

Study Protocol

A pilot randomised controlled trial to test the efficacy of an online-program on disease-related psychological distress and quality of life in patients with chronic inflammatory rheumatic disease (RELIEVE).

11.03.2024

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List of Abbreviations

Abbreviation	Meaning
ACT	Acceptance and Commitment Therapy
AE	Adverse Event
AQoL-8D	Assessment of Quality of Life - 8 dimensions
CBT	Cognitive Behavioural Therapy
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRO	Contract Research Organisation
DRKS	German Clinical Trials Register (Deutsches Register Klinischer Studien)
EDC-System	Electronic Data Capture System
EULAR	European Alliance of Associations for Rheumatology
GCP	Good Clinical Practice
HADS-D	Hospital Anxiety and Depression Scale - German Version
HLS-EU-Q16	European Health Literacy Survey - short form
ICD	International Statistical Classification of Diseases and Related Health Problems
ICF	Informed Consent Form
ICH	International Conference for Harmonization
IEC	Independent Ethics Committee
ITT-Population	Intention-to-Treat-Population
LOCF	Last Observation Carried Forward
MCID	Minimum Clinically Important Difference
MMRM	Mixed Linear Model for Repeated Measures
NEQ	Negative Effect Questionnaire for Psychotherapy
NPS	Net Promoter Score
PD	Private Lecturer (Privatdozent)
PGA	Patient Global Assessment of Disease Activity
PGIC	Patients' Global Impression of Change
PHQ-9	Patient Health Questionnaire
PP-Population	Per-Protocol-Population
PsA	Psoriatic Arthritis
PSS-10	Perceived Stress Scale-10
QoL	Quality of Life
RA	Rheumatoid Arthritis
RCT	Randomised Controlled Trial

Abbreviation	Meaning
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SES6G	Self-Efficacy for Managing Chronic Disease 6-Item Scale - German version
SLE	Systemic Lupus Erythematosus
UG	Entrepreneurial Company (Unternehmergesellschaft)
UK	United Kingdom
WSAS	Work and Social Adjustment Scale

Study Protocol

Protocol Title:

A randomised controlled trial to test the efficacy of an online program on disease-related psychological distress and quality of life in patients with chronic inflammatory rheumatic diseases (RELIEVE).

German Protocol Title:

Eine randomisierte, kontrollierte Pilotstudie zur Überprüfung der Wirksamkeit eines Online-Programms auf die krankheitsbezogene psychische Belastung und die Lebensqualität von Patienten mit chronisch-entzündlichen rheumatischen Erkrankungen (RELIEVE).

Table 1: Study information.

Protocol Identifier:	RELIEVE
Amendment Number:	2
Investigational Medical Device:	Vila Health (trade name Vila RaVie) (Software version: 1.5)
Study Phase:	Not applicable
Study Lead:	PD Dr. med. Johannes Knitza
Version:	4.0
Version Date:	11-March-2024

Confidential

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Sponsor Signature Page

The people signing hereby declare that they have read this protocol and agree to its contents.

DocuSigned by:



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11.03.2024

Signature

Date of Signature

Table 2: Study lead information.

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Investigator Signature Page

This page will be filled in for each Investigator taking part in this randomised controlled study. A list of all sites and respective Investigators will be provided separately.

The individuals signing this document affirm that they have read this protocol and accept its terms. They state that the study will be carried out and recorded in full compliance with the protocol (and amendments), the Declaration of Helsinki, the current Good Clinical Practice (GCP) guidelines set forth in this document by the International Conference for Harmonization (ICH), and any applicable regulatory requirements. They will also make sure that copies of this research protocol and the ICH GCP guidelines are available to sub-Investigator(s) and other relevant staff members so that they can carry out their responsibilities in accordance with the instructions of this document.

DocuSigned by:

1D9F7C95D3FA4C6...

11.03.2024

Signature

Date of Signature

Table 3: Investigator information.

Name, academic degree:	PD Dr. med. Johannes Knitza
Function/Title:	Rheumatologist
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Protocol Amendment Summary of Changes

Table 4: Document history.

Document History		
Document	Date	Comments (if applicable)
Protocol Version 1.0	29-September-2023	
Protocol Version 2.0	30-November-2023	Changes according to Comments Ethikkommission der Universitätsklinik Gießen und Marburg in letter from 27.10.2023 (AZ.: 23-252 BO). Additionally small textual corrections.
Protocol Version 3.0	09-January-2024	Addition of two secondary endpoints to include and test alternative questionnaire (PHQ-9 and GAD-7) to HADS-D in pilot study
Protocol Version 4.0	11-March-2024	Change of inclusion criteria 3.a to: "HADS ≥ 8 points on at least one scale (depression/anxiety)" Minor corrections and textual updates.

1 Protocol Summary

1.1 Synopsis

Table 5: Study synopsis.

Name of intervention	Vila RaVie
Manufacturer	Vila Health UG
Intended purpose	Improvement of disease-related psychological distress and quality of life, in patients with chronic inflammatory rheumatic diseases.
Sponsor (contact person)	Vila Health UG (haftungsbeschränkt) Laura Korcik Chausseestraße 86 10115 Berlin Mail: laura.korcik@vila-health.com Phone: +49 170 2238853
Study lead	PD Dr. med. Johannes Knitza Institute for Digital Medicine Philipps-University and University Hospital of Giessen and Marburg Baldingerstrasse 35043 Marburg Emergency contact: 064215862589
Contract Research Organization	novineon CRO GmbH Prof. Dr. med. Marc O. Schurr Friedrich-Miescher-Straße 9 72076 Tübingen, Germany
Title	A pilot randomised controlled trial to test the efficacy of an online program on disease-related psychological distress and quality of life in patients with chronic inflammatory rheumatic diseases (RELIEVE).
Short title	RELIEVE
Study registry number	DRKS00032862
Study type and design	Randomised controlled trial. Patients are recruited at the study site and online. The diagnosis of all patients is documented at the study site or confirmed by a physician. This monocentre study in Germany will follow a randomised, controlled, parallel-group design. Male and female patients with RA, PsA, or SLE (≥ 18 years) and disease-related psychological distress are eligible. The respective indications will be included according to their epidemiological frequency. It is expected that recruitment will be completed within 12 weeks. At day 0, subjects will be screened and, after confirmation of eligibility, randomly assigned to 1 of the following 2 study interventions: Control (No access to the online program): Subjects in the control group will continue having unrestricted access to all therapies which are considered as care as usual and additionally receive a flyer about mental health in chronic inflammatory rheumatic diseases. After completion of the study, they receive access to the online program.

	Intervention (Use of the online program).
Study site	Institute for Digital Medicine Philipps-University and University Hospital of Giessen and Marburg Baldingerstrasse 35043 Marburg
Aims of the study	The purpose of this study is to exploratively describe the efficacy of an online program in patients with chronic inflammatory rheumatic diseases (RA, PsA, or SLE). Moreover, the disease-related psychological distress and quality of life will be assessed. Subjects will use the application on their own in addition to their usual therapy for their chronic inflammatory rheumatic disease.
Endpoints	<p><u>Primary:</u></p> <p>Change in psychological distress and quality of life after 12 weeks of treatment compared to baseline. Changes are compared between the intervention and the control group.</p> <ul style="list-style-type: none"> • Disease-related psychological distress is measured with the Hospital Anxiety and Depression Scale – German Version (HADS-D). • Health-related quality of life is measured with Assessment of Quality of Life - 8 dimensions (AQoL-8D) questionnaire. <p><u>Secondary:</u></p> <p>Change in patients' self-efficacy, health literacy, stress levels, work ability, and social function after 12 weeks of treatment compared to baseline. The change will be compared between the intervention and control groups.</p> <ul style="list-style-type: none"> • Self-efficacy is measured with the Self-Efficacy for Managing Chronic Disease 6-Item Scale - German version (SES6G) questionnaire). • Health literacy is measured with the European Health Literacy Survey - short form (HLS-EU-Q16). • Stress levels are measured with the Perceived Stress Scale (PSS-10) • Work Ability and Social Function are measured with the Work and Social Adjustment Scale (WSAS). • Degree of depression severity is measured with the Patient Health Questionnaire-9 (PHQ-9). • Severity of anxiety is measured with the General Anxiety Disorder-7 (GAD-7) <p><u>Exploratory:</u></p> <p>Exploratory outcome variables are the change in pain, general change, and disease status from the patient's perspective. Additionally, the acceptance and usability of the intervention will be measured. Change after 12 weeks of treatment compared to baseline will be compared between the intervention and control groups.</p> <ul style="list-style-type: none"> • The current pain level at the respective measurement time points is assessed using the Patient Pain Scale (PPS). • General change from the patient's perspective in relation to the disease since the start of treatment is measured with the Patients' Global Impression of Change (PGIC) questionnaire. • The current disease status of the respective underlying disease from the patient's perspective at the respective measurement time points is measured with the Patient Global Assessment of Disease Activity (PGA). • The acceptance of the intervention with the online program by the treated patients is recorded by means of the Net Promoter Score (NPS).

	<p><u>Safety:</u></p> <p>Data concerning the safety of the patients is recorded at baseline and after 6 and 12 weeks of treatment. Differences between the intervention and control group will be reported.</p> <p>Self-assessed negative effects and impacts of psychotherapy are recorded using the Negative Effect Questionnaire for Psychotherapy (NEQ, slightly adapted to digital therapy, see 8.2.1 for further information). Other adverse events will be documented in writing</p>
Inclusion and exclusion criteria	<p><u>Inclusion criteria:</u></p> <p>A subject (male and female adults) is eligible to be included in the study only if all of the following criteria apply:</p> <ol style="list-style-type: none"> 1. At least 18 years of age at the time of signing the informed consent. 2. Proven diagnosis as Rheumatoid Arthritis (ICD-Codes M05.3, M05.8, M05.9, M06.0, M06.1, M06.2, M06.3, M06.4, M06.8 or M06.9), Psoriasis Arthritis (ICD-Codes L40.5†M07.0*, L40.5†M07.2*, L40.5†M07.3*) or Systemic Lupus Erythematosus (ICD-Code M32.0, M32.1, M32.8, M32.9) 3. Disease-related psychological distress <ol style="list-style-type: none"> a. HADS ≥ 8 points on at least one scale (depression/anxiety) b. Minimum impairment of QoL, i.e., score on the AQoL-8D-Score ≤ 73.3 % 4. Access to the internet via PC, laptop, tablet, or smartphone and valid private e-mail address. 5. Sufficient knowledge of the German language as assessed by the investigator. 6. Provision of written informed consent. <p><u>Exclusion criteria:</u></p> <ol style="list-style-type: none"> 1. Currently undergoing psychotherapy treatment. 2. Psychotherapy in the last 6 months. 3. Suicidality (Score > 0 on question 9 of the Patient Health Questionnaire (PHQ-9) and clinical impression of principle investigator, see 8.2. "Safety Assessment"): "Over the last 2 weeks, how often have you been bothered by any of the following problems: Thoughts that you would be better off dead or hurting yourself in some way"? Patients answered the question on a scale of 0 to 3 (0 = "not at all", 1 = "on single days", 2 = "on more than half of the days", 3 = "almost every day"). 4. Acute mental crisis. 5. Motor or mental impairment that makes independent use of the online program difficult/impossible. 6. Use of an online-program or app like Vila RaVie in the last 6 months before study entry. 7. Employee of Vila Health, medac or novineon CRO. 8. Legal incapacity or limited legal capacity, or incarceration. 9. Inability to understand or communicate reliably with the Investigator or considered by the Investigator to be unable to or unlikely to co-operate with the protocol requirements. 10. Any other conditions or factors which in the opinion of the Investigator may interfere with study conduct.
Intervention group	<p>In the intervention group patients receive access to the online program. Besides access to the online program, patients maintain their usual therapy.</p> <p>Patients receive access to the online program for the entire duration of the observation period (12 weeks). They will use the online program independently and on their own compatible device (smartphone / laptop / PC /</p>

	<p>tablet). Data collection takes place at T0, T1 and T2 by means of questionnaires, to which the patients receive access via a link sent by email.</p> <p>T0 (baseline): Collection of demographic data and initial completion of questionnaires. Receiving the code to unlock the online program.</p> <p>T1 (day 45): Email to patients requesting completion of questionnaires 5 days before the questionnaires are to be completed. 1 reminder for completion will be sent on the day on which the questionnaires are to be completed 1 additional reminder after 3 to 6 days. Questionnaires will be closed after 8 to 9 days.</p> <p>T2 (day 90): Email to patients requesting completion of questionnaires 7 days before the questionnaires are to be completed. 1 reminder for completion will be sent on the day on which the questionnaires are to be completed 1 additional reminder after 3 to 6 days. Questionnaires will be closed after 8 to 9 days.</p> <p>Adverse events and medication changes will be collected during the entire study phase from screening to follow-up.</p> <p>The total duration of study participation will be 12 weeks per subject.</p>
Control group	<p>Subjects in the control group will continue having unrestricted access to all therapies which are considered as care as usual in Germany. No specific therapy is prescribed, but patients are free to choose treatments they or their healthcare provider deem necessary. In addition, they will receive a flyer informing about mental health in chronic inflammatory rheumatic diseases. The flyer also refers to the EULAR recommendations to integrate patient education into the treatment of people with inflammatory rheumatic diseases and links to further publicly available sources of information for the respective indications. After completion of the study, the control group receives access to the online program (outside the study).</p> <p>Data collection will occur at T0, T1, and T2 via online questionnaires to which patients will be given access via a link.</p> <p>T0 (day 1): Collection of demographic data and initial completion of questionnaires.</p> <p>T1 (day 45): Email to patients requesting completion of questionnaires 5 days before the questionnaires are to be completed. 1 reminder for completion will be sent on the day on which the questionnaires are to be completed 1 additional reminder after 3 to 6 days. Questionnaires will be closed after 8 to 9 days.</p> <p>T2 (day 90): Email to patients requesting completion of questionnaires 7 days before the questionnaires are to be completed. 1 reminder for completion will be sent on the day on which the questionnaires are to be completed 1 additional reminder after 3 to 6 days. Questionnaires will be closed after 8 to 9 days. At the end of the observation period, patients are given access to the online program, but no further data collection occurs.</p>
Planned number of participants	<p>A sample size of 51 patients per study arm, i.e., 102 patients in total, is considered necessary to meet the primary and secondary study objectives.</p>
Planned statistical analyses	<p>The study has an exploratory design which aims to describe the efficacy of the online program on improvement of disease-related psychological distress and quality of life in patients with chronic inflammatory rheumatic diseases. The differences between the intervention and control group in the described primary, secondary and, where applicable, exploratory endpoints will be statistically analysed. As this is an exploratory trial, no adjustment of the type-I error-rate due to multiple testing is performed and test results are considered significant if the two-sided p-value is below 0.1.</p> <p><u>Hypotheses regarding the primary endpoints:</u></p> <p><i>Psychological distress</i></p>

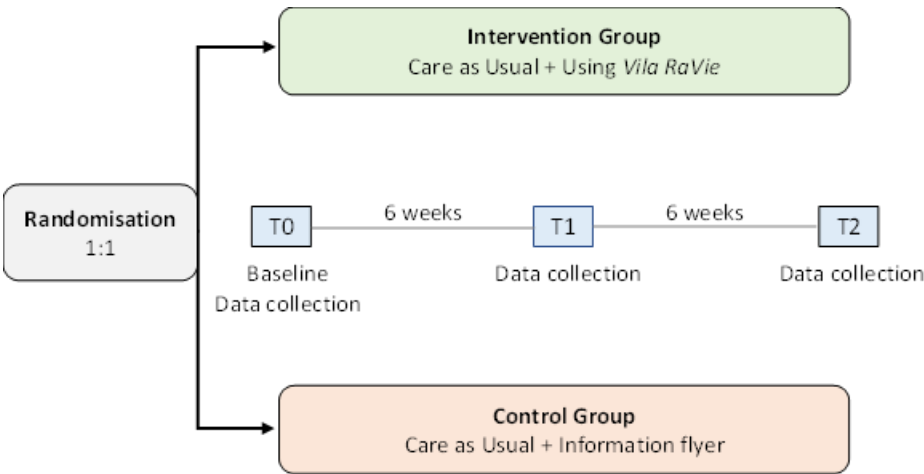
	<p>H0: no difference in change from baseline (Visit T0) after 12 weeks of treatment in disease-related psychological distress as assessed by the HADS-D total score between intervention and control groups.</p> <p>H1: difference in change from baseline (Visit T0) after 12 weeks of treatment in disease-related psychological distress as assessed by the HADS-D total score between intervention and control groups.</p> <p><i>Quality of life</i></p> <p>H0: no difference in change from baseline (Visit T0) after 12 weeks of treatment in quality of life as assessed by the AQoL-8D between intervention and control groups.</p> <p>H1: difference in change from baseline (Visit T0) after 12 weeks of treatment in quality of life as assessed by the AQoL-8D between intervention and control group.</p> <p><u>Analysis Sets</u></p> <p>Intention-to-Treat (ITT)-Population:</p> <p>All randomised patients with at least baseline values, regardless of missing data or drop-out during the study, analysed in the study arm to which the patients were randomised, regardless of the treatment actually received.</p> <p>The ITT-population is used for the main analyses of the study.</p> <p>Per-Protocol (PP)-Population:</p> <p>All randomised patients who completed the study without major protocol deviations.</p> <p>The PP-population is used for a sensitivity analysis of the main analyses.</p> <p>Completer:</p> <p>Subpopulation of all randomised patients who completed all questionnaires.</p> <p>The completer subpopulation is used for a sensitivity analysis of the main analyses.</p> <p><u>Interference statistics</u></p> <p><i>Continuous variables:</i></p> <p>Differences between both study arms are calculated using a mixed linear model for repeated measures (MMRM) with treatment, visit, treatment*visit, baseline value, and disease as covariates. The least squares (LS) mean difference (including confidence interval) including effect size calculated using Cohen's d (including confidence interval) is used as the effect estimator. Effect estimators are calculated for T1 (after 6 weeks of treatment) and T2 (after 12 weeks of treatment).</p> <p><i>Binary variables:</i></p> <p>Differences between the two study arms will be examined using Fisher's exact test. The risk ratio, odds ratio, and risk difference (including confidence interval) will be reported as effect estimates. Effect estimators are calculated for T1 (after 6 weeks of treatment) and T2 (after 12 weeks of treatment).</p> <p><u>Descriptive statistics</u></p> <p>The following descriptives are reported for all patient characteristics and endpoints:</p> <p>Continuous variable:</p> <ul style="list-style-type: none">• Number of patients (n)• Arithmetic mean (mean value)• Standard deviation (SD)
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	<ul style="list-style-type: none"> • Median • 25% quantile and 75% quantile • Minimum (min) and maximum (max) <p>Categorical variable:</p> <ul style="list-style-type: none"> • Number of patients (n) • Percentage of patients (%) <p><u>Missing Values</u></p> <p>All dropouts will be documented together with the reason for the dropout.</p> <p><i>Continuous variables:</i></p> <p>Since by its properties in a MMRM missing values are already considered and interpolated, no imputation is performed for the primary analysis. As a sensitivity analysis, missing values are imputed using LOCF (Last Observation Carried Forward).</p> <p><i>Binary variables:</i></p> <p>For the primary analysis, patients with missing data are assumed to be non-responders. As a sensitivity analysis, missing values are imputed using LOCF.</p> <p><u>Subgroup Analysis</u></p> <p>Subgroup analyses will be performed considering:</p> <ul style="list-style-type: none"> • Therapeutic indication: Separate evaluation of all randomised patients according to diagnosed underlying disease (RA, PSA or SLE) and their respective ICD-Codes. • Change in medication: Separate evaluation of all randomised patients after adjustment of the medication of the underlying disease during the study (subgroups: medication adjustment: yes / no). • Age group: Separate evaluation of all randomised patients according to age (subgroups: age 18 – 65 years and 65 years and older). <p><u>Sensitivity Analyses</u></p> <p>Sensitivity analyses are performed based on the PP-Population and Completers.</p> <p><u>Sample Size Determination</u></p> <p>Assumptions for sample size determination:</p> <ul style="list-style-type: none"> • 1:1 randomised RCT • Power: 0.8 • Significance level: 0.1 (two-sided) • Effect size: 0.5
Schedule of the study	<p>Patients are recruited at the study site and online. After collection of baseline characteristics and screening for eligibility, patients are assigned randomly to the intervention or control group if they are considered eligible to participate in the study. Patients then either receive access to the online program in addition to standard of care treatment (intervention group) or continue standard of care treatment solely (control group). Both intervention and control group remain on their treatment for 12 weeks. During this period, primary, secondary, exploratory and safety endpoints are surveyed at T0 (baseline), T1 (6 weeks) and T2 (12 weeks). After the 12-week treatment period, the study participation time is finished.</p>

	<p>Participants of the control group receive access to the online intervention after the treatment period has ended, but no further data is recorded.</p> <p>Study start (defined as first patient first visit): End of February 2024</p> <p>Last patient last visit: End of June 2024</p> <p>Estimated study completion: End August</p>
Planned publication of study results	Study results will be published in the DRKS study register and in scientific journals after completion of the study and analysis of the study data.
Version and date of study protocol	Version 4.0, 05.03.2024

1.2 Scheme

Figure 1: Study Scheme.



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1.3 Schedule of Activities

Procedure / Assessment	T0			T1	T2	End of study	Notes
	Pre-Screening	Screening	Baseline				
	D -14 to -1	D 0	D 1 (+ up to 3 days after D0)	D 45 +/- 5 days)	D 90 +/- 7 days)	Patients of the control group receive access to the online program. No further Data collection.	
Informed consent		X					
Online visit		X					
Demographic data	X ^b		X				
Inclusion/exclusion criteria		X ^a					
Medical history		X ^a					
HADS-D	X			X	X		
AQoL-8D	X			X	X		
SES6G			X	X	X		
HLS-EU-Q16			X		X		
PSS-10			X	X	X		
WSAS			X	X	X		
PHQ-9			X	X	X		
GAD-7			X	X	X		
Patient Pain Scale			X	X	X		
PGA			X	X	X		
PGIC				X	X		
NPS					X ^c		

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Procedure / Assessment	T0			T1	T2	End of study	Notes
	Pre-Screening	Screening	Baseline				
	D -14 to -1	D 0	D 1 (+ up to 3 days after D0)	D 45 +/- 5 days)	D 90 +/- 7 days)	Patients of the control group receive access to the online program. No further Data collection.	
Start / change of medication with indication of the reasons and the new medication.		X ^a		X ^a	X ^a		See chapter 6.4
Start / change of non-drug concomitant treatment.		X ^a		X ^a	X ^a		See chapter 6.4
In case of study discontinuation: reasons for discontinuation.				X	X	X ^a	
Adverse events				X	X		See chapter 10.3
NEQ				X ^c	X ^c		See chapter 10.3
PHQ-9 (Suicidality)		X ^a					
	AqoL-8D: Assessment of Quality of Life – 8 dimensions; D: Days; HADS-D: Hospital Anxiety and Depression Scale – German Version; HLS-EU-Q16: European Health Literacy Survey – short form; NEQ: Negative Effect Questionnaire for Psychotherapy adjusted to digital intervention (i.e. exchanged the word “Therapie” with “Online-Programm”; items 16 and 19 removed); NPS: Net Promoter Score (intervention group only); PGA: Patient Global Assessment of Disease Activity; PGIC: Patients’ Global Impression of Change; PHQ-9: Patient Health Questionnaire-9; GAD-7: General Anxiety Disorder-7; PSS-10: Perceived Stress Scale-10; SES6G: Self-Efficacy for Managing Chronic Disease 6-Item Scale – German version; WSAS: Work and Social Adjustment Scale; Medical history: Indication, duration of illness, disease activity, comorbidities, current drug treatment, current non-drug treatment						

^a data entered by investigator^b only gender, age and indication^c only for intervention group

2 Introduction

The online program Vila RaVie is a web application designed to support patients with chronic inflammatory diseases, such as inflammatory rheumatic diseases, to strengthen health-related quality of life and alleviate the psychological burden resulting from a chronic inflammatory disease. Furthermore, it aims to increase self-efficacy, health literacy, work and social functioning and reduce stress levels of patients with chronic inflammatory diseases.

2.1 Study Rationale

The primary study objective is to exploratively describe the efficacy of using the online program on disease-related psychological distress (depression, anxiety) and quality of life in adult patients with RA, PsA, or SLE.

This study is a pilot study to evaluate the efficacy of the online program on a variety of endpoints. While a clear study hypothesis shall be defined, the results should also be seen as exploratory in nature. P-Values will be calculated for all endpoints, regardless of whether they are defined as primary, secondary, or exploratory endpoint. As this is an exploratory trial, no adjustment of the type-I error-rate due to multiple testing is performed and test results are considered significant if the two-sided p-value is below 0.1.

2.2 Scientific Background

2.2.1 Chronic inflammatory rheumatic diseases and their impact on mental health: rheumatoid arthritis, psoriatic arthritis, and systemic lupus erythematosus

Chronic inflammatory diseases are characterized by autoimmune mediated inflammatory reactions. They pose a significant health problem, as around 5% of the population in Germany are affected by one or more chronic inflammatory disease [1]. Chronic inflammatory rheumatic diseases in particular affect 2.2 – 3.0% of adults in Germany, which means approximately 1.5 – 2.1 million adults. The largest share of patients suffers from RA (0.42 – 1.85%), while 0.11 – 0.32% of patients have PsA and 0.037 – 0.14% SLE [2]. The occurrence of the respective chronic inflammatory rheumatic diseases varies with certain patient characteristics like sex. Women are in general more often affected than men. This predominance ranges from women suffering ~1.5 times more from PsA [3, 4], 3 times more often from RA [5] up to 9 times more often from SLE [6] than men.

Table 6: Prevalence of chronic inflammatory diseases.

Indication	Prevalence
Chronic inflammatory disease	4.7% [1]
RA	0.42 - 1.85% [2]
PsA	0.11 – 0.32% [2]
SLE	0.037 – 0.14% [2]
RA: Rheumatoid Arthritis; PsA: Psoriasis Arthritis; SLE: Systemic Lupus Erythematosus	

People with chronic diseases often suffer from disease-related psychological stress in addition to the symptoms of their physical disease. In this context, disease-specific symptoms of the individual disease often play only a subordinate role. Although each chronic disease is associated with subject-specific symptoms and medical treatments, psychosocial challenges exist independently across all chronic diseases, and the nature and extent of patients' distress are similar [7-9]. This particularly applies to chronic inflammatory rheumatic diseases [10, 11].

In patients with chronic inflammatory rheumatic diseases, anxiety and depression belong to the most prevalent comorbidities: about 15 – 25% of patients suffer from depressive symptoms, and around 15 – 30% from anxiety [4, 12-15]. Likewise, the patients' self-image and self-efficacy are shaped and negatively influenced by the chronic disease. [10]. The combination of the symptomatology of the disease and the psychological burden leads to a reduced quality of life in many patients. Therefore, in addition to controlling the underlying chronic disease, reducing the psychological burden and increasing the quality of life of the affected patients are important therapeutic goals [16].

A variety of therapeutic methods help patients in improving their quality of life and reducing their psychological distress. These methods include cognitive behavioural therapy (CBT), mindfulness techniques and acceptance commitment therapy (ACT).

The efficacy of psychological interventions in patients with chronic inflammatory rheumatic diseases has already been demonstrated in various studies [7, 17-25]. Psychological interventions are widely recognized in this field and are recommended in the guidelines for RA [26, 27].

In addition to evidence-based approaches to improve psychological distress, living with a chronic illness requires a certain level of health literacy to enable participatory decision making and to improve patient sovereignty. Evidence-based programs aimed at increasing patients' knowledge of their disease as well as improving their self-management have already achieved success across indications in improving psychological distress and quality of life [28-30]. A therapeutic approach that considers the health literacy of patients with chronic diseases is therefore extremely promising.

The importance of the treatment of psychological stress in chronically ill patients contrasts with an insufficient health care situation with insufficient availability of psychotherapeutic treatment [31]. While many patients are affected by mental symptoms due to their disease, they are rarely asked by physicians about it: in a UK study, 74 % of patients with autoimmune rheumatic disease report of never or rarely being asked about psychological symptoms in their clinic. In Germany, a shortage of psychotherapeutic care is widely recognized [32]. Accordingly, the possibilities for psychological therapy of chronic illnesses are severely limited, both in specialist care and in psychotherapy [33]. Therefore, there is a great therapeutic need for the treatment of psychological stress in chronically ill patients.

2.2.2 The online intervention examined in this study

The online program Vila RaVie aims to support patients with chronic inflammatory diseases in coping with disease-related psychological stress and in managing their disease. The program aims to improve the health status of chronically ill patients by reducing psychological stress, improving their quality of life, and promoting the ability to actively cope with the disease. To address the diverse challenges and varying needs of chronically ill people, the online program offers a wide range of interventions, all of which have been proven effective in treating chronically ill people and are in line with the latest

scientific findings. These include interventions from cognitive-behavioural therapy, acceptance and commitment therapy, metacognitive therapy and mindfulness-based cognitive therapy. In addition, it provides practical everyday knowledge for maintaining and promoting psychosocial health and promotes skills in disease and symptom management. The online program can be regarded as a necessary and self-evident component of a multidisciplinary therapy of chronic inflammatory diseases, which enables patients to cope with the disease actively and independently. As a digital health application, Vila RaVie is accessible to all those affected, regardless of their respective life and care situation.

The online program is a browser-based web application that guides patients step-by-step over 90 days through a simulated dialogue that addresses various disease-related topics. Each step consists of an interaction lasting approximately 5 - 15 minutes, which may consist of an interactive exercise or a video or audio message, for example. The individual steps build on each other and address the topic areas of self-image, everyday life and environment, thoughts and feelings, body and symptoms, friends and family, acceptance, and health and empowerment. The content covered is automatically summarized, is available to the patient throughout the prescription period, and can be downloaded for long-term use. In addition, there is the option to access guided audio exercises for quick support in difficult moments and to repeat exercises already completed. Additionally, users have the option to keep a diary, e.g., to note down the things they are grateful for or have done well. The application is designed to be self-explanatory and for sole use by the patient and does not require any active role of physicians or psychotherapists.

The RELIEVE study investigates the online program for patients with RA, PsA and SLE. These three indications are associated with a high rate of comorbidities and represent both common and rare diseases [34]. In all three indications, many patients suffer from high psychological stress and a reduced quality of life in addition to the underlying disease [7-9]. Initial internet-based psychotherapeutic approaches have already achieved success [31]. The online program offers a promising therapeutic option for patients affected by these three indications to improve disease consequences such as psychological distress and reduced quality of life and is intended to help patients to cope better with the consequences of their disease.

2.3 Benefit/Risk Assessment

2.3.1 Risk Assessment

Study Intervention and Study Procedures

There is no additional risk to be expected from either the study intervention or any of the study procedures.

2.3.2 Benefit Assessment

Subjects in the Intervention Group will benefit directly from the treatment with the online program. The online program is believed to reduce psychological distress and improve patients' quality of life.

2.3.3 Overall Benefit Risk Conclusion

Given the nature of the intervention and its expected low risk profile, the benefits of the study intervention outweigh expected risks for the subjects.

The risk reduction measures implemented are considered suitable. In the case of events that pose an unreasonable risk to the subject's safety, the application of the intervention is suspended (Section 7).

Participants can be included if there has been a consultation by the relevant ethics committee. All investigations will be conducted in compliance with the clinical study protocol, the Declaration of Helsinki, International Council for Harmonization and Good Clinical Practices (ICH GCP), and any additional applicable regulatory requirements.

3 Objectives and Endpoints

Table 7: Objectives and endpoints.

Objectives	Endpoints
Primary	
The primary outcome variables are changes in psychological distress and quality of life at T2 compared with T0. The changes are compared between the intervention and the control group.	<p>Hospital Anxiety and Depression Scale - German Version (HADS-D). Patients' psychological distress in depression and anxiety. Assessment of disease-related psychological distress using the HADS-D questionnaire, which assesses depression and anxiety symptoms.</p> <p>Quality of life (Assessment of Quality of Life - 8 dimensions [AQoL-8D]). Health-related quality of life is measured by means of the AQoL-8D, which asks about quality of life using 8 dimensions.</p>
Secondary	
The secondary outcome variables are the change in patients' self-efficacy, health literacy, stress levels, work ability, and social function, depression and anxiety symptoms severity at T2 compared to T0. The change will be compared between the intervention and control groups.	<p>Self-efficacy (Self-Efficacy for Managing Chronic Disease 6-Item Scale - German version, SES6G). Patients' self-efficacy in relation to their disease is assessed with the SES6G questionnaire.</p> <p>Health literacy (European Health Literacy Survey - short form, HLS-EU-Q16). The health literacy of the patients is surveyed by means of the HLS-EU-Q16 questionnaire.</p> <p>Perceived Stress (Perceived Stress Scale, PSS-10). Patients' stress levels in situations where they perceive their lives as uncontrollable, unpredictable, and overloaded are assessed with the PSS-10.</p> <p>Work Ability and Social Function (Work and Social Adjustment Scale, WSAS). Patients' self-assessed functioning in the areas of work, home, social and personal leisure, and relationships is assessed using the WSAS.</p> <p>Depression severity (Patient Health Questionnaire-9, PHQ-9). The severity of depressive symptoms is measured by means of the PHQ-9.</p> <p>Anxiety severity (General Anxiety Disorder-7, GAD-7). The severity of anxiety symptoms is measured by means of the GAD-7.</p>
Exploratory	
The exploratory outcome variables are the change in pain, general change, and disease status from the patient's perspective. Additionally, the acceptance of the intervention will be measured. Data is collected at T2 compared to T0. The change will be compared between the intervention and control groups.	<p>Pain (Patient Pain Scale, PSS). The current pain level at the respective measurement time points is assessed using the Patient Pain Scale.</p> <p>General change from the patient's perspective (Patients' Global Impression of Change, PGIC). The general change in relation to the disease since the start of treatment from the patient's perspective is surveyed by means of the PGIC.</p>

Objectives	Endpoints
	<p>Assessment of the disease status from the patient's perspective (Patient Global Assessment of Disease Activity, PGA). The current disease status of the respective underlying disease from the patient's perspective at the respective measurement time points is assessed by means of the PGA.</p> <p>Acceptance of the intervention (Net Promoter Score, NPS). The acceptance of the intervention with Vila RaVie by the patients in the intervention group is recorded by means of the NPS. No group comparison will be conducted.</p>
Safety	
<p>Data concerning the safety of the patients is recorded at T0, T1 and T2. Differences between the intervention and control group will be reported.</p>	<p>Adverse events (Negative Effect Questionnaire for Psychotherapy, NEQ, as well as written documentation). Self-assessed negative effects and impacts of psychotherapy are recorded using the NEQ (adapted to digital therapy). Other adverse events will be documented in writing.</p>
<p>AQoL-8D: Assessment of Quality of Life - 8 dimensions; HADS-D: Hospital Anxiety and Depression Scale – German Version; HLS-EU-Q16: European Health Literacy Survey - short form; NEQ: Negative Effect Questionnaire for Psychotherapy; NPS: Net Promoter Score; PGA: Patient Global Assessment of Disease Activity; PGIC: Patients' Global Impression of Change; PSS-10: Perceived Stress Scale-10; WSAS: Work and Social Adjustment Scale; PHQ-9: Patient Health Questionnaire-9; GAD-7: Anxiety severity (General Anxiety Disorder-7</p>	

4 Study Design

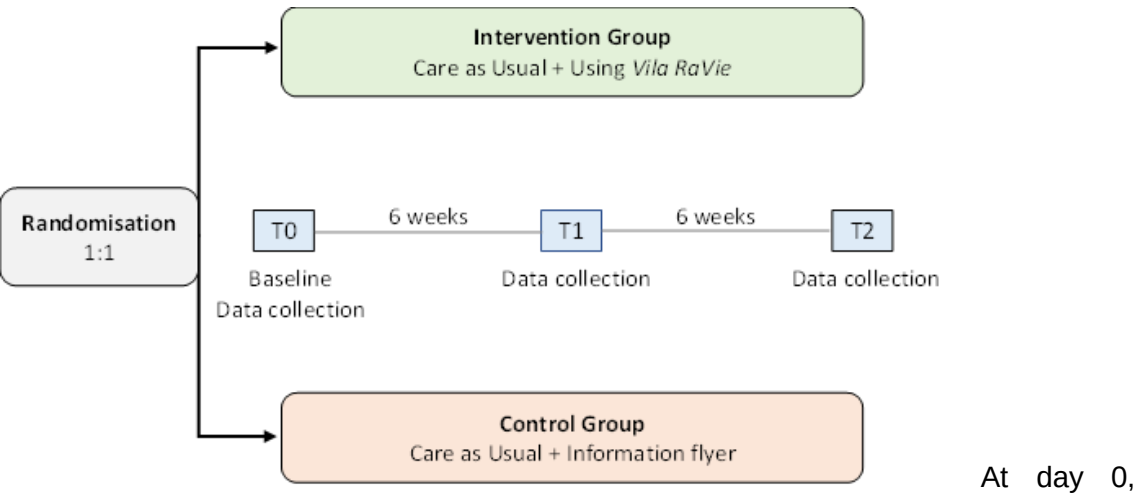
4.1 Overall Design

Patients are recruited at the study site, via rheumatologists across Germany and online. All recruitment channels refer to the study website <https://vilaravie.de/studie>), where potential participants receive further information and can declare their interest. They are then added to the study database for a pre-screening. If they are eligible for the study based on pre-screening, a physician will conduct a screening via telephone conversation and subsequently (if inclusion criteria are still met and informed consent is given) they are included in the study. The diagnosis of all patients is confirmed by a physician's letter or diagnosis confirmation sheet, signed by a physician. This monocentre study in Germany will follow a randomised, controlled, parallel-group design. Male and female patients with RA, PsA or SLE (≥ 18 years) and disease-related psychological distress are eligible. The 3 indications will be enrolled according to their epidemiological frequency. It is expected that recruitment will be completed within 12 weeks.

The primary study objective is to exploratively describe the efficacy of the online program on psychological distress and quality of life of adult patients with chronic inflammatory rheumatic diseases, compared with not using it. Subjects will use the application on their own. They will keep their usual therapy, are allowed to change it as necessary and to seek additional therapy of their primary illness according to standard of care, but without a treatment of comorbidities, e. g., psychological counselling.

Key aspects of the study design are shown in Figure 1.

Figure 2: Study Scheme.



At day 0, subjects will be screened and, after confirmation of eligibility, randomly assigned to 1 of the following 2 study interventions:

1. Control (no access to the online program),
2. Intervention (the online program).

In the control group patients will be treated with standard of care and additionally receive an information flyer about mental health in chronic inflammatory rheumatic diseases. The flyer refers to the EULAR recommendations to integrate patient education into the treatment of people with inflammatory rheumatic diseases and links to further publicly

available sources of information for the respective indications. They do not receive access to the online program. Subjects in the control group will continue having unrestricted access to all therapies which are considered standard of care in Germany. No specific therapy is prescribed, but patients are free to choose treatments they or their healthcare provider deem necessary. Data collection will occur at T0, T1, and T2 via online questionnaires to which patients will be given access via a link sent by email. After completion of the study, the control group will receive access to the online program.

T0 (day 1): Collection of demographic data and initial completion of questionnaires. Patients receive the code to unlock the online program after completion of questionnaires.

T1 (day 45): Email to patients requesting completion of questionnaires 5 days before the questionnaires are to be completed. 1 reminder for completion will be sent on the day on which the questionnaires are to be completed 1 additional reminder after 2 to 4 days. Questionnaires will be closed after 8 to 9 days.

T2 (day 90): Email to patients requesting completion of questionnaires 7 days before the questionnaires are to be completed. 1 reminder for completion will be sent on the day on which the questionnaires are to be completed 1 additional reminder after 3 to 6 days. Questionnaires will be closed after 10 to 11 days.

Adverse events and medication changes will be collected during the entire study phase from randomisation to follow-up.

In the intervention group patients receive access to the online program via an access code for registration, that is sent via e-mail.

Patients receive access to Vila for the entire duration of the observation period (12 weeks). They will use Vila independently and on their own compatible device (smartphone / laptop / PC / tablet). Data collection takes place at T0, T1 and T2 by means of questionnaires, to which the patients receive access via a link.

The total duration of study participation will be 12 weeks per subject.

For more information on the specific time points indicated for the scheduled study visits and required procedures, please refer to section 1.3.

4.2 Subject and Study Completion

A sample size of 51 patients per study arm, i.e., 102 patients in total, is considered necessary to meet the primary and secondary study objectives.

4.3 Start/End of Study Definition

Start of the study: date of the first informed consent signature by the first subject.

Study completed: subjects have finished all phases of the study including the last scheduled procedure shown in the schedule of activities (refer to section 1.3). 1.3

End of the study: the last subject has completed the date of the last scheduled procedure shown in the Schedule of Activities.

Information on study termination or discontinuation criteria is provided in section 7.

4.4 Scientific Rationale for Study Design

The study design was chosen to investigate the efficacy of using Vila RaVie on psychological distress and quality of life of adult patients with chronic inflammatory rheumatic diseases.

The study is open label for the subject and the Investigator. Scores of the questionnaires will be calculated automatically by the EDC-System, minimizing assessment bias.

The allocation bias was minimized by allocating subjects randomly to study intervention. The allocation ratio Control Group to Intervention Group will be 1:1.

4.5 Distribution of Sex

Male and female patients with RA, PsA or SLE will be included in the study. The influence of sex will be evaluated using a subgroup analysis.

Subjects will be stratified according to their diagnosis (RA, PsA or SLE) and according to the sex of the patients. Equal distribution of sexes among participants will be aimed at. However, as women are more often affected by RA, PsA and SLE, a predominance of female participants is to be expected for the study (see chapter 2.2.1).

5 Study Population

Only subjects to which all inclusion criteria given in Sections 5.1 apply will be randomised.

5.1 Inclusion Criteria

A subject (male and female adults) is eligible to be included in the study only if all of the following criteria apply:

- 1. At least 18 years of age at the time of signing the informed consent.
- 2. Proven diagnosis as Rheumatoid Arthritis (ICD-Codes M05.3, M05.8, M05.9, M06.0, M06.1, M06.2, M06.3, M06.4, M06.8 or M06.9), Psoriatic Arthritis (ICD-Codes L40.5†M07.0*, L40.5†M07.2*, L40.5†M07.3*) or Systemic Lupus Erythematosus (ICD-Code M32.0, M32.1, M32.8, M32.9)

Table 8: ICD codes to be included in the study.

Rheumatoid Arthritis	M05.3 M05.8 M05.9 M06.0 M06.1 M06.2 M06.3 M06.4 M06.8 M06.9
Psoriatic Arthritis	L40.5†M07.0* L40.5†M07.2* L40.5†M07.3*
Systemic Lupus Erythematosus	M32.0 M32.1 M32.8 M32.9

- 3. Disease-related psychological distress
 - a. HADS ≥ 8 points on at least one scale (depression/anxiety)
 - b. Minimum impairment of QoL, i.e., score on the AQoL-8D-Score ≤ 73.3 %
- 4. Access to the internet via PC, laptop, tablet, or smartphone and valid private e-mail address.
- 5. Sufficient knowledge of the German language as assessed by the investigator.
- 6. Provision of written informed consent for the use of the data.

5.2 Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply.

- 1. Currently undergoing psychotherapeutic treatment.
- 2. Psychotherapy in the last 6 months.

3. Suicidality (Score > 0 on question 9 of the Patient Health Questionnaire (PHQ-9) and clinical impression of principle investigator) "Over the last 2 weeks, how often have you been bothered by any of the following problems: Thoughts that you would be better off dead or hurting yourself in some way"? Patients answered the question on a scale of 0 to 3 (0 = "not at all", 1 = "on single days", 2 = "on more than half of the days", 3 = "almost every day").
4. Acute mental crisis.
5. Motor or mental impairment that makes independent use of the online program difficult/impossible.
6. Use of an app similar to Vila RaVie in the last 6 months before study entry.
7. Employee of Vila Health, medac or Novineon.
8. Legal incapacity or limited legal capacity, or incarceration.
9. Inability to understand or communicate reliably with the Investigator or considered by the Investigator to be unable to or unlikely to co-operate with the protocol requirements.
10. Any other conditions or factors which in the opinion of the Investigator may interfere with study conduct.

5.3 Screening Failure

Subjects who consent to participate in the study but are not subsequently randomly assigned to study treatment are considered screening failures. Minimal information from pre-screening and screening (if applicable) of subjects who are defined as screening failures is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements [35].

5.4 Dropouts

If a subject has already been randomly assigned to study treatment and discontinues the study prematurely for any reason, the subject is defined as a "dropout". The data obtained from dropouts will be used in the evaluation to the largest possible extent. The reasons for the dropout will be documented.

6 Study Intervention and Concomitant Therapy

6.1 Study Intervention

The study intervention is detailed in Table 8.

Table 9: Study intervention.

	Control	Intervention
Identifier	Care as usual	Care as usual + Vila RaVie
Brief Description	Patients do not have access to Vila RaVie and will be treated with care as usual.	Vila RaVie is a web-based intervention for addressing disease-related psychological stress and quality of life of patients with rheumatic diseases. Vila RaVie utilizes methods based on cognitive-behavioural therapy, acceptance and commitment therapy and other established interventions. Core functions are: Box (summary of the developed strategies). Care (guided audio exercises for quick support in difficult moments). Journal (Journal function for recording positive moments of everyday life as an optional additional function).
Manufacturer		Vila Health UG, Germany

The key functions of the applications are described in the following subsections.

Main function

Journey: Patients will go through a structured program (Journey) with a series of modules (Stations) that build on each other and cover the various topics listed below. Within the individual 5 – 15-minute interactions (Steps), the patient can expect a simulated dialogue that leads through the Journey in a motivating and empathetic way and, through the question-answer exchange, reproduces the elements of a therapeutic conversation. It is recommended to complete the steps according to the given order.

Structure of the Journey:

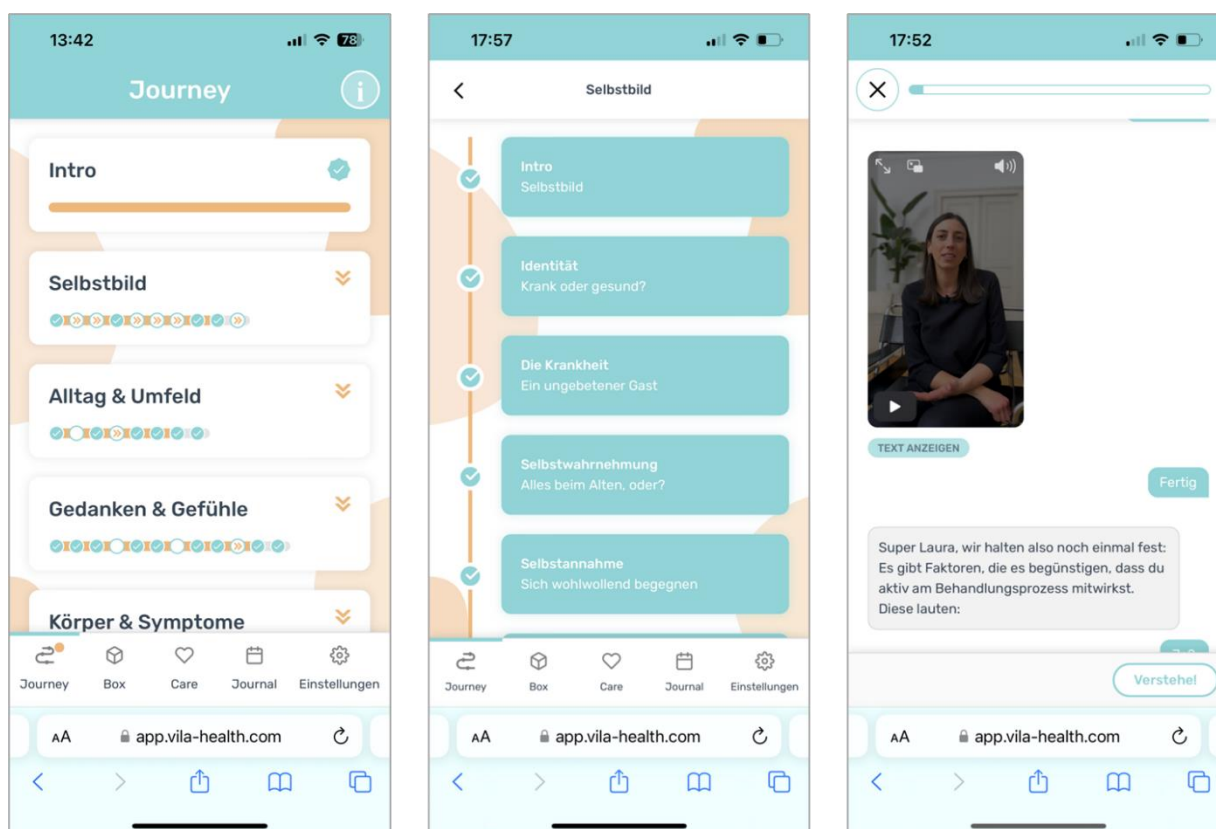
- 8 stations with a total of 80 steps.
- Each step includes an interaction of approx. 5 – 15 minutes.
- Topic area of the stations:
 - Self-image
 - Everyday life & environment
 - Thoughts & feelings
 - Body & symptoms
 - Friends & family
 - Acceptance

- Health & empowerment
- At the end

Vila RaVie also provides elements to better illustrate and lighten up the Journey and to promote adherence, such as

- Interactive exercises: free text input and / or question-answer alternation with a predefined selection of answer options.
- Video and audio messages to guide subsequent exercises or to explain specific content in more detail.
- Fictional characters whose answers and thoughts on specific tasks and content are presented as encouraging and supportive examples.
- Gamification elements: Progress bars, awards, summaries and feedbacks, graphics, images, quotes, proverbs.
- Support function: reminder emails.

To complete the program within 12 weeks, it is recommended to complete one step per day.



Additional functions

Box: The strategies developed for the Journey dialogs are automatically summarized by the application and are available to the patient at any time (during the prescription

period). It is possible to download the prepared strategies and contents of the box in PDF form, so they can be used beyond the prescription period.

Care: Here patients will find guided audio exercises for quick support in difficult moments (e.g., painful episodes). The exercises are introduced and explained in the Journey and can be reapplied here as needed.

Journal: Diary function for recording positive moments of everyday life as an optional additional function.

6.1.1 Set-Up

Vila RaVie is available via any current mobile or desktop browser (smartphone, tablet, notebook, or PC). No installation is required, but internet access and a current web browser are needed.

Patients need a valid e-mail address to create an account. This does not have to include a clear name and identity.

The application is designed to be self-explanatory and for sole use by the patient.

6.1.2 Application and Study Intervention

After set-up, subjects will use the application on their own as an add-on to their usual therapy for their chronic inflammatory rheumatic disease.

It is recommended to complete one step a day and according to the given order.

The subject can interrupt the application at any time and then continue from the point where the program was left.

The total duration of application use will be 90 days.

6.2 Measures to Minimize Bias: Randomization and Blinding

Table 10: Randomization and blinding.

Subject identification, intervention assignment and stratification	<p>Each subject is identified by a unique subject identification code that is assigned when the contact data of the subject are entered in the database for the pre-screening process. Depending on the EDC-system used, an additional Patient-ID may be assigned after informed consent.</p> <p>A unique randomization number in ascending numerical order within each stratum (see below for details on stratification) will be created in the EDC-system. The number encodes the subject's assignment to one of the following two study interventions: A. Intervention and B. Control.</p> <p>Subjects will be stratified according to their diagnosis (RA, PsA or SLE) and according to the sex of the patients.</p> <p>The main diagnosis for each subject will be recorded in the case report form (CRF).</p> <p>After all inclusion and exclusion criteria have been checked, and the subject is classified as eligible by the investigator, the randomization process will be started by the investigator. The result of the randomization will be provided by the application and the application will be automatically set up to "Intervention" or "Control". The allocation will not be discernible from the application until the randomization process for a subject was triggered by the investigator.</p>
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Blinding Level	The investigators and the subjects will not be blinded.
Unblinding	Not applicable.

Only subjects who meet all eligibility criteria can be included into the study.

The Investigator will keep a record relating the unique subjects’ identifiers and the names of all subjects who have given their informed consent, to allow easy checking of data in subject files, when required. This record will also include the date of subject’s enrolment and completion, as well as subjects who could not be randomly assigned to study intervention for whatever reason.

6.3 Treatment after the End of the Study

Subjects will continue their usual therapy for their chronic inflammatory rheumatic diseases used throughout the study.

After the end of the study, subjects of the control group will be offered access to Vila RaVie for 90 days. Patients who received Vila RaVie during the study will not have further access to Vila RaVie. No further questionnaires have to be completed.

6.4 Concomitant Therapy

Concomitant therapies will be recorded for drug and non-drug concomitant treatments according to the Schedule of Activities (section 1.3).

The investigator will document prescription medication during the screening visit. At T1 and T2 the participants will be asked if the medication was changed and if yes, the investigator will contact the subject to record changes in the medication in a structured manner.

The same process will be implemented for non-drug concomitant treatments.

7 Discontinuation of Study Intervention and Subject Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

It is unlikely that a discontinuation of the study intervention is necessary. If the study intervention is discontinued, the subject will remain in the study. The reason for discontinuation will be recorded and data will be collected as far as possible (section 1.3).

7.2 Subject Discontinuation/Withdrawal from the Study

A subject may withdraw from the study at any time at their own request without giving reasons. The subject will not suffer any disadvantage as a result. The subject will be permanently discontinued from the study at that time. Subjects who discontinued from the study may not re-enter the study. If the subject withdraws consent for disclosure of future information, Vila Health may retain and continue to use any data collected before such a withdrawal of consent. The already documented data will not be deleted from the EDC-System, but no further data will be added after the timepoint of the withdrawal.

The reasons for the withdrawal from the study will be documented if known.

7.3 Premature Discontinuation of the Complete Study

Vila Health may discontinue the complete study at any time, for ethical or safety reasons. A premature termination or suspension of the study can also be caused by regular violations of the study protocol that compromise the evaluation of the study.

If the study is prematurely terminated or suspended, Vila Health UG shall promptly inform the investigators, the ethics committee, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

7.4 Replacement of Subjects

Subjects who prematurely discontinue the study after having been randomly assigned to study intervention will not be replaced.

The data obtained from dropouts will be used in the evaluation to the largest possible extent.

7.5 Lost to Follow-up

Subjects will be considered lost to follow-up if they repeatedly fail to submit the scheduled questionnaires and are unable to be contacted by the study site within 4 weeks.

The following actions must be taken if a subject fails to submit the scheduled questionnaires:

- The site must attempt to contact the subject and reschedule the submission of the questionnaires as soon as possible and remind the subject to respond to the questionnaire. The subject is to be educated about the importance of keeping the assigned schedule.
- From the 3 contact attempts at least 1 needs to be conducted via telephone to clarify whether an AE/SAE is the reason for failing to submit the questionnaires.

Should the subject continue to be unreachable (3 documented contact attempts via phone or e-mail, at least 1 via phone), they will be considered “lost to follow-up” after 4 weeks. Their data will be continued as “last observation carried forward”.

8 Study Assessments and Procedures

Prior to performing any study assessments, the Investigator will obtain written informed consent as specified in Appendix 2.

Study procedures and their timing are summarized in the Schedule of Activities (section 1.3). Compliance with the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

Demographic data will be collected at screening and will include age, sex, educational background, occupational status, marital status.

For medicinal characteristics the following parameters will be collected during screening: disease with written confirmation by a physician, duration of disease, severity of disease, comorbidities (other than depression/anxiety), drug treatment, non-drug treatment.

No specific sequence is defined if several procedures are to be performed at the same nominal time. Immediate safety concerns should be discussed with Vila Health UG immediately upon occurrence or awareness to determine if the subject should continue or discontinue study intervention. All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria.

8.1 Efficacy Assessment

8.1.1 Primary Objectives

The primary outcome variables are changes in psychological distress and quality of life at time T2 (after 12 weeks of treatment) compared to T0 (baseline before starting treatment). Changes will be compared between the intervention and control groups. The operationalization of the endpoints is described below.

8.1.1.1 Hospital Anxiety and Depression Scale – German Version (HADS-D)

The questionnaire is used to assess anxiety and depression in the past week in patients with physical diseases. The data is recorded with two subscales with 7 items each. Each item has four possible answers, which are evaluated with the scores 0 - 3. The total score can be regarded as a measure of general psychological distress, while the evaluation of the subscales provides information about depressive and anxious symptoms. Higher values mean a higher level of distress.

Analysis

The value range for the total score is between 0 and 42 points. The lower limit, above which there is evidence of psychological distress on the total score (Anxiety and Depression scale combined), is 14 points. The minimum clinically important difference (MCID) ranges from 1.4 to 5.7 points.

For the depression subscale, the range of scores is 0 to 21 points, with a lower cutoff of 8 points. The classification according to the severity of the symptoms is made in four stages:

- 0 – 7 points: no depression
- 8 – 10 points: light depression
- 11 – 15 points: moderate depression
- ≥ 16 points: severe depression

The MCID for the depression subscale ranges from 2 to 3.3 points.

For the anxiety subscale, the value range is between 0 and 21 points, and the lower limit is also 8 points. The classification according to the severity of symptoms is made in four stages:

- 0 – 7 points: no anxiety
- 8 – 10 points: light anxiety
- 11 – 14 points: moderate anxiety
- 15 – 21 points: severe anxiety

The MCID for the anxiety subscale ranges from 2 to 3.8 points.

8.1.1.2 Assessment of Quality of Life – 8 Dimensions (AQoL-8D)

The questionnaire records the health-related quality of life of the patients in the past week based on 35 questions assigned to the eight dimensions "Independent living," "Satisfaction," "Mental health," "Coping with illness," "Relationships," "Self-esteem," "Pain," and "Senses". The dimensions "Independent Living," "Pain," and "Senses" form the physical dimension, while the remaining five dimensions are combined to form the psychosocial dimension. There are between four and six answer options per question.

Analysis

Evaluation as a psychometric instrument

Depending on the number of answers for a question, a score from 1 to 4, 1 to 5 or 1 to 6 is assigned to each of the answers and summed up over all questions. The lower the total score, the better the quality of life. The range of values for the total score is between 35 and 176 points. This number can also be expressed as a percentage by normalizing it to the range 0 – 100 %. Then, 35 corresponds to 100 % and 176 corresponds to 0 %.

Weighted evaluation

The total score is also evaluated as a preference-weighted score with a range of 0 to 1. The closer the total score is to 1, the better the quality of life. The MCID for the preference-weighted value is 0.06 points.

8.1.2 Secondary Objectives

The secondary outcome variables are the change in self-efficacy, health literacy, perception of stress, patients' ability to work and social function, and severity of depression and anxiety symptoms at time T2 (after 12 weeks of treatment) compared to T0 (baseline before starting treatment). Change will be compared between the intervention and control groups. The operationalization of the endpoints is described below.

8.1.2.1 Self-Efficacy for Managing Chronic Disease 6-Item Scale – German Version (SES6G)

The SES6G measures the patient's perceived self-efficacy at the current time. The questionnaire contains 6 items, each with a Likert scale of 1 – 10, where a value of 1 corresponds to the assessment "not at all confident" with regard to the item being surveyed,

and a value of 10 corresponds to the assessment “absolutely confident” with regard to the item being surveyed.

Analysis

For the analysis, the mean value is calculated for all 6 items. The value range is thus between 1 and 10. The lower the value, the worse the patient’s self-efficacy. An MCID for the SES6G has not yet been published. If more than two values are missing, the questionnaire cannot be evaluated.

8.1.2.2 European Health Literacy Survey – short form (HLS-EU-Q16)

The HLS-EU-Q16 measures patients’ self-assessed health literacy using 16 items, each with 4 response options (very easy, fairly easy, fairly difficult, very difficult).

Analysis

For the evaluation of the questionnaire, a dichotomization of the answers takes place, whereby the answers “very easy” and “fairly easy” receive the value of 1 point, the answers “fairly difficult” and “very difficult” receive the value of 0 points. Then a sum score is formed over all 16 items. Accordingly, the range of values is between 0 and 16 points, with a lower value representing poorer health literacy. The following classifications of health literacy can be made:

- ≥ 13 points: sufficient health literacy
- 9 – 12 points: problematic health literacy
- ≤ 8 points: inadequate health literacy

If more than two values are missing, the questionnaire cannot be evaluated.

8.1.2.3 Perceived Stress Scale (PSS-10)

The PSS-10 captures the level of stress patients perceive in situations where they feel their lives are uncontrollable, unpredictable, and overloaded. The PSS-10 includes 10 questions that ask patients to rate their thoughts and feelings, related to the content of each question, over the past month. The rating is made on a Likert scale from 0 (“never”) – 4 (“very often”).

Analysis

For the analysis, the PSS-10 can be divided into the two subscales helplessness and self-efficacy, but the evaluation can also be done as a total score:

- The subscale helplessness consists of the items 1, 2, 3, 6, 9, 10, its value range is between 0 and 24 points.
- The self-efficacy subscale consists of items 4, 5, 7, 8. The values for the items must be inverted for the evaluation. The value range is between 0 and 16 points.
- The total score is calculated from the sum of the items of the two subscales, whereby the values of the self-efficacy subscale are also inverted first. The value range for the total score is between 0 and 40 points. The MCID for the total score is 11 points.

Both for the subscales and the total score, higher values stand for an increased stress level.

8.1.2.4 Work and Social Adjustment Scale (WSAS)

The WSAS measures patients' self-assessed functional ability in the areas of work, household, social and personal leisure time, and relationships. Patients rate on a scale of 0 to 8 how severely they feel limited by the disease in each area, with a score of 0 representing "not limited at all" and a score of 8 representing "very severely limited."

Analysis

The WSAS is evaluated as a sum score with a value range from 0 to 40:

- 0 – 9 points: low impairment
- 10 – 19 points: moderate impairment
- ≥ 20 points: severe impairment

8.1.2.5 Patient Health Questionnaire-9 (PHQ-9)

The PHQ-9 assesses for the presence and severity of depressive symptoms. The PHQ-9 includes 9 questions and patients rate on a scale of 0 to 3 according to how often they have been bothered by the in the questions described problems over the last 2 weeks, with a score of 0 representing "not at all", 1= "Several days", 2= "More than half the days", and 3= "Nearly every day".

Analysis

The PHQ-9 is evaluated as a sum score with a value range from 0 to 27:

- 0 – 4 points: None-minimal (Depression Severity)
- 5 – 9 points: Mild (Depression Severity)
- 10 – 14 points: Moderate (Depression Severity)
- 15 – 19 points: Moderately severe (Depression Severity)
- 20 – 27 points: Severe (Depression Severity)

8.1.2.6 Generalized Anxiety Disorder-7 (GAD-7)

The GAD-7 assesses for the presence and severity of anxiety symptoms. The GAD-7 includes 7 questions and patients rate on a scale of 0 to 3 according to how often they have been bothered by the in the questions described problems over the last 2 weeks, with a score of 0 representing "not at all", 1= "Several days", 2= "More than half the days", and 3= "Nearly every day".

Analysis

The GAD-7 is evaluated as a sum score with a value range from 0 to 21:

- 0 – 4 points: Minimal anxiety
- 5 – 9 points: Mild anxiety
- 10 – 14 points: Moderate anxiety
- 15 – 21 points: Severe anxiety

8.1.3 Explorative Objectives

The exploratory outcome variables are the change in pain, general changes and disease status from the patient's perspective at the indicated time points (see section 1.3) compared to T0. Change will be compared between the intervention and control groups. Additionally, the acceptance of the intervention will be measured. The operationalization of the endpoints is described below.

8.1.3.1 Patient Pain Scale

To evaluate the pain of patients, patients rate their worst perceived pain in the past 24 hours on a scale of 0 to 10, with a score of 0 representing no pain and a score of 10 representing worst pain.

Analysis

For the analysis, the mean values of the patients' data from the intervention and control groups are calculated.

8.1.3.2 Patients' Global Impression of Change (PGIC)

The PGIC records the general change in relation to the disease since the start of treatment from the patient's perspective. Patients describe the change of their disease on the one hand using 7 response options (no change or worsening, hardly any change, a little better, somewhat better, moderately better, better, much better) and on the other hand on a scale from 0 to 10, where a value of 0 indicates a significant improvement, a value of 10 indicates a significant worsening, and a value of 5 indicates no change.

Analysis

For the analysis, the mean values of the patients' statements from the intervention and the control group are formed for the two assessments of the changes.

8.1.3.3 Patient Global Assessment of Disease Activity (PGA)

The PGA records the disease status of the respective underlying disease from the patient's perspective. Patients describe their current disease status on a scale of 0 to 10, with a score of 0 representing no noticeable discomfort and a score of 10 representing worst possible discomfort from the disease.

Analysis

For the analysis, the mean values of the patients' statements from the intervention and control groups are formed.

8.1.3.4 Net Promoter Score (NPS)

The acceptance of Vila RaVie in the intervention group is determined by means of the question "How likely is it that you will recommend Vila RaVie to others". Patients of the intervention group who used Vila RaVie rate the question on a scale from 0 (unlikely) to 10 (extremely likely).

Analysis

The NPS is calculated by taking the difference between the percentage of those who answered the question with 9 or 10 minus the percentage of those who answered the question with 0 to 6. The value range for the NPS is between 100 and -100; the larger the value, the more likely patients are to recommend Vila RaVie.

8.2 Safety Assessment

Data concerning the safety of the patients is recorded at T0, T1 and T2. Differences between the intervention and control group will be reported. Suicidality: If subjects score > 0 on question 9 of the Patient Health Questionnaire (PHQ-9) during the initial screening visit, participants are not included in the study and recommendations are made by the investigator to seek professional help.

8.2.1 Negative Effect Questionnaire for Psychotherapy (NEQ)

The NEQ measures the self-assessed negative effects and impact of psychotherapy using 20 items, each with 5 response options (extent of impairment: not at all, somewhat, moderately, strongly, very strongly). In addition, patients rate whether they think the impairment per item occurred due to therapeutic treatment or other circumstances [36]. For the reason that the intervention is an online program, minimal adjustments are made (items 7,9,13,15,16,19).

8.2.2 Other adverse events

Other adverse events are documented in writing.

The evaluation of whether the adverse events that have occurred are related to the treatment is carried out with the help of a panel of experts (Safety Board).

8.3 Warnings and Precautions

No special warnings and precautions are considered necessary for the investigation studied.

9 Statistical considerations

Background & Summary: The primary study objective is to exploratively describe the efficacy of using the online program on disease-related psychological distress (depression, anxiety) and quality of life in adult patients with RA, PsA, or SLE.

This study is a pilot study to evaluate the efficacy of the online program on a variety of endpoints. While a clear study hypothesis shall be defined, the results should also be seen as exploratory in nature. P-Values will be calculated for all endpoints, regardless of whether they are defined as primary, secondary, or exploratory endpoint. As this is an exploratory trial, no adjustment of the type-I error-rate due to multiple testing is performed and test results are considered significant if the two-sided p-value is below 0.1.

9.1 Statistical Hypotheses

Hypotheses regarding the primary endpoints:

Psychological distress

H0: no difference in change from baseline after 12 weeks of treatment in disease-related psychological distress between intervention and control groups.

H1: difference in change from baseline after 12 weeks of treatment in disease-related psychological distress between intervention and control groups.

Quality of life

H0: no difference in change from baseline after 12 weeks of treatment in quality of life between intervention and control groups.

H1: difference in change from baseline after 12 weeks of treatment in quality of life between intervention and control group.

9.2 Analysis Sets

9.2.1 Intention-to-Treat (ITT)-Population

All randomised patients with at least baseline values, regardless of missing data or drop-out during the study, analysed in the study arm to which the patients were randomised, regardless of the treatment actually received.

The ITT-population is used for the main analyses of the study.

9.2.2 Per-Protocol (PP)-Population

All randomised patients who completed the study without major protocol deviations.

The PP-population is used for a sensitivity analysis of the main analyses.

9.2.3 Completer

Subpopulation of all randomised patients who completed all questionnaires.

The completer subpopulation is used for a sensitivity analysis of the main analyses.

9.2.4 Safety Population

All randomised patients who received study treatment analysed in the respective study arm of the treatment (access to the online program or standard of care + information flyer).

The Safety population is used for the main analyses of the study for all safety endpoints.

9.3 Statistical Analysis

Statistical analysis will be performed using the statistics software R and the version used will be specified in the statistical analysis plan (SAP), which, if possible, should be finalized before the first visit of the first subject. The SAP will describe the subject populations to be included in the analyses, and procedures for accounting for missing data. It will contain a more comprehensive explanation than described below of the methodology used in the statistical analyses. The SAP will also contain the rules and data handling conventions to be used to perform the analyses.

9.3.1 General Analytical Methods

Interference statistics

Continuous Variable:

Differences between both study arms are calculated using a mixed linear model for repeated measures (MMRM) with treatment, visit, treatment*visit, baseline value, and disease as covariates. The least squares (LS) mean difference (including confidence interval) including effect size calculated using Cohen's d (including confidence interval) is used as the effect estimator. Effect estimators are calculated for T1 (after 6 weeks of treatment) and T2 (after 12 weeks of treatment).

Binary variable:

Responder analyses are performed exploratively for the primary endpoints.

Differences between the two study arms will be examined using Fisher's exact test. The risk ratio, odds ratio, and risk difference (including confidence interval) will be reported as effect estimates. Effect estimators are calculated for T1 (after 6 weeks of treatment) and T2 (after 12 weeks of treatment).

Descriptive statistics

The following descriptives are reported for all patient characteristics and endpoints:

Continuous variable:

- Number of patients (n)
- Arithmetic mean (mean value)
- Standard deviation (SD)
- Median
- 25% quantile and 75% quantile
- Minimum (min) and maximum (max).

Categorical variable:

- Number of patients (n)
- Percentage of patients (%)

Missing ValuesContinuous variable:

Since by its properties in a MMRM missing values are already considered and interpolated, no imputation is performed for the primary analysis. As a sensitivity analysis, missing values are imputed using LOCF (Last Observation Carried Forward).

Binary Variable:

For the primary analysis, patients with missing data are assumed to be non-responders. As a sensitivity analysis, missing values are imputed using LOCF.

9.3.2 Efficacy Analyses

Table 11: Planned analysis per endpoints.

Endpoint	Analysis
HADS-D	<ul style="list-style-type: none"> • LS mean difference T1 vs. T0 and T2 vs. T0 • LS mean difference and binary analyses of the subscales “depression” and “anxiety” • Binary analysis with an MCID of 0.5 x standard deviation of the average change of the total score in both study arms (% of patients who improved according to the MCID at T1 vs. T0 and T2 vs. T0) • Sensitivity binary analysis with an MCID of 5.7 for the total score, 3.3 for the subscale “depression” and 3.8 for the subscale “anxiety” (% of patients who improved according to the MCID at T1 vs. T0 and T2 vs. T0)
AQOL-8D	<p><u>Utility weighted analysis</u></p> <ul style="list-style-type: none"> • LS mean difference T1 vs. T0 and T2 vs. T0 • Binary analysis with a MCID of 0.06 (% of patients who improved by 0.06 points at T1 vs. T0 and T2 vs. T0) <p><u>Analysis of total value</u></p> <ul style="list-style-type: none"> • LS mean difference T1 vs. T0 and T2 vs. T0
SES6G	<ul style="list-style-type: none"> • LS mean difference T1 vs. T0 and T2 vs. T0
HLS-EU-Q16	<ul style="list-style-type: none"> • LS mean difference T1 vs. T0 and T2 vs. T0 • Percentage of patients changing from ≤ 8 points to $\geq$ points and from 9 – 12 points to $\geq$ points (descriptive analysis)
PSS-10	<ul style="list-style-type: none"> • LS mean difference T1 vs. T0 and T2 vs. T0 for both subscales
WSAS	<ul style="list-style-type: none"> • LS mean difference T1 vs. T0 and T2 vs. T0 for both subscales
PHQ-9	<ul style="list-style-type: none"> • LS mean difference T1 vs. T0 and T2 vs. T0
GAD-7	<ul style="list-style-type: none"> • LS mean difference T1 vs. T0 and T2 vs. T0
Patient Pain Scale	<ul style="list-style-type: none"> • Descriptive analysis (cf. section 9.3.1)
PGIC	<ul style="list-style-type: none"> • Descriptive analysis (cf. section 9.3.1)
PGA	<ul style="list-style-type: none"> • Descriptive analysis (cf. section 9.3.1)
NPS	<ul style="list-style-type: none"> • Descriptive analysis (cf. section 9.3.1)
NEQ	<ul style="list-style-type: none"> • Descriptive analysis (cf. section 9.3.1)
AQoL-8D: Assessment of Quality of Life - 8 dimensions; HADS-D: Hospital Anxiety and	

Depression Scale – German Version; HLS-EU-Q16: European Health Literacy Survey - short form; NEQ: Negative Effect Questionnaire for Psychotherapy; NPS: Net Promoter Score; PGA: Patient Global Assessment of Disease Activity; PGIC: Patients' Global Impression of Change; PSS-10: Perceived Stress Scale-10; WSAS: Work and Social Adjustment Scale; PHQ-9: Patient Health Questionnaire-9; GAD-7; Generalized Anxiety Disorder-7; LS: least squares; MCID: minimal clinically important difference.

9.3.3 Safety Analyses

The safety analysis will be a descriptive summary of adverse events and the NEQ.

9.3.4 Subgroup Analysis

9.3.4.1 Therapeutic indication

Separate evaluation of all randomised patients according to diagnosed underlying disease (RA, PsA or SLE). ICD-Codes will be mapped to indications according to this table:

Table 12: Planned subgroup analysis per indication and corresponding ICD codes.

Rheumatoid Arthritis	M05.3 M05.8 M05.9 M06.0 M06.1 M06.2 M06.3 M06.4 M06.8 M06.9
Psoriasis Arthritis	L40.5†M07.0* L40.5†M07.2* L40.5†M07.3*
Systemic Lupus Ery- thematosus	M32.0 M32.1 M32.8 M32.9

9.3.4.2 Change in medication

Separate evaluation of all randomised patients after adjustment of the medication of the underlying disease during the course of the study (subgroups: medication adjustment: yes / no).

9.3.4.3 Age group

Separate evaluation of all randomised patients according to age (subgroups: age 18 – 65 years and 65 years and older).

9.3.5 Sensitivity Analyses

Sensitivity analyses are performed based on the PP-Population and Completers.

9.4 Sample Size Determination

Assumptions for sample size determination:

- 1:1 randomised RCT
- Power: 0.8
- Significance level: 0.1 (two-sided)
- Effect size: 0.5 (including an assumed drop-out rate of 20 %)

Calculation of the total number of patients required:

51 patients per study arm (102 patients in total).

G-Power (Version 3.1.9.7) was used for sample size calculation [28].

9.5 Protocol Deviations

The investigator(s) is (are) not permitted to deviate from the study protocol. For this purpose, training for the participating physician(s) will be provided at the beginning of the study. Nevertheless, if a protocol deviation occurs, this must be reported to the sponsor immediately. Corrective measures will be reviewed on a case-by-case basis.

9.6 Data Management

9.6.1 Data Collection and Transfer

Standardized eCRF modules will be used to capture all data required by the study schedule (chapter 1.3). Data entry will be performed online using a standard browser to access the EDC-System of the clinical solutions provider Castor.

The eCRF contains programmed automatic edit checks that validate data immediately upon entry. Additionally, data management may issue electronic queries for datapoints entered by the site. Site staff will answer these queries via the eCRF.

After the database has been cleaned and locked, data management will export electronic datasets from the database and transfer them to statistics in encrypted form for analysis.

9.6.2 Data Quality

All data in this project are captured in eCRFs and stored into an electronic clinical database. Quality control and data validation procedures such as programmed automatic edit and consistency checks ensure data validity and accuracy immediately at the point of entry into this database. The database application which is used to capture electronic clinical trial data is protected from unauthorized access. It is, among other features, access restricted, contains rights and roles functionalities, provides electronic authentication of data entries, maintains an electronic audit trail and provides appropriate data backup functionalities.

There is no original data, e.g., in the form of a patient file, for this study as most of the data are documented directly by the participants in the EDC system. The data for informed consent, medical history (Indication, duration of illness, disease activity, comorbidities, current drug treatment, current non-drug treatment), medication and side effects / AEs are documented during remote visits (telephone calls or online meetings) by the investigator by direct questioning of the subjects and documentation in the EDC system. As the investigator is not the regular local physician for the participants, there is no classical patient file where the data are collected.

Since there is practically no original data (source data) available, classical monitoring of the data, i.e., comparison of source data with the data in the eCRF by external monitors, is not possible.

To verify the participant's diagnosis and age, a form signed by the attending physician or a physician's letter is uploaded by the subject to the EDC system and matched against the entered data during the screening process by the study team data management.

9.6.3 Database Lock

After the CRO and the sponsor agreed on the timepoint of database closure, the sponsor will give a written authorization for database closure. Closing the database includes withdrawing writing permissions in EDC systems (so that no more changes can be made to the data), final data export and storage in the customer project folder.

If errors are discovered after the database has been closed, it is up to the sponsor to decide whether to re-open the database. A re-opening of all or selected sites must be ordered in writing. Both, the re-opening and the re-closure of the database, will be documented.

10 Supporting Documentation and Operational Considerations

10.1 Regulatory and Ethical Considerations

The trial protocol was prepared based on the CONSORT Statement (Consolidated Standards of Reporting Trials) and DIN EN ISO 14155 “Clinical investigation of medical devices for human subjects - Good clinical practice”.

All requirements of Regulation (EU) 2017/745 (MDR) and the Medizinproduktegesetz (MPDG) are considered, especially with regard to reporting of serious adverse events (SAEs) and product defects.

This trial will be conducted in accordance with the Declaration of Helsinki and the professional regulations of the respective state medical association. A consultation of the treating physician by the responsible ethics committee is provided. The trial will only begin after consultation with the relevant ethics committee(s) has taken place. Possible additional requirements of the ethics committee(s) will be complied with, if applicable. Any subsequent protocol amendment will be submitted to the Ethics Committee(s) for approval.

Participation in the study is voluntary. The investigators will assure that each participant, regardless of the enrolment in the trial, will receive best practice medical treatment.

10.2 Confidentiality

Personal data will be processed in accordance with the relevant national and international legislation and good clinical practice. Data will only be processed for the purpose of the trial. Individual patient's medical information will be recorded in the CRF database only in pseudonymised form.

All participants in this study must provide informed consent for data processing. If no informed consent is given by the participant, the participant will be excluded from the clinical investigation. Data protection is carried out in accordance with the applicable regulations (General Data Protection Regulation, GDPR).

10.3 Adverse Events and Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

According to Regulation (EU) 2017/745, an adverse event (AE) is any untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational device. A serious adverse event (SAE) is defined as any AE that led to a) death, b) serious deterioration in the health of the subject, that resulted in any of the following: 1) life-threatening illness or injury, 2) permanent impairment of a body structure or a body function, 3) hospitalisation or prolongation of patient hospitalisation, 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, 5) chronic disease, or c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect.

Because this study uses a CE marked device and has no requirement of an approval or notification with the authority, reporting of serious adverse events is not required.

The reporting of incidents and recalls is done according to the legally applicable reporting requirements and according to Vila's internal working instruction on incidents and recalls. A procedure is also in place via the "Corrective and Preventive Action (CAPA)" process instruction to identify and deal with product defects or other problems in a coordinated manner. Any errors in the software program, such as incorrect calculations or recommendations, fall under this. The process instruction regulates how deviations in the product or the accompanying materials are dealt with once they become known. Extensive documentation is also carried out as part of these processes.

Nevertheless, a modified "Negative Effect Questionnaire for Psychotherapy" (NEQ, see chapter 8.2) will be used to record self-assessed negative effects and impacts of the psychotherapy for T1 and T2. Additional medical events can be reported by the subject as free text in the EDC system.

If a patient reports a negative impact from treatment or enters an additional medical event, the investigator will be automatically informed by the system to contact the patient and record the event in a structured manner (e.g., with start and end date, severity, outcome, relation to the software program) and to instruct the participant on further actions (if necessary, e.g., to contact the attending physician).

10.4 Final study report and publication

The responsible ethics committee is informed in due time about the termination of the study.

Within one year after completion of the clinical trial, the final report on the clinical trial, covering all significant events of the trial, is submitted to the ethics committee and the summary will be published in the DRKS register.

11 References

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12 Appendices

12.1 Information flyer Control Group

PSYCHISCHE GESUNDHEIT

BEI CHRONISCH ENTZÜNDLICH-RHEUMATISCHEN ERKRANKUNGEN

Eine chronische Erkrankung führt neben den körperlichen meist auch zu psychischen Belastungen. Daher ist die Fähigkeit zum aktiven und selbstbestimmten Umgang mit der Erkrankung von zentraler Bedeutung, um den Gesundheitszustand positiv zu beeinflussen und die Lebensqualität zu verbessern bzw. zu erhalten.

Dies kann z.B. durch Patientenschulungen gefördert werden - mit dem übergeordneten Ziel, Menschen dabei zu unterstützen und zu befähigen, ihren Alltag mit der Erkrankung zu bewältigen. Sie werden daher als integraler Teil der Versorgung von Menschen mit entzündlich-rheumatischen Erkrankungen empfohlen.*

Weitere Informationen zu den einzelnen Indikationen finden Sie auf dem Portal des Bundesministeriums für Gesundheit:

Rheumatoide Arthritis

Systemischer Lupus erythematoses

Psoriasis Arthritis

*Quelle: Paternann J, Ehlebracht-König I, Lind-Albrecht G, Gentz E, Reusch A, Küffner R, Müller-Ladner U, Braun J. EULAR-Empfehlungen für die Schulung von Patienten mit entzündlich-rheumatischen Gelenkerkrankungen. Z Rheumatol. 2016 Mar;75(2):187-99. German. doi: 10.1007/s00395-015-0020-z. PMID: 26744185

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12.2 Financial compensation for participants

Estimated time commitment for participants:

- Completion of online program = 13.0h
- Completion of questionnaires (T0, T1, T2) = 1.5h

Methodology: Total time commitment (1.5h) multiplied with German minimum wage per h (12€) = 174€; reduced by -74€ as access to the online program is also seen as benefit. Thus, 100€ financial compensation is seen as reasonable.

Compensation: 100€ in form of an WUNSCHGUTSCHEIN online voucher (redeemable in an online shop of choice), distributed via email after completion of T2. Additionally, among all participants (who completed the study), 1 additional 100€ WUNSCHGUTSCHEIN voucher is raffled by a lottery in the end of the study. Thus, 1 winner can double its financial compensation by lottery.