the clinical investigation without the prior written consent of Elona Health GmbH. I have read the non disclosure statement and agree that all information provided during this clinical trial must be kept confidential.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Elona Health GmbH. I will discuss this material with them to ensure that they are fully informed about the products and the study.

Investigator's name	
Investigator's signature	
Institution	Heinrich-Heine-Universität Düsseldorf Klinische Psychologie Universitätsstraße 1 40225 Düsseldorf
Date	

Glossary

AE	Adverse event
ADE	Adverse device event
bCBT	blended Cognitive Behavioural Therapy
CBT	Cognitive Behavioural Therapy
CIP	Clinical Investigation Plan
CRF	Case Report Form
CV	Curriculum Vitae
DD	Device deficiency
GCP	Good clinical practice
iCBT	internet-delivered Cognitive Behavioural Therapy
IB	Investigator's brochure
IFU	Instructions for Use
EC	Ethics Committee
TAU	Treatment as usual, Face to face CBT

Synopsis

Title	Pilot study to evaluate a digital health application for the blended treatment of unipolar depression and anxiety disorder in adults
Clinical study type	Pivotal
Product name	Elona v1.1.0 (Elona)
Sponsor	n/a (study analogous to MPG §23b)
Indication under investigation	Elona is a new digital health application that supports outpatient psychotherapy in the treatment of mental illnesses through an intelligent delivery of therapeutic content between regular therapy sessions. Elona is indicated for use in patients who have experienced one or more of the following conditions: ● mild to severe depression ● panic disorder ● anxiety disorder ● Somatoform disorder
Investigation purpose	The purpose of this study is to demonstrate safe and effective use of Elona in blended CBT settings with patients suffering from mild to moderate depression or an anxiety disorder. This study will be used as pivotal evidence to support the clinical evaluation as part of CE conformity.
Product status	The product is a CE-marked class I medical device.
Primary Objective(s)	**Primary efficacy objective** Demonstrate the effectiveness of Elona when combined with TAU in the self-assessment of depressive or anxiety symptoms after completion of treatment after 6/12 weeks (pre-mid-post difference of BDI-II, BAI, PSWQ, PHQ-9, GAD-7). **Primary safety objective** Demonstrate that Elona blends into TAU and provides digital interventions as intended.
Secondary Objective(s)	**Secondary efficacy objective**

	Demonstrate the superior effectiveness of Elona combined with in-person CBT sessions (bCBT) compared to TAU (i.e., only in-person CBT) for improving *quality of life* and reducing *symptoms of anxiety/ depression* symptoms (WHOQOL-BREF and BAI) and the following patient-relevant structural and procedural improvements: *self-efficacy, work and social adjustment, mental health literacy, work alliance and indicators of adherence* after 6/12 weeks (pre-mid-post difference of SWE, WSAS, MHLS, WAI-SR and non-standardized Items). Additionally, this study tests whether patients receiving bCBT with Elona report fewer negative effects of therapy (assessed with the NEQ) compared to patients receiving TAU.
Study design	To test the effectiveness and safety of Elona a randomized, multi-center, single-blind (patient) controlled trial (RCT) for patients with a clinical diagnosis of depression (ICD-10: F32.x, F33.x, F34.x) and anxiety (ICD-10: F4XXXXXX) based on ICD-10 criteria is planned. The RCT comprises two arms for each Diagnosis: Both arms receive weekly face-to-face CBT treatment over a 12-week period. Participants assigned to the treatment group will additionally use the Elona digital health application. Participants assigned to the control group will not use Elona (i.e., TAU) in the first 12 weeks, but get access to Elona afterwards. Participants will be randomly assigned to one of the two conditions.
Sample size	50 subjects per group (200 total)
Enrollment strategy	The investigation is planned to start at the beginning of January 2022. Subjects are enrolled during the first sessions of their standard-of-care psychotherapeutic treatment by participating psychotherapists in the investigation sites. Subjects are expected to be enrolled within the first eight weeks after the start of the study.
Inclusion/exclusion criteria	**Inclusion criteria:**

	All subjects must have been diagnosed with one of the following ICD-10 diagnoses: ● F32.0: Mild depressive episode ● F32.1: Moderate depressive episode ● F32.2: Severe depressive episode ● F32.8: Other depressive episodes ● F32.9: Depressive episode, unspecified ● F33.0: Recurrent depressive disorder, current episode mild ● F33.1: Recurrent depressive disorder, current episode moderate ● F33.2: Recurrent depressive disorder, current episode severe ● F33.8: Other recurrent depressive disorders ● F33.9: Recurrent depressive disorder, unspecified ● F34.0: Cyclothymia ● F34.1: Dysthymia ● F34.8: Other persistent mood [affective] disorders ● F34.9: Persistent mood [affective] disorder, unspecified ● F40.0 Agoraphobia ● F40.00 Agoraphobia without panic disorder ● F40.01 Agoraphobie with panic disorder ● F40.1 Social phobias ● F40.2 Specific (isolated) phobias ● F40.8 Other phobic anxiety disorders ● F40.9 Phobic anxiety disorder, unspecified ● F41.0 Panic disorder [episodic paroxysmal anxiety] ● F41.1 Generalized anxiety disorder ● F41.2 Mixed anxiety and depressive disorder ● F41.3 Other mixed anxiety disorders ● F41.8 Other specified anxiety disorders ● F41.9 Anxiety disorder, unspecified ● F45.2 Hypochondriacal disorder Subjects further need to be between the age of 18 and 65, possess sufficient German language skills (in writing and reading), possess a smartphone (iOS or Android operating system) with internet access, provide signed and dated informed

	consent and are willing to comply with the protocol. **Exclusion criteria:** All subjects without the inclusion ICD-10 diagnosis criteria as well as subjects with the following ICD-10 diagnoses are excluded: ● F0x.x: Organic, including symptomatic, mental disorders ● F1x.x Mental and behavioural disorders due to psychoactive substance use (except F17.x) ● F2x.x: Schizophrenia, schizotypal and delusional disorders ● F31: Bipolar affective disorder ● F32.3: Severe depressive episode with psychotic symptoms ● F33.3: Recurrent depressive disorder, current episode severe with psychotic symptoms Subjects with acute suicidality (operationalized via BDI II screening question and first checkup), subjects under the age of 18, subjects without any access to a smartphone (iOS or Android operating system) with internet access and subjects without German language proficiency are excluded from this study. If a subject is currently enrolled or is planning to participate in a potentially confounding drug or device trial during the study, enrollment into this study needs to be pre-approved.
Study procedures and assessment	Assessments will take place at baseline (T0), mid 6-week treatment (T1) and 12-week after treatment start (T2). Self-report data are collected including basic demographic questions via an online questionnaire.
Safety assessments	All adverse events (AEs) that occur from the time of enrollment through study exit will be collected and reported to the principal investigator and the manufacturer during the study. Additionally, any device deficiencies related to the Elona device will be collected.
Statistics	For each primary objectives, a 2 (between: TAU+Elona vs. TAU) × 3 (within: T0= baseline vs. T1=6/ T2=12 weeks of treatment) RCT Intention-to-treat analyses

	design will be used. (Repeated measurements analysis of variances)

Synopsis (German)

Titel	Pilotstudie zur Evaluation einer digitalen Gesundheitsanwendung zur verzahnten Behandlung der unipolaren Depression und Angststörung bei Erwachsenen
Art der Klinischen Studie	Pilotstudie
Name des Medizinproduktes	Elona v1.2.0 (Elona)
Sponsor	n/a (Studie analog zu MPG §23b)
Indikation unter klinischer Prüfung	Elona ist eine neue digitale Gesundheitsanwendung, die die ambulante Psychotherapie bei der Behandlung von psychischen Erkrankungen durch eine intelligente Bereitstellung von therapeutischen Inhalten zwischen den regulären Therapiesitzungen unterstützt. Elona ist für den Einsatz bei Patienten indiziert, die an einer oder mehreren der folgenden Erkrankungen leiden: ● leichte bis schwere Depression ● Panikstörung ● Angststörungen ● Somatoforme Störungen
Prüfungszweck	Der Zweck dieser Studie ist der Nachweis der sicheren und effektiven Anwendung von Elona in verzahnter Verhaltenstherapie mit Patienten, die an leichter bis mittelschwerer Depression oder einer Angststörung leiden. Diese Studie wird als Evidenz zur Unterstützung der klinischen Bewertung im Rahmen der CE-Konformität verwendet.
Produktstatus	Das Produkt ist ein CE-gekennzeichnetes Medizinprodukt der Klasse I.
Primäre Ziele	**Primäres Wirksamkeitsziel** Nachweis der Effektivität von Elona in Kombination mit regulärer psychotherapeutischer Behandlung in der Selbsteinschätzung depressiver Symptome nach Abschluss der Behandlung nach 6/12 Wochen (Pre-Mid-Post-Differenz des BDI-II, BAI, PSWQ, PHQ-9, GAD-7) in Vergleich zu TAU. **Primäres Sicherheitsziel** Es soll gezeigt werden, dass Elona sich in die reguläre psychotherapeutische

	Behandlung einfügt und die digitalen Interventionen wie vorgesehen zur Verfügung stellt.
Sekündäre Ziele	**Sekundäres Wirksamkeitsziel** Nachweis der Effektivität von Elona in Kombination mit regulärer psychotherapeutischer Behandlung bei der Selbsteinschätzung des Lebensqualitätsindex, der negativen Effekte von der Behandlung der therapeutischen Allianz, der Adhärenz und der mentalen Gesundheitskompetenz nach Abschluss der Behandlung nach 6/12 Wochen (WHOQOL-BREF, SWE, ASAS, MHLS, NEQ, WAI-SR sowie nicht-standardisierte Items.). im Vergleich zu TAU.
Studiendesign	Um die Wirksamkeit und Sicherheit von Elona zu testen, ist eine RCT für Patient:innen mit einer klinischen Diagnose von Depression (ICD-10: F32.x, F33.x, F34.x) und Angststörung (F40.x, F41.x) basierend auf den ICD-10 Kriterien geplant. Die eine Gruppe der Proband:innen erhalten eine TAU (wöchentliche psychotherapeutische Behandlung in Person) über einen Zeitraum von 12 Wochen, sowie direkten Zugang zu der App. Die andere Gruppe erhält ebenfalls TAU, allerdings erst nach 12 Wochen zugang zur App.
Fallzahlen	40 ProbandInnen pro Gruppe je Diagnose (insges. 160 plus ca. 20% Drop-Out), insges. n=200
Einschreibungsstrategie	Der Beginn der Studie ist für Anfang Januar 2022 geplant. Die ProbandInnen werden während der ersten Sitzungen ihrer psychotherapeutischen Standardbehandlung durch die teilnehmenden Psychotherapeuten an den Untersuchungsstandorten eingeschrieben. Es wird erwartet, dass die ProbandInnen innerhalb der ersten acht Wochen nach Studienbeginn eingeschrieben werden.
Einschluss-/Ausschlusskriterien	**Einschlusskriterien:** Bei allen ProbandInnen muss eine der folgenden ICD-10-Diagnosen gestellt worden sein: • F32.0 Leichte depressive Episode

	• F32.1 Mittelgradige depressive Episode • F32.2 Schwere depressive Episode ohne psychotische Symptome • F32.8 Sonstige depressive Episoden • F32.9 Depressive Episode, nicht näher bezeichnet • F33.0 Rezidivierende depressive Störung, gegenwärtig leichte Episode • F33.1 Rezidivierende depressive Störung, gegenwärtig mittelgradige Episode • F33.2 Rezidivierende depressive Störung, gegenwärtig schwere Episode ohne psychotische Symptome • F33.8 Sonstige rezidivierende depressive Störungen • F33.9 Rezidivierende depressive Störung, nicht näher bezeichnet • F34.0 Zyklothymia • F34.1 Dysthymia • F34.8 Sonstige anhaltende affektive Störungen • F34.9 anhaltende affektive Störung, nicht näher bezeichnet • F40.0 Agoraphobie • F40.00 Agoraphobie ohne Angabe einer Panikstörung • F40.01 Agoraphobie mit Angabe einer Panikstörung • F40.1 Soziale Phobien • F40.2 spezifische (isolierte) Phobien • F40.8 sonstige phobische Störungen • F40.9 phobische Störung, nicht näher bezeichnet • F41.0 Panikstörung (episodisch paroxysmale Angst) • F41.1 Generalisierte Angststörung • F41.2 Angst und depressive Störung, gemischt • F41.3 Andere gemischte Angststörungen • F41.8 sonstige spezifische Angststörungen • F41.9 Angststörung, nicht näher bezeichnet • F45.2 hypochondrische Störung

	Des Weiteren müssen die ProbandInnen zwischen 18 und 65 Jahre alt sein, über ausreichende Deutschkenntnisse (Schreiben und Lesen) verfügen, ein Smartphone (iOS- oder Android-Betriebssystem) mit Internetzugang besitzen, eine unterschriebene und datierte Einverständniserklärung abgeben und bereit sein, das Studienprotokoll zu befolgen. **Ausschlusskriterien:** Alle ProbandInnen ohne die Einschlusskriterien sowie ProbandInnen mit den folgenden ICD-10-Diagnosen werden ausgeschlossen: ● Akute Suizidalität ● F00 Demenz bei Alzheimer-Krankheit ● F1x.x Psychische und Verhaltensstörungen durch psychotrope Substanzen (außer F17.x) ● F2x.x Schizophrenie, schizotype und wahnhafte Störungen ● F31 Bipolare affektive Störung ● F32.3 Schwere depressive Episode mit psychotischen Symptomen ● F33.3 Rezidivierende depressive Störung, gegenwärtig schwere Episode mit psychotischen Symptomen ProbandInnen mit akuter Suizidalität (operationalisiert über BDI-II-Screeningfrage und Erstuntersuchung), ProbandInnen unter 18 Jahren, ProbandInnen ohne Zugang zu einem Smartphone (iOS- oder Android-Betriebssystem) mit Internetzugang und ProbandInnen ohne ausreichende deutsche Sprachkenntnisse sind von dieser Studie ausgeschlossen. Wenn ein Proband derzeit an einer potenziell störenden Arzneimittel- oder Medizinproduktstudie teilnimmt oder plant, während der Studie daran teilzunehmen, muss die Aufnahme in diese Studie vorab genehmigt werden.
Studienablauf und Erhebung	Die Erhebungen finden zu Beginn (T0), zur Mitte der 6-wöchigen Behandlung (T1) und 12 Wochen nach Behandlungsbeginn (T2) statt. Es werden Selbstauskunftsdaten einschließlich grundlegender demographischer Fragen mittels eines Online-Fragebogens erhoben.

Sicherheitsbewertung	Alle unerwünschten Nebenwirkungen, die vom Zeitpunkt der Aufnahme in die Studie bis zum Studienende auftreten, werden gesammelt und der Studienleitung und dem Hersteller während der Studie gemeldet. Zusätzlich werden alle Gerätedefekte, die sich auf das Elona-Gerät beziehen, erfasst.
Statistik	Varianzanalyse mit wiederholten Messungen der zwei Gruppen zu drei Messzeitpunkten.

1. General

1.1 Introduction

This CIP outlines the objectives of the clinical investigation. The proposed design is based on scientific and ethical principles, which will be outlined in more detail in the following chapters.

The CIP and all subsequent amendments to the CIP are prepared by the principal investigator, agreed upon between the manufacturer and the principal investigator and accepted by the coordinating investigators, and are recorded with a justification for each amendment.

1.2 Identification of the clinical investigation plan

Title of the clinical investigation: Pilot study to evaluate a digital health application for the blended treatment of unipolar depression and anxiety disorder in adults

Clinical Investigation reference number: EL-P01DEP

Version or date of the CIP: 2.2 (01.08.2021)

Revision history

Version	Date	Created and reviewed by	Description
0.1	23.03.2021	Magnus Schückes	Initial document creation
1.0	10.04.2021	Magnus Schückes, Dr. Peter Neudeck	Publish document
1.1	13.04.2021	Prof. Dr. Reinhard Pietrowsky, Jan Kalde	Review of document
2.0	15.04.2021	Magnus Schückes, Dr. Peter Neudeck	Approval of document
2.1	01.08.2021	Magnus Schückes, Dr. Peter Neudeck	Update and approval
2.2	15.12.2021	Jan Kalde	Update and approval

1.3 Sponsor

Sponsor:
n/a (study analogous to MPG §23b)

Manufacturer of the investigational device:
Elona Health GmbH, Schirmerstraße 61, 40211 Düsseldorf, Germany

1.4 Principal investigator, coordinating investigator and investigation site(s)

Principal investigators	**Principal investigator:** Prof. Dr. Reinhard Pietrowsky Head of Research Team Clinical Psychology Heinrich-Heine-Universität Düsseldorf Klinische Psychologie Universitätsstraße 1 40225 Düsseldorf, Germany **Coordinating investigator:** Jan Kalde (M.Sc.) Doctoral student Heinrich-Heine-Universität Düsseldorf Klinische Psychologie Universitätsstraße 1 40225 Düsseldorf, Germany
Investigation site(s)	Psychotherapeutische Institutsambulanz der Heinrich-Heine-Universität Graf-Adolf-Straße 63 40210 Düsseldorf, Germany Praxis am Volksgarten Dr. Peter Neudeck Volksgartenstraße 36 50677 Köln, Germany Psychotherapeutische Praxis Jan Kalde Mauritiussteinweg 98 50676 Köln, Germany AVT Institutsambulanz Barbarossaplatz Barbarossaplatz 2 50674 Köln, Germany Dr. Hans - Dieter Dumpert, Lisa Kolley, Dr. Christian Laier, Christina Noce Psychotherapeutische Praxis Petra Gütgemann Friesenplatz 21 50672 Köln, Germany AVT GmbH Akademie für Verhaltenstherapie Venloer Str. 47-53 50672 Köln

As the principal investigator, Prof. Dr. Reinhard Pietrowsky is responsible for the management and integrity of the design, conduct, and reporting of the research project and for managing, monitoring, and ensuring the integrity of any collaborative relationships. Additionally, he is responsible for the direction and oversight of compliance, financial, personnel, and other related aspects of the research project and to assure research is conducted in accordance with national regulations. Reinhard Pietrowsky is Professor for Clinical Psychology and psychotherapist at the Heinrich Heine University Düsseldorf, a licenced supervisor for therapists in training and chair of the institutional clinic for psychotherapy of the university.

As the coordinating investigator, Jan Kalde (M.Sc.) is working with and under the direction of the principal investigator. He supports, facilitates and coordinates the daily clinical trial activities and works with the principal investigator, department, manufacturer, and institution to support and provide guidance on the administration of the compliance, financial, personnel and other related aspects of the clinical study. Jan Kalde received his Master of Science in Psychology from the University of Klagenfurt and is a doctoral student in Clinical Psychology at the Heinrich Heine University Düsseldorf. During his studies, he gained considerable insights into computer-based interventions and applications to change the feelings of subjects. He is further a licensed psychological psychotherapist, in which he gained more experience in the daily application of iCBT, including app-based interventions.

2. Identification and description of the investigational device

2.1 Summary description of the investigational device.

Elona is a digital health application that supports patients in outpatient psychotherapy in the treatment of mental illnesses (depression, anxiety/panic disorders, somatoform disorders) through an intelligent delivery of therapeutic content between regular therapy sessions. With Elona, psychotherapists can assign interventions, helpful activities, exercises and psychoeducational resources that provide patients with information and treatment techniques related to their mental illness and are available beyond the regular therapy session through the Elona smartphone application. The content is based on current and evidence-based therapeutic methods in psychotherapy. By using psychometric questionnaires and exercises, Elona individualizes the content to the needs of the patient. The application is designed to strengthen the active cooperation and participation of patients in outpatient psychotherapy and integration of therapeutic contents in the daily life of the patient, and thus increases the adherence to outpatient psychotherapy, reduces the patient's symptomatology and improves quality of life.

Elona provides a two-sided interface for therapists and patients alike. With the Elona smartphone application, users (i.e. patients) can use the following functions:

- **Psychotherapeutic interventions**: Patients can access psychoeducational content related to the treatment in multimedia form and work with psychotherapeutic interventions that are individualized to their needs.
- **Exercises & activities:** Patients perform exercises discussed in the therapy session with the help of the Elona application and further document and reflect on these.
- **Diagnostics & Checkups:** Patients complete their anamnesis, diagnostics, and regular checkups to measure progress in the application.
- **Diary:** Patients record their self-perceived progress in dealing with their mental illness.
- **Therapy organization & reflection:** Patients use the application to make appointments and reflect on therapy sessions.
- **Profile:** Patients create their own profile and customize usage settings.

With the Elona Web application, users (i.e., care providers) can use the following features:

- **Intervention Catalog:** Therapists search for and retrieve indication-relevant interventions and corresponding exercises.
- **Treatment plan:** Therapists create indication-specific treatment plans for their patients.
- **Assignment of content:** Therapists assign relevant content and exercises to their patients in the Elona smartphone application.
- **Therapy organization & reflection:** Therapists use the app to make appointments and reflect on therapy sessions.

Name and number of the model	Elona v1.1.0

As a software, the medical device is not in contact with tissue or body fluids.

2.2 Details concerning the investigational device and its manufacturer

Elona Health GmbH (Schirmerstraße 61, 40211 Düsseldorf, Germany) is a medical device manufacturer with a focus on digital health applications and digital therapeutics for the treatment of mental disorders.

2.3 Traceability during and after the clinical investigation

As a software, the product will show no differences between participants.

All Participants will receive an individual serial number, which will be written on all paper-pencil questionnaires as well as their individual file.

2.4 Intended purpose of the investigational device in the proposed clinical investigation.

This study investigates the efficacy and safety of the Elona device. Elona leverages a blended therapy approach in the treatment of patients with depression and anxiety disorder by adding a smartphone application to the usual face-to-face psychotherapy (treatment as usual).

The Elona application is designed to strengthen the active cooperation and participation of patients in outpatient psychotherapy and integration of therapeutic contents in the daily life of the patient, and, thus, increases the adherence to outpatient psychotherapy as well as patient self-management, reduces the patient's symptomatology and improves quality of life.

2.5 Intended populations and indications

The medical device is intended for patients suffering from mental disorders, especially depression, panic and anxiety disorders.

2.6 Training and experience needed to use the investigational device based on risk assessment

The manufacturer has compiled documentation on known and foreseeable hazards associated with the medical device in both normal and fault conditions according to ISO 14971:2020. According to the manufacturer’s risk analysis there are no unacceptable risks that can originate from the use of Elona. As such, the device is classified as software safety class A (from EN 62304:2015 par. 4.3).

Irrespective of the risk associated with the medical device, patients and psychotherapists will undergo an onboarding/training before using Elona. Patients will receive a common onboarding procedure within the Elona application. Psychotherapists will undergo a 1h training session prior to usage.

2.7 IB and IFU

The Investigator's brochure (IB) and Instructions for Use (IFU) are provided in a separate document.

3. Justification for the design of the clinical investigation

The design of this clinical investigation is based on the evaluation of pre-clinical data and the results of the manufacturer's clinical evaluation as well as the manufacturer’s risk assessment. The clinical evaluation includes an assessment and analysis of clinical data (effectiveness and safety) of similar devices that are used in a guided or blended CBT setting. Please refer to the IB for more information on similar devices.

This clinical investigation is designed accordingly to evaluate whether the Elona is suitable for the intended purpose of supporting outpatient psychotherapy in the treatment of mental illnesses through an intelligent delivery of therapeutic content between regular therapy sessions among a population of people with depression or anxiety disorder. This study shall ensure that the results obtained have clinical relevance and scientific validity and address the clinical investigation objectives, in particular the benefit-risk profile of the investigational device.

4. Benefits and risks of the investigational device, clinical procedure, and clinical investigation

4.1 Anticipated clinical benefits

Blended cognitive behavioral therapy (bCBT) refers to a traditional face-to-face CBT treatment, while including digital interventions (e.g. internet, smartphone or virtual reality) in the treatment. This integrated treatment extends aspects of face-to-face therapy by providing patients further information and tailored interventions according to their individual treatments in therapy through a smartphone or internet application (Berger et al., 2011).

Early studies on this topic have shown augmented effects of bCBT compared to face-to-face-only therapy (Erbe et al., 2017; Kleiboer et al., 2016; Krieger et al., 2014; Thase et al., 2017). Subjects receiving bCBT had a greater reduction in symptoms of depression, improved therapeutic progress, and higher mental health-related quality of life (Schuster et al., 2020).

4.2 Anticipated adverse device effects

The manufacturer has compiled documentation on known and foreseeable hazards associated with the medical device in both normal and fault conditions according to ISO 14971:2020.

The following adverse device effects are anticipated:

- The loss or deterioration of device functions (including loss of privacy) can lead to temporarily increased panic and/or anxiety, frustration, and/or decreased adherence.
- Erroneous data transfer can lead to device non-functionality and consequently to temporarily increased anxiety, decreased adherence, and/or decreased therapeutic alliance.
- Use errors can lead to device non-effectiveness, confusion, frustration, and/or decreased therapeutic alliance
- Unintended use can lead to device non-effectiveness, confusion, frustration, and/or decreased therapeutic alliance

4.3 Risks associated with participation in the clinical investigation

While using the application, all participants will receive a face-to-face CBT (treatment as usual). The participants could face a deterioration of their general symptoms of depression or anxietxy. Furthermore, the increase of these symptoms could trigger, similar to other forms of psychotherapy, other symptoms of mental diseases.

4.4 Steps that will be taken to control or mitigate the risks.

All subjects will receive TAU during the investigation by licensed psychotherapists or psychotherapists in training under supervision (1:4 ratio). The respective psychotherapist supervises the subject throughout the study through regular interactions (TAU) and serves as a risk-mitigating clinician between the patient, the medical device and the clinical investigation.

Besides, psychotherapists and subjects will have one or more contact persons of the manufacturer for questions regarding the usage of the device or the investigation beyond classical clinical questions (see also chapter 14)

4.5 Rationale for benefit-risk ratio

According to the manufacturer's risk analysis there are no unacceptable risks that can originate from the use of Elona (see IB for more information). The device is classified as software safety class A (EN 62304:2015)

The severity of the potential harm has been categorized as negligible (No physical or mental harm) and/or minor (Results in injury or (mental) impairment not requiring medical intervention).

The anticipated benefits outweigh the anticipated risks considerably.

5 Objectives and hypotheses of the clinical investigation

5.1 Purpose and claims for clinical performance

The purpose of this study is to demonstrate safe and effective use of Elona in blended CBT settings with patients suffering from mild to moderate depression. This study will be used as pivotal evidence to support market approval of the Elona medical device.

5.2 Objectives

5.2.1 Primary objective(s)

5.2.1.1 Primary efficacy objective

Demonstrate the superiority of Elona when combined with TAU in comparison to TAU only in the self-assessment of depressive or anxiety symptoms after completion of treatment after 6 weeks and 12 weeks (pre-mid-post difference of BDI-II, BAI, PSWQ, PHQ-9, GAD-7).

5.2.1.2 Primary safety objective

Demonstrate that Elona blends into TAU and provides digital interventions as intended.

5.2.2 Secondary objective(s)

Furthermore, the combination of Elona and TAU will increase the working alliance of the therapy, the general quality of life, health status and satisfaction with the treatment. Additionally, the combination of Elona and TAU will increase adherence to the therapy, compliance to CBT homework and subject's competence regarding their psychological well-being (WHOQOL-BREF, SWE, ASAS, MHLS, NEQ, WAI-SR, Adherence).

5.3 Hypotheses

5.3.1 Primary hypotheses

1.
2.

P1/1: Depression Patients receiving bCBT with Elona experience stronger improvements in depression symptoms (BDI-II, PHQ-9) compared to patients receiving TAU after 6/12 weeks of treatment.
P1/2: Anxiety Patients receiving bCBT with Elona experience stronger improvements in anxiety symptoms (BAI, PTWQ, GAD-7) compared to patients receiving TAU after 6/12 weeks of treatment.

5.3.2 Secondary hypotheses

1.
2.
3.

S2: Patients receiving bCBT with Elona experience stronger improvements in their quality of life (assessed with the WHOQOL- BREF) compared to patients receiving TAU after 12 weeks of treatment.
S3: Patients receiving bCBT with Elona experience stronger improvements in their work and social adjustment (assessed with the WSAS) compared to patients receiving TAU after 12 weeks of treatment.

S4: Patients receiving bCBT with Elona experience stronger improvements in their self-efficacy (assessed with the SWE) compared to patients receiving TAU after 6/12 weeks of treatment.
S5: Patients receiving bCBT with Elona experience stronger improvements in their mental health literacy (assessed with the MHLS) compared to patients receiving TAU after 6/12 weeks of treatment.
S6: Patients receiving bCBT with Elona show higher adherence (assessed through self- and psychotherapist-report) compared to patients receiving TAU after 6/12 weeks of treatment.
S7: Patients receiving bCBT with Elona report fewer therapy-related negative events compared to patients receiving TAU after 6/12 weeks of treatment.
S8: Patients receiving bCBT with Elona show a stronger working alliance (assessed through self- and psychotherapist-report) compared to patients receiving TAU after 6/12 weeks of treatment.

5.4 Risks and anticipated adverse device effects

Risks and anticipated adverse device effects are assessed throughout the study.

6. Design of the clinical investigation

6.1 General

To test the effectiveness and safety of Elona a cohort study for patients with a clinical diagnosis of depression (including ICD-10: F32.x, F33.x) or anxiety disorder (including ICD-10: F40.x, F41.x) based on ICD-10 criteria is planned. The RCT comprises two arms: Subjects assigned to the treatment group will get access to the Elona device. The other group will get access to Elona after 12 weeks. All groups will have full access to TAU (weekly face-to-face psychotherapeutic treatment) over a 12-week period. For the primary/secondary objectives, two 2x3 RCT Intention-to-treat analyses (pre vs. mid vs. post) design will be used.

Assessments will take place at baseline (T0), mid 6-week treatment (T1) and 12-week after treatment start (T2) as a self-report. Self-report data are collected including basic demographic questions via a online questionnaire. The questionnaire includes the Beck Depression Inventory Version 2 (BDI II (Kühner et al., 2007), the Beck Anxiety Inventory (BAI) (Margraf & Ehlers, 2007) and the Penn State Worry Questionnaire (PSWQ) (Glöckner-Rist & Rist, 2006). Both groups receive the brief version of the quality of life scale by the World Health Organization (WHOQOL- BREF (Angermeyer et al., 2002)), the Work and Social Adjustment Scale (WSAS (Mundt, J., Marks, I., Shear, M., & Greist, J., 2002)), German version: ASAS (Heissel, A., Bollmann, J., Kangas, M. et al., 2021), a self-efficacy scale (SWE) (Jerusalem & Schwarzer, 2003), the Negative Effects Questionnaire (NEQ) (Rozental et al., 2019), Working Aliance Inventory - Kurzform (WAI-SR) (Wilmers, F., Munder, T., Leonhart, R., Herzog, T., Plassmann, R., Barth, J., & Linster, H. W., 2008) and the Mental Health Literacy Scale (MHLS) (O'Connor, M., & Casey, L., 2015). Also, as part of the International Consortium for Health Outcomes Measurement (ICHOM) guidelines (Obbarius et al., 2017), the Patient Health Questionnaire (PHQ-9 (Spitzer, 1999), German Version PHQ-9 (Löwe et al., 2004)) and Generalized Anxiety Disorder 7 (GAD-7) is used.

Also, participants of both groups will further receive five non-standardized one-item 5-score questions (1-5), in which they are asked how willingly they comply with homework or interventions..

6.1.1 Intervention

Elona is a digital health application that builds on the bCBT approach. By being a clinician-led treatment, it fully integrates with TAU and supports patients in transferring and applying relevant knowledge, exercises and interventions from the therapeutic sessions to their daily lives. It thereby intensifies the treatment through repetition of content, helps following through with CBT homework, tracks and visualizes treatment progress and generally helps to comply with content covered in therapy sessions as part of TAU. The application will therefore be used in parallel to regular face-to-face therapy (12 weeks) and can be accessed without access by the subject, however, the device is intended for use under normal conditions for a period of less than 20 minutes daily.

6.1.2 Control group

The control group will receive TAU and get access to Elona after 12 weeks.

6.1.3 Completion of clinical investigation

The clinical investigation will be completed after 160 subjects will have received 12 weeks of CBT (T2).

6.2 Investigational device(s) and comparator(s)

In this clinical investigation, no comparators beyond TAU will be tested.

6.3 Subjects

6.3.1 Inclusion criteria for subject selection.

All subjects must have been diagnosed with one of the following ICD-10 diagnoses:

- F32: Depressive episode
- F32.0: Mild depressive episode
- F32.1: Moderate depressive episode
- F32.2: Severe depressive episode without psychotic symptoms
- F32.8: Other depressive episodes
- F32.9: Depressive episode, unspecified

- F33: Recurrent depressive disorder
- F33.0: Recurrent depressive disorder, current episode mild
- F33.1: Recurrent depressive disorder, current episode moderate
- F33.2: Recurrent depressive disorder, current episode severe without psychotic symptoms
- F33.8: Other recurrent depressive disorders
- F33.9: Recurrent depressive disorder, unspecified

- F34: Persistent mood [affective] disorders
- F34.0: Cyclothymia
- F34.1: Dysthymia
- F34.8: Other persistent mood [affective] disorders
- F34.9: Persistent mood [affective] disorder, unspecified

- F40.0 Agoraphobia
- F40.00 Agoraphobia without panic disorder
- F40.01 Agoraphobie with panic disorder
- F40.1 Social phobias
- F40.2 Specific (isolated) phobias
- F40.8 Other phobic anxiety disorders
- F40.9 Phobic anxiety disorder, unspecified

- F41.0 Panic disorder [episodic paroxysmal anxiety]
- F41.1 Generalized anxiety disorder
- F41.2 Mixed anxiety and depressive disorder
- F41.3 Other mixed anxiety disorders
- F41.8 Other specified anxiety disorders
- F41.9 Anxiety disorder, unspecified

- F45.2 Hypochondriacal disorder

Subjects further need to be between the age of 18 and 65, possess sufficient German language skills (in writing and reading), possess a smartphone (iOS or Android operating system) with internet access, provide signed and dated informed consent and are willing to comply with the protocol.

6.3.2 Exclusion criteria for subject selection.

All subjects without the inclusion ICD-10 diagnosis criteria as well as subjects with the following ICD-10 diagnoses are excluded:

- F0x.x: Organic, including symptomatic, mental disorders
- F1x.x Mental and behavioural disorders due to psychoactive substance use (except F17.x)
- F2x.x: Schizophrenia, schizotypal and delusional disorders
- F31: Bipolar affective disorder
- F32.3: Severe depressive episode with psychotic symptoms
- F33.3: Recurrent depressive disorder, current episode severe with psychotic symptoms

Subjects with acute suicidality (operationalized via BDI II screening question and first checkup), subjects under the age of 18, subjects without any access to a smartphone (iOS or Android operating system) with internet access and subjects without German language proficiency are excluded from this study. If a subject is currently enrolled or is planning to participate in a potentially confounding drug or device trial during the study, enrollment into this study needs to be pre-approved.

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

If a subject wants to withdraw from the clinical investigation, the missing data will be blanked in the dataset and excluded from the evaluation. Reasons for withdrawal will be collected.

Subjects will not be replaced during the investigation, as all subjects undergo a standardized, but highly individual treatment. The study will be started with 20% of additional subjects to account for possible drop-out.

If a subject’s condition worsens during the investigation (irrespective of the reason) and he/she needs to receive treatment in an inpatient setting, the subject will be excluded from the study.

6.3.4 Point of enrolment

Subjects are enrolled during the first therapy sessions that are intended for diagnosis.

6.3.5 Point of randomization

Participants will be randomized after signing the informed consent and general diagnosis (Depression/ Anxiety group) using an online-randomization tool.

6.3.6 Total expected duration of the clinical investigation

The clinical investigation is expected to start in January 2022 and conclude mid 2022.

6.3.7 Expected duration of each subject's participation

All subjects will receive a total of 12 weeks of CBT.

6.3.8 Number of subjects

Each group will include 40 subjects totalling 160 subjects across both conditions for both diagnosis groups.

6.3.9 Enrolment period

Subjects are expected to be enrolled within the first eight weeks after the start of the study.

6.3.10 Relationship of investigation population to target population

The investigation and target population are both patients suffering from depression or anxiety disorder between 18-65 years of age who have experience and an affinity for smartphone use. Patients should be currently in outpatient psychotherapeutic treatment.

6.3.11 Information on vulnerable population

Subjects in this study are patients diagnosed with depression or anxiety disorder and therefore highly vulnerable.

6.4 Procedures

All subjects in this clinical investigation undergo TAU which includes weekly face-to-face psychotherapy including different interventions for people suffering from depression/ anxiety, all based in CBT.

Beyond TAU, subjects receive access to the Elona medical device. Elona consists of above-mentioned recognised treatment elements of CBT. It provides psychoeducative content about the underlying mental illness (depression, anxiety/panic disorders, somatoform disorders), proposes exercises, methods and techniques that augment the outpatient psychotherapeutic treatment to the patient’s daily routine. By retrieving regular check-ups, Elona responds individually to patients’ feedback and adjusts the contents accordingly. Elona is a smartphone application that can be accessed via the internet at any time from the patient’s device. The duration of use is not specified, however, the manufacturer recommends using it for 60 minutes over the course of a week. The usage can be spread over multiple days (e.g. 5 x 12 minutes).

Due to the relatively small number of subjects in each group in this pilot study, the baseline characteristics could be slightly different and compromise the outcome of the clinical investigation or the interpretation of results. To minimize this factor, basic demographic data (e.g. age, education, prior therapy) and the different diagnosed types of depression and anxiety disorder will be collected at T0 next to outcome instruments and analyzed for possible covariances.

Assessments will take place at baseline (T0), mid 6-week treatment (T1) and 12-week after treatment start (T2). Furthermore, all participants will have access to additional hours of CBT (if necessary) as part of standard of care. as well as have access to the medical device.

All data will be kept for ten years. After this period, all data (including paper testing) will be erased/ shredded. The collected data can be used in following studies regarding the Elona device or other bCBT applications.

6.5 Monitoring plan

Please refer to chapter 8 Data Management.

7. Statistical design and analysis

The population of this intention-to-treat study will include subjects undergoing CBT. Subjects will receive online questionnaires at start (T0), mid-6-sessions (T1) and endpoint (T2). Besides this, participants will fill out a basic demographic data questionnaire at T0.

The (2x3 design) data will be analyzed through repeated measure analysis of variance (ANOVA) at 95% confidence interval. The hypotheses are tested at a significance level alpha 0,05 (two-sided) and 0,025 (one-sided) and powers between 0,8 and 1 minus alpha. Considering the small sample size of this pilot-study, effect sizes and superiority margins will be collected for the following main study. Due to the nature of this pilot study, the power could be decreased if necessary.

In this pilot-study a relatively small sample size of 40 subjects each group is chosen to collect first data on this novel medical device, which then can be used to better plan and conduct a subsequent main study. A termination based on statistical grounds is therefore not intended. The repeated measurement analysis requires a finalized survey. Interim results may be obtained if demanded by the manufacturer.

Beyond that, the following considerations will be taken into account:

- Potential confounding factors will be reported by the coordinating investigator.
- Due to the form of this pilot study there could be an adjustment of the error probabilities. In this case, the investigator has to keep track of these changes.
- Missing data will be labeled and excluded from the analysis. Suspicious data will be reported to the investigators and, if possible, discussed. Drop outs will be labeled and excluded from the analysis.
- No changes to the statistical plan will be permitted without the written approval of the principal investigator.

8. Data management

The data management follows Good Clinical Data Management Practices (GCDMP) curated by the Society for Clinical Data Management (SCDM). The data management process is designed to deliver an error-free, valid, and statistically sound database.

8.1 Data collection

For data collection, we will make use of an online solution for electronic data capture (EDC) to assess patient reported outcomes electronically. Accordingly, we will make use of electronic case report files (eCRF). Participants and therapists will receive text messages including a link to the respective eCRF which can be answered on a smartphone or by using a web browser. Data collected in the eCRF will be automatically entered into the database. For all scales, responses to each item are mandatory, thereby avoiding missing data for single items of a scale. Participants and therapists will receive a reminder message 24 hours and 4 days after the first invitation to the eCRF if they did not yet answer the eCRF.

8.2 CRF tracking and data entry

Participants progress and the completion of eCRFs can be tracked in the EDC system. Data entry is performed automatically within the EDC tool.

8.3 Data validation

Data validity will be ensured by assessing all measures digitally (via eCRFs). Thereby, only the provided scale points can be chosen and inconsistent or out of range data will be impossible. Furthermore, all scale items will be obligatory, thus for each item a response is required, leading to no missing data except participants stop the assessment early without providing responses on the remaining questions. Participants will be reminded to complete the assessment 24 hours and 4 days after the initial invitation to motivate the submission of complete data.

Quality controls of the recorded data will be undertaken at regular intervals (i.e., once per week) by inspecting the exported data.

8.4 Database locking

All data management activities need to be completed prior to database lock. To ensure this, a pre-lock checklist is used and completion of all activities is confirmed. Once the principal investigator agrees on locking, the database is locked and clean data is extracted for statistical analysis. Generally, no modification in the database is possible. Only in case of a critical issue or for other important operational reasons, the principal investigator(s) can modify the data even after the database is locked. Any changes after database locking

requires proper documentation and an audit trail has to be maintained with sufficient justification for updating the locked database. Data extraction is done from the final database after locking.

8.5 Data retention

The database is stored online on protected servers within the EDC. Exported data is secured by the coordinating investigator in several electronic copies (e.g., hard drives) which are stored in a locked safe. Stored data will be checked for accessibility, readability and accuracy. Access to the data will be ensured throughout the retention period of ten years.

After this period, all data will be erased. The collected data can be used in following studies regarding the Elona device or other bCBT applications.

8.6 Subject privacy

The confidentiality of records that could identify participants is protected, respecting the privacy and confidentiality rules by all parties involved at all times throughout the clinical investigation. Unauthorized access to data is inhibited. Confidentiality will be ensured by providing each participant with a pseudonymized, randomly generated participant ID. The mapping of participants' identities and names to participant IDs is neither known to the investigators nor to the participating therapists, so anonymity is ensured.

The principal investigator or investigation site provides direct access to source data during and after the clinical investigation for monitoring, audits, ethics committee (EC) review, and regulatory authority inspections. As required, the principal investigator or investigation site shall obtain permission for direct access to source documents from the subject, psychotherapist and regulatory authorities before starting the clinical investigation.

9. Amendments to the CIP

The principal investigator will submit any significant amendment to the CIP, including a justification for this amendment, to the appropriate regulatory authorities and to the investigators to obtain approval from their Ethics Board, if applicable. Administrative amendments to the CIP will be submitted to the Ethics Board and appropriate regulatory authorities for notification, if applicable. Any revisions or amendments to the CIP or Informed Consent Form, along with a statement of justification for the changes, will be submitted to all affected regulatory authorities and governing Ethics Boards, according to applicable regulations. All amendments to the CIP shall be agreed between the manufcaturer and the principal investigator(s). Approval by regulatory agencies and Ethics Board (where applicable) must be obtained prior to implementing a CIP revision at the site.

In case the investigator will propose any appropriate modification(s) of the CIP or the investigational device, the manufcaturer will review this proposal and decide whether the modification(s) will be implemented.

10. Deviations from clinical investigation plan

A deviation from the CIP is defined as an event within the study that did not occur according to the CIP.

The investigator is not allowed to deviate from the CIP without prior approval of the EC except to protect the rights, safety and well-being of human subjects under emergency circumstances.

For medically justifiable conditions which preempt a subject's ability to complete a study-required procedure, it may be permitted to report only one deviation which will apply to all visits going forward. This may also apply for other unforeseen situations (e.g. the subject permanently refuses to complete a study-required procedure and the data will not contribute to the primary endpoint analysis). However, prior approval by the coordinating investigator is required for such situations.

Any deviation from the CIP shall be recorded together with an explanation for the deviation. Deviations shall be reported to the principal investigator within five working days. Reporting of all other study deviations should comply with Ethics Board policies and/or local laws and must be reported to the principal investigator as soon as possible upon the investigation site becoming aware of the deviation. The manufacturer is responsible for analyzing deviations and assessing their significance

Examples of study deviations include but are not limited to:

- Failure to obtain proper patient informed consent
- Failure to collected required study data
- Inclusion/exclusion criteria not met

11. Device accountability

The manufacturer assures that access to the investigational devices is controlled and the investigational devices is only used in the clinical investigation and according to the CIP. As the investigational device consists of a software, the manufacturer and principal investigator ensures that:

- the name of persons who downloaded and used the device are recorded
- the date of the download is recorded
- the dates of use are recorded
- subjects using the device are identified (within the limits of software application, i.e. through password access)
- the date on which the device is deinstalled/removed from the subject is recorded

Written procedures are established for the entire process of device accountability.

12. Statements of compliance

This study will be conducted according to the Declaration of Helsinki, the Clinical Investigation Plan, Good Clinical Practice (ISO 14155:2020) and in accordance to national and local laws, regulations, standards, and requirements.

The clinical investigation shall not begin until all required approvals and documents from the Ethics Board and regulatory authorities, if needed, have been received. Any additional requirements imposed by the Ethics Board or regulatory authority shall be followed, if appropriate.

This study will be conducted in compliance with international ethical and scientific quality standards, known as good clinical practice (GCP). GCP includes review and approval by an independent Ethics Board before initiating a study, continuing review of an ongoing study by an Ethics Board and obtaining and documenting the freely given informed consent of a subject before initiating the study.

This study is designed to reflect the GCP principles outlined in ISO 14155:2020 and other international clinical requirements outlined below. These include the protection of the rights, safety and well-being of human subjects, controls to ensure the scientific conduct and credibility of the clinical investigation and the definition of responsibilities of the manufacturer and investigators. In accordance with ISO 14155:2020, the manufacturer shall avoid improper influence on, or inducement of, the subject, monitor, any investigator(s) or other parties participating in, or contributing to, the clinical investigation. All investigators shall avoid improper influence on or inducement of the subject, manufacturer, monitor, other investigator(s) or other parties participating in or contributing to the clinical investigation. Adverse Event and Device Deficiency handling in this study is ISO 14155:2020 compliant.

All sites will follow and comply with:

- ISO 14155:2020 “Clinical investigation of medical devices for human subjects — Good clinical practice”
- Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013)
- Council Directive 93/42/EEC of 14 June 1993 concerning medical devices (Medical Device Directive, MDD)
- The procedures described within this CIP
- Ethic Board requirements

The study will be publicly registered prior to first enrollment in accordance with the Declaration of Helsinki in a WHO International Clinical Trials Portal.

Approval of the CIP and CIP amendments is required from the following groups prior to any study procedures at a study site:

- Principal investigator(s)
- independent medical ethics committee or institutional review board
- the manufacturer, if required

Similarly, approval of subsequent revisions to the CIP is required at each study site from the above-mentioned groups prior to implementation of the revised CIP at the site.

An insurance for this clinical trial is not required by law. It is further to add, that the investigators and manufacturer consider the risks of this clinical trial to be negligible. Subjects in this trial are further receiving regular psychotherapeutic treatment, which serves as an additional supervision of the subjects.

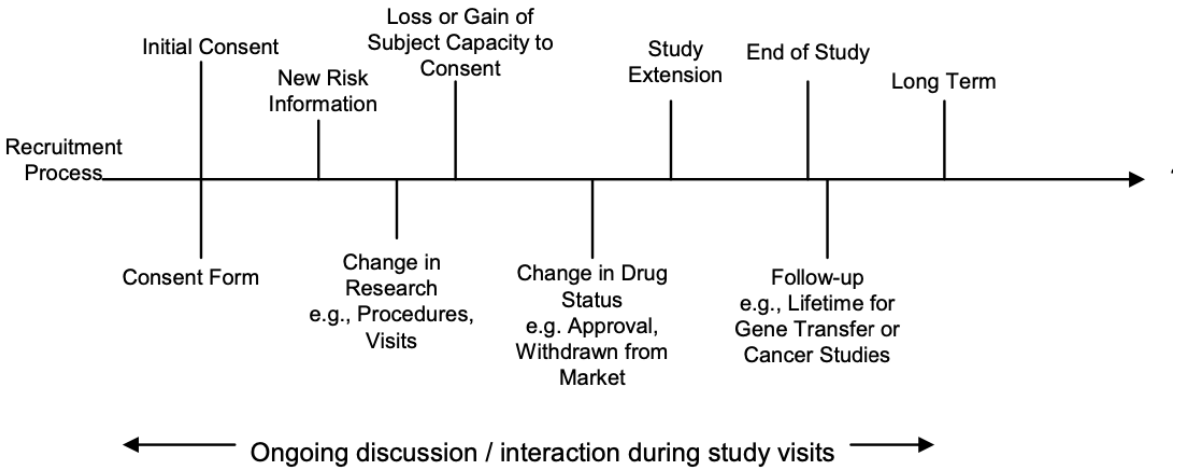
13. Informed consent process

The informed consent process is central to the ethical conduct of this study. It is an on- going conversation between the human research subject and the investigator that begins before consent is given and continues until the end of the subject's involvement in the research. While the principal investigator provides various tools for the investigator to optimize this conversation, the most important feature of informed consent is the investigator's commitment to the process.

The investigators provide information to subjects being comprehensive, concise, clear, relevant, and understandable as a part of the informed consent. In order to ensure readability, the informed consent form should not exceed a reasonable length. Moreover, the investigator has to verify the understanding of the subject by doing an interview

13.1 Goals of the informed consent process

The goals of the informed consent process are to give the subject information about the study, to ensure the subject has time to consider all options, to answer all of the subject's questions before any decision is made and to ultimately obtain the subject's voluntary informed consent to participate in the study. The task of the investigator is to continue informing the subject throughout the study and continue to re-affirm subject consent to participate throughout the study.



Investigator responsibilities in regard to informed consent

13.2 Investigator responsibilities in regard to informed consent

The investigator is responsible for the following tasks:

- Obtain consent before initiating study-specific procedures.
- Provide a quiet, comfortable, and private setting for the informed consent process whenever possible.
- Explain the consent process to the subject.
- Make sure the subject has time to consider all options; allow the subject to take the form home before signing (whenever possible).
- Consider the subject's reading abilities. Check to make sure the CIP has not disallowed subjects unable to read. If enrollment of limited or non-readers is allowed, involve an impartial witness in the informed consent process.
- Answer all questions the subject may have.
- To the extent possible, make sure the subject understands enough information about the study to give informed consent.
- To the extent possible, make sure the subject can consent free from coercion or other undue influence.
- Since the informed consent process continues throughout the subject's participation in the study, consent should be informally verified on a continuing basis.
- Significant new information must be given to the subject, and continuing consent documented in some way; for example, new risk information presented to the subjected in an addendum to be signed by subjects who agree to continue to participate.

During the informed consent process, the investigator should consider the following issues:

- Was the subject alert and, in your opinion, able to read and understand the language in the consent form?
- If the subject was unable to read the consent form, and limited or non-readers were allowed to participate, did you have an impartial witness present for the entire process? (An impartial witness is someone with adequate reading ability who is independent of the trial, who cannot be unfairly influenced by people involved in the trial, who attends the informed consent process while the consent form is being read to the subject, who reads the informed consent form and any other written information supplied to the subject, and who is willing to attest to this by signing the consent form.)
- Was the subject under any pressure (for example, family pressure, lack of medical insurance) to participate in the research? Was this discussed?
- Did the subject take time to carefully read the consent form, or read it along with you?
- Were the risks as set forth in the consent form carefully explained to the subject?
- Are there any other risks or concerns not stated in the consent form and were these explained to the subject?
- Was the subject asked if he or she had any questions about the study?
    - Did the subject have any questions or concerns?
    - Were the subject's questions answered?
    - Was the subject satisfied with the answer(s) they were provided?

- Did the person conducting the consent discussion check for subject understanding by asking some basic questions about the research? Did the responses reflect adequate understanding?
- Did the subject express a clear decision to proceed with the study?
- Was the consent form signed by the person who conducted the informed consent discussion?
- Was the consent form signed by a witness (if required)?
- Was the consent form signed by the Principal Investigator (if required)?
- If a Legally Authorized Representative is allowed to sign for the subject, were additional concerns about the subject's understanding and assent considered and addressed?

13.3 Description of the informed consent process in circumstances where the subject is unable to give it

Subjects can only participate in this study if they are able to give their consent by themself (see inclusion/exclusion criteria).

14. Adverse events, adverse device effects, and device deficiencies

14.1 Adverse events and adverse device effects

All adverse events (AEs) regardless of their severity or relationship to the Elona device or study procedure will be collected throughout a subject's participation, starting from the time the informed consent form is signed. Reporting of these events to the manufacturer will occur on an AE form, including event description, date of AE, treatment, resolution, assessment of both the seriousness of the AE and the relatedness to the Elona device. Each AE must be recorded on a separate AE CRF. The principal investigator shall report all AEs to the manufacturer and, where appropriate, to ECs and the regulatory authority within 5 working days. Documented pre-existing conditions are not considered AEs unless the nature or severity of the condition has worsened. In addition, AEs impacting users or other persons, non-subject adverse events will be collected.

In case of serious adverse events, the manufacturer is to be contacted immediately by the investigation site and/or principal investigator per the manufacturer's contact information.

14.2 Device deficiencies

Device deficiency (DD) information will be collected throughout the study and reported to the manufacturer. note that DDs that result in an Adverse device effect (ADE) to the subject should be captured as an AE only. DD that did not lead to an AE but could have let to a serious adverse device effect (SADE) (i.e., if suitable action had not been taken, if intervention had not been made, or if the circumstances had been less fortunate) require immediate reporting.

For DDs that require immediate reporting, the manufacturer is to be contacted immediately by the investigation site and/or principal investigator per the manufacturer's contact information.

14.3 Adverse events and device deficiency definition and categorization

For the purpose of this CIP, AE, ADE, and DD are defined and classified according to ISO 14155:2020

Definitions	
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated. Note 1 to entry: This definition includes events related to the investigational medical device or the comparator. Note 2 to entry: This definition includes events related to the procedures involved. Note 3 to entry: For users or other persons, this definition is restricted to events related to the use of investigational medical devices or comparators.
Adverse Device Effect (ADE)	Any adverse event related to the use of an investigational medical device. Note 1 to entry: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. Note 2 to entry: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device. Note 3 to entry: This includes 'comparator' if the comparator is a medical device.

Device Deficiency (DD)	Any inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance Note 1 to entry: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling. Note 2 to entry: This definition includes device deficiencies related to the investigational medical device or the comparator.
Seriousness	
Serious Adverse Event (SAE)	Any adverse event that led to any of the following 1. death, 2. serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following: a. a life-threatening illness or injury, or b. a permanent impairment of a body structure or a body function including chronic diseases, or c. in-patient or prolonged hospitalization, or d. medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function, 3. foetal distress, foetal death, a congenital abnormality, or birth defect including physical or mental impairment Note 1 to entry: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE)	Any adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Serious Adverse Device Effect (USADE)	Amy serious adverse device effect which by its nature, incidence, severity or outcome

	has not been identified in the current risk assessment.

14.4 Reporting of Adverse events, adverse device effects, and device deficiencies

All reported AEs and DDs will be reviewed by the manufacturer. AEs and DDs will be classified according to the definitions provided in ISO 14155:2020. Upon receipt of a AE or DD at the manufacturer, a representative will review it for completeness and accuracy and whenever necessary will request clarification and/or additional information from the (principal) investigator.

For emergencies regarding a USADE, SAE and/or SADE the manufacturer is to be contacted immediately by the investigation site and/or principal investigator per the manufacturer's contact information.

Regulatory reporting of AEs and DDs will be recorded and reported according to local regulatory requirements.

15. Vulnerable population

The subject pool comprises people suffering from depression or anxiety disorder and are therefore considered vulnerable. In order to identify and protect the vulnerable population, subjects will undergo two to six diagnostic hours of psychotherapy in which the subject or the therapist can both decide to exclude the subject from the study (see exclusion criteria).

Subjects receive a detailed brochure about the participation and study procedure. The participants will receive a copy of the informed consent and can withdraw the consent without restrictions referring to their psychotherapeutic treatment. After the clinical investigation, subjects can receive further CBT and/or will be invited to a 2,5 month checkup.

16. Suspension or premature termination of the clinical investigation

The principal investigator or regulatory authorities may decide to suspend or prematurely terminate the clinical study (e.g. if information becomes available that the risk to study subjects is higher than initially indicated). If the clinical study is terminated prematurely or suspended, the clinical investigators shall be promptly informed of the termination or suspension and the reason(s) for this. The investigator shall then promptly inform the reviewing Ethics Board, the study subjects, and the psychotherapists.

The principal investigator, Ethics Board or Regulatory Authority may decide to suspend or prematurely terminate an investigation site (e.g. in case of expiring approval of the reviewing Ethics Board, non-compliance to the CIP or lack of enrollment). If an investigation site is prematurely terminated, the principal investigator shall promptly inform the investigator(s) of

the termination or suspension and the reason(s) for this. The investigator shall then promptly inform the reviewing Ethics Board, if required, the study subjects, and the psychotherapists.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definite outcomes, investigators must assess whether to continue, modify or immediately stop the clinical study in the respective investigation site and immediately inform the manufacturer and Ethics Board, if applicable. Risks will be continuously monitored, assessed and documented by the investigators.

In case of early investigation site suspension or termination, subjects will be followed-up as per standard of care.

16.1 Planned study closure

Study closure is a process initiated by distribution of a study closure letter. Study closure is defined as closure of a clinical study that occurs when the principal investigator and/or regulatory requirements have been satisfied per the CIP and/or by a decision by the principal investigator or regulatory authority, whichever occurs first. The study closure process is complete upon distribution of the final report. Ongoing Ethics Board oversight is required until the overall study closure process is complete. Upon study closure, subjects should be managed and followed per psychotherapist/physician discretion

16.2 Early termination or suspension

Early Termination is the closure of a clinical study that occurs prior to meeting defined endpoints. This is possible for the whole study or a single center. Study suspension is a temporary postponement of study activities related to enrollment and distribution of the product. This is possible for the whole study or a single center.

16.2.1 Study termination or suspension

Possible reasons for considering study suspension or termination of the study include but are not limited to:

- Adverse events associated with the system or product under investigation which might endanger the safety or welfare of the subject
- Observed/suspected performance different from the product’s design intent
- Decision by the principal investigator or regulatory body (where the study is operating under regulatory body authority)
- Technical issues of the medical device

16.2.2 Investigator/center termination or suspension

Possible reasons for clinical investigator or center termination or suspension include but are not limited to:

- Failure to obtain initial Ethics Board approval
- Persistent non-compliance to the clinical investigation plan (e.g. failure to adhere to inclusion/exclusion criteria)
- Lack of enrollment

- Noncompliance to regulations and the terms of the CIP (e.g. failure to submit data in a timely manner, failure to follow-up on data queries and monitoring findings in a timely manner, etc.)
- Ethics Board suspension of the center
- Fraud or fraudulent misconduct is discovered (as defined by local law and regulations)
- Investigator request (e.g. no longer able to support the study)

16.2.3 Procedures for termination and suspension

The principal investigator will promptly inform the clinical investigators of the termination or suspension and the reasons and inform the regulatory authority(ies) where required. In the case of study termination or suspension for reasons other than a temporary Ethics Committee approval lapse, the investigator will promptly inform the Ethics Committee along with the reason(s) for termination or suspension. In the case of study termination, the investigator must inform the subjects and may inform the personal psychotherapist of the subjects to ensure appropriate care and follow-up is provided. In the case of a study suspension, subject enrollment must stop until the suspension is lifted. In the case of a study suspension, enrolled subjects should continue to be followed out of consideration of their safety, rights and welfare.

If a subject decides to terminate his/her psychotherapy or to terminate his/her participation in the investigation, the psychotherapist will share the Chiffre with the coordinating investigator, so the data can be erased and/or labeled. At no point, the investigator will get access to the clear subjects data.

17. Publication policy

17.1 Registration in publicly accessible database

In accordance with the Declaration of Helsinki, a description of the clinical investigation shall be registered in a WHO International Clinical Trials Portal before the start of recruitment activities. The content shall be updated throughout the conduct of the clinical investigation and the results entered at completion of the clinical investigation.

17.2 Management of publication

Results may be submitted for publication. If results from this study will be published, they will be handled according to the following guidelines.

17.3 Criteria for determining authorship

Publications will adhere to authorship criteria defined by the International Committee of Medical Journal Editors (ICMJE, Uniform requirements for manuscripts submitted to biomedical journals, www.icmje.org). Individual authorship criteria defined by the target journal or conference will be followed when it differs from ICMJE criteria.

Authors, including the manufacturer's personnel, must at a minimum meet all of the conditions below:

- Substantial contribution to conception and design, or acquisition of data, or analysis and interpretation of data
- Drafting the article or revising it critically for important intellectual content
- Final approval of the version to be published
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Decisions regarding authorship and contributor-ship will be made by the principal investigator. The selected authors will be responsible for drafting the publication. All selected authors must fulfill the authorship conditions stated above to be listed as authors, and all contributors who fulfill the conditions must be listed as authors.

All investigators not listed as co-authors will be acknowledged as the "Elona Clinical Study Investigators" and will be individually listed according to the guidelines of the applicable scientific journal when possible and affiliation. Any other contributors will be acknowledged by name with their specific contribution indicated.

17.4 Transparency

Transparency of study results will be maintained by the following means:

- A final report, describing the results of all objectives and analysis, will be distributed to all investigators, Ethics Board and competent Authorities when required by local law
- Submitting for publication the primary study results after the study ends
- Disclosing conflicts of interest (e.g., financial) of the co-authors of publications according to the policies set forth by the corresponding journals and conferences

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