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Study Protocol of a randomised controlled trial on SISU, a software agent providing a brief intervention for self-help to uplift psychological well-being.

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Abstract

Introduction: Only a minority of people living with mental health problems are getting professional help. As digitalisation moves on, the possibility of providing internet- and mobile-based interventions (IMIs) arises. One type of IMIs are fully automated conversational software agents (chatbots). Software agents are computer programs that can hold conversations with a human by mimicking a human conversational style. Software agents could deliver low-threshold and cost-effective interventions aiming at promoting psychological well-being in a large number of individuals. The aim of this trial is to evaluate the clinical effectiveness and acceptance of the brief software agent-based IMI SISU in comparison to a waitlist control group (WL). **Methods and Analysis:** Within a two-group randomised controlled trail, a total of 120 participants will be recruited in Germany, Austria and Switzerland. Assessment takes place before (t1), during (t2) and after (t3) the interaction with SISU, as well as 4 weeks after randomisation (t4). Primary outcome is psychological well-being (WHO-5). Secondary outcomes are emotional well-being (FS-D), psychological flexibility (FAH-II), quality of life (AQoL-8D), satisfaction with the intervention (ZUF-8) and side effects (INEP). Examined mediators and moderators are sociodemographic variables, personality (BFI-10), emotion regulation (ERQ), alexithymia (TAS-20), centrality of events (CES), treatment expectancies (CEQ) and technology alliance (TAI-SF). Data analysis will be based on intention-to-treat principles. SISU guides participants through a three-day intervention. SISU is based on a modified version of the paradigm of expressive writing and acceptance and commitment therapy-based principles. The brief intervention consists of three modules. Participants work through the intervention on three consecutive days. **Ethics and Dissemination:** This trial has been approved by the ethics committee of the Ulm University (No. 448/18, 18.02.2019). Results will be submitted for publication in a peer-reviewed journal and presented at conferences.

Strengths and limitations of this study:

- ➔ To our knowledge, this is the first full-scale RCT on a chatbot delivering a brief psychological intervention to uplift psychological well-being.
- ➔ Results on user acceptance will help to gain further insights for requirements due to the fully automated presentation form of psychological internet interventions.
- ➔ Technology alliance and side effects will be monitored.
- ➔ Dropout rate is to be kept small by automated guidance and prompts.

Trial registration: The trial is registered at the WHO International Clinical Trials Registry Platform via the German Clinical Studies Trial Register (DRKS): DRKS00016799 (date of registration: 25.04.2019). In case of important protocol modifications, trial registration will be updated. This is protocol version number 1.

Keywords: Chatbot, software agent, psychological well-being, internet and mobile-based interventions, writing, positive psychology intervention, digital

INTRODUCTION

The global direct and indirect economic costs of mental disorders are estimated at 2.5 trillion US $ [1]. Thus, untreated mental disorders are a public health concern worldwide. However, the majority of individuals living with mental disorders do not receive any health care supply [2–4]. In Europe, only about 25% of people with mental disorders receive professional treatment [5].

On the one hand, there are societal barriers to receiving adequate mental health care offers. On the other hand, there are barriers on the side of individuals, keeping them from seeking professional help [6]. The latter aspect comprises fear of stigmatization [7,8], restrictions of time and location [9,10], negative attitudes towards pharmacological and psychotherapeutic treatments [11], negative experiences with professionals [12,13] or missing conscientiousness for diseases [14]. In order to overcome some of these barriers and to improve mental health care at a large scale, digital means are frequently discussed options.

Digitalization sets societal changes in motion in various fields [15]. Other than in the areas of work, economy, and science, new technologies slowly emerge in the field of mental health care. Internet-based and mobile-based Interventions (IMIs) can provide low-threshold, flexible interventions that are resource-, time- and location-independent [9,10] and can be as effective as traditional face-to-face psychotherapy [16]. As such, they might help to reduce societal and individual barriers to mental health care and expand supply offers [9,16,17]. At this point, their effectiveness and cost-effectiveness could be established for the prevention [18] and treatment of mental disorders [9,19–24] and chronic somatic diseases [25] as well for positive mental health promotion purposes [26–29].

IMIs are highly standardised, manualised computer programs, which can be seen as digitized therapeutic interventions [9,30]. While they have without doubt substantial merits, some limitations still restrict their scalability and widespread roll-out. As yet, for example, IMIs seem to work best if they provide any form of human guidance alongside the digital program [31,32]. However, fully unguided interventions could be a more cost-effective way of providing digital interventions (e.g.,[33]). Thereby, professional guidance does not only limit the cost-effectiveness, but also necessitates health care infrastructures that might not always be at place at a large (enough) scale.

Evidence shows that the effectiveness of IMIs might be in part attributable to other effect factors than in face-to-face therapy [34]. In comparison to face-to face therapy, the therapeutic alliance might not be as relevant as effect factor [35]. Instead, other factors, e. g. an agreement on tasks and goals [35] or the fostering of self-efficacy [34], have been discussed. Software agents could combine the best of both worlds, as they seem to have the potential to human-machine alliance [36]. Delivering IMIs by software agents could compensate for some of the

disadvantages of conventional computer program-based IMIs (e.g.,[37]. Amongst others, they could show human-like, immediate responses with regards to user input [38].

A software agent or "chatbot" is a computer program that can hold a fully automated text-based conversation in real-time with people via a chat-interface (e.g., smartphone application) by using a natural language style [38]. The growing interest and body of research about software agents [39,40] is realised in various populations and contexts, such as problem solving and stress [41–43]. In the context of clinical psychology and psychotherapy, research on software agents is sparse [44] but could create opportunities for the field regarding the provision of mental health services. Software agents could be used to convey therapeutic contents and brief interventions [45,46]. Establishing contact to a software agent might not be as stigmatising as using formal mental health services like starting a face-to-face therapy or asking a general practitioner for possibilities of mental health care [47]. Furthermore, they are flexible regarding location and time [48], can be used anonymously [49,50] and provide personalization through implicit customization [51]. Therefore, software agents could help to overcome barriers and provide psychological and health behaviour change interventions on a large scale in the future.

Current mental health software agents are primarily based on cognitive behavioural therapy [44]. However, other popular approaches with proven effectiveness in face-to-face settings could also readily be realized in a digital form, such as writing interventions [52] and acceptance and commitment-based approaches [53].

Writing with the aim of improving health has a long history [54]. In the current literature, the labelling of this kind of intervention varies: Terminology includes expressive writing [55], benefit-finding writing [52], or therapeutic writing (e.g., [56]). Regardless of terminology, the writing intervention to be investigated in this study will refer to the process of freely and emotionally writing about a positive personal life event without paying attention to spelling or grammar. The call to write about personal life events, to tell a story, seems to go straight at the centre of subjective experiences [57], which in turn is the main medium in traditional face-to-face therapy. It has been shown that writing interventions can be highly time- and cost-efficient [58]. A recent meta-analysis shows that writing interventions can help to improve general psychological health (SMD=-0.46, 95% CI -.86, -0.06) [59]. Finally, a meta-analysis from Bolier and colleagues[60] found an effect of Cohen's *d* = 0.34 (95% CI 0.22, 0.45) for positive interventions to uplift cognitive and/or affective appraisal of one´s life as a whole and d=0.20 (95% CI 0.09, 0.30) optimal functioning including mastery, hope and purpose in life.

Acceptance and Commitment Therapy (ACT) [61] aims at acceptance, mindfulness and value-based living and has been found to be effective in the prevention of stress and the increase of well-being [27,62]. The efficacy of ACT-based interventions in general and ACT-based IMIs in particular has been indicated in a number of studies and systematic reviews. Within a

randomised-controlled trial, Fledderus and colleagues (2012) investigated an ACT-based IMI for people living with depression. The authors found significant reductions in depression, anxiety, fatigue, experiential avoidance and improvements in positive mental health, compared to a waitlist control condition (effect sizes Cohen´s *d* = 0.51 to 1.00) [29]. In their meta-analysis, Brown and colleagues[63] examined 10 randomised controlled trials investigating the effectiveness of ACT in the treatment of depressive or anxiety symptoms and well-being in adult populations. ACT interventions were compared to passive control groups (N=3), active control groups (N=4) or both (N=3). The authors found small effect sizes regarding the improvement of depression (*g* = 0.24, 95% CI: 0.04 - 0.45) whilst the heterogeneity of conditions and outcome measures on anxiety and well-being was too high to draw firm conclusions. Spijkerman and colleagues [28] examined 15 randomised controlled trials in adults with various mental problems and healthy populations. Mindfulness interventions, of which the authors include ACT, were compared to passive control groups (N=10), active control groups (N=5) or both (N=2). The authors found small to medium effect sizes concerning the improvement of depression (*g* = 0.29, 95% CI: 0.13 - 0.46), anxiety (*g* = 0.22, 95% CI: 0.05 - 0.39) and well-being (*g* = 0.23, 95% CI: 0.09 - 0.38) [28].

We developed a software agent called SISU (**S**oftware agent providing an **I**ntervention for **S**elf-help to **U**plift psychological well-being and finnish word for inner strength) with the aim to provide an easily deployable software agent that improve peoples´ well-being. Therefore, SISU combines therapeutic writing and acceptance- and commitment-based principles. Results of a feasibility trial on SISU [64] showed that SISU is feasible in terms of user acceptance and the potential of the software agent to deliver a brief writing intervention. Thus SISU is feasible to be implemented within a confirmatory clinical trial. Hence, the present study is designed to investigate the clinical effectiveness and acceptance of the Software agent SISU thereby focussing on the following specific research questions:

1. Is SISU effective in uplifting psychological well-being compared to the WL at T3 (primary outcome)?

2. Is SISU effective regarding the secondary outcomes flourishing, quality of life, and psychological flexibility compared to the WL at T3?

3. Which factors are associated with, moderate or mediate the effects of SISU?

4. Is the intervention associated with side effects?

5. What is the level of acceptance (satisfaction, adherence) with the intervention?

6. Does SISU have the potential to act as a therapeutic agent?

METHODS

Study Design

This is a two- arm, parallel randomised controlled trial (RCT) with the intervention group SISU (IG) and a waiting list control group (WL). The IG receives the online-based intervention guided by the SISU software agent. The WL receives the intervention 4 weeks later. Primary and secondary outcomes will be assessed over a period of four weeks. Assessments will take place at screening (T0), baseline (t1), intermediately one day after randomisation (t2), post-treatment two days after randomisation (t3) as well as four weeks follow-up (t4).

The present study is conducted and will be reported in accordance with the CONSORT 2010 guidelines for RCTs [65] and the guidelines for executing and reporting IMI research [66]. The study protocol follows recommendations of the SPIRIT 2013 Checklist for clinical trial protocols [67].

Recruitment

Recruitment has started in May 2019 and will be continued until the targeted sample size of N=120 has been reached. We recruit in German speaking countries, Germany, Austria and Switzerland. Recruitment strategies comprise a dynamic, broad on- and offline recruitment strategy. Offline recruitment will be conducted via posters and flyers at different universities, psychosocial counselling services and city libraries. Online recruitment strategies will comprise postings on social media, websites and institutions of higher education as well as the Studicare®-website. StudiCare is a project that offers a broad assortment of internet-based interventions for psychological and behavioural issues [68]. Interested persons will get access to the screening at unipark.de via QR-code, link or via email on request. Directly after the screening eligible participants will automatically receive informed consent for signing via email. Apart from the recruitment, the study will be fully conducted online.

Eligibility criteria

Participants will be eligible for inclusion in the present trial if they are (a) 18 years or older, (b) willing to take part in this study, (c) have internet access and an email address, (d) have a low psychological well-being (WHO-5 $\leq$ 52) and (e) possess sufficient German language skills.

Study Procedures

If eligibility criteria are fulfilled, applicants will receive an online information letter including detailed information about study procedure and informed consent. They will be informed that they can withdraw from the intervention and/or study at any time without any negative consequences. After signing the informed consent, participants will be randomised to the IG or WL condition. Following, they will receive their individual ID and get an invitation for the

baseline questionnaire (t1) at unipark.de via email. Afterwards, participants will learn about their group membership. The IG will get in contact with SISU and the intervention using the end-to-end encrypted online messaging app "Wire" after finishing baseline (t1). SISU guides participants through a writing intervention on three consecutive days using a standardised conversation script. Each writing intervention is automatically followed by an assessment. Subjects who are part of the WL will receive access to SISU four weeks after randomisation. If participants complete questionnaires for t3 and t4 they will each time get the chance to win a 10€ gift card for Amazon as a monetary incentive to promote retention and follow-up completion.

Randomisation and blinding

Participants will be randomised to either IG or WL. An academic assistant (JM) from the Department of Clinical Psychology and Psychotherapy at the University Ulm, not otherwise involved in the trial and blinded towards all further procedures, will perform the allocation. A permuted block randomisation with 4, 6, 8 and 12-block-size and an allocation ratio of 1:1 will be used. The randomisation list will be created by a well-accepted website (https://www.sealedenvelope.com). Whereas blinding of participants is not possible, data collectors and data analysts are blinded regarding group membership.

Intervention

The intervention consists of the interaction with a software agent (SISU) that provides a brief intervention. The interaction will be implemented using the online messaging service "Wire". The writing instruction provided by SISU is based on the paradigm of positive expressive or narrative writing (notions are used synonymously) as well as acceptance and commitment therapy [ACT; 69]. The software agent was developed at Ulm University. The version of SISU used for this study was improved through participant feedback collected in the feasibility trial [64]. Revisions included the enrichment of the instruction for writing about positive life events with elements of ACT (more mindfulness exercises, authenticity of the dialog through reduction of repetitions, interactions on reported life events) and elements for the reconstruction of narrative identity. In its core, the software agent application remains the unmodified version of the one used in the feasibility trial.

Using Wire Services SDK enables programmatic end-to-end encrypted communication with other Wire users. Thanks to this encryption, messages sent by SISU or participants are not accessible by third parties, including the service provider. We further protect participation data by hosting SISU on premises and by encrypting the data at rest, thus limiting the access to our research group. The communication logic is implemented as a finite-state machine. Our SISU implementation parses incoming messages based on a fixed set of rules and responds with

an appropriate answer. In addition, SISU can react to external triggers, such as (a) conversation timeouts (i.e., the participant has not responded in a set time frame), (b) Unipark events (i.e., participant has completed an external survey), and (c) scheduled events (e.g., daily participation reminder at pre-defined time frames).

SISU guides participants through the intervention on three consecutive days, mimicking a human conversational style. Participants are guided to write each day at the same time for 10-20 minutes about a self-chosen autobiographical, positive life event. The intervention structure is basically the same over the three days. However, on day 1 there is psychoeducation in the beginning additionally. The instructions for the writing tasks are followed by the narratives of the participants. Participants are instructed to write about a meaningful, outstanding positive life event on day 1 and about an outstanding positive event from adulthood on day 2. On day 3 participants are guided to write about their best possible future. The paradigm of therapeutic writing is supplemented with ACT-based mindfulness exercises and metaphors. After the writing task, SISU encourages participants to experience the positive emotions due to the reported event in the present moment. Mindfulness exercises are provided by an audio file right after the writing intervention, whilst ACT-metaphors are integrated into the conversational content. Participants are encouraged to practice on a daily basis. To increase adherence, SISU reminds participants at 24 hour intervals. More details on intervention contents can be derived from Table 1. For an illustration of content and chronological structure see Figure 1.

Table 1

Content and techniques of the writing tasks as delivered by SISU

Module title	Module Content	Focused ACT technique
1 Introduction	Therapeutic writing, ACT	Psychoeducation
2 Writing tasks	Instructions for writing about a positive autobiographical life events	
3 Thoughts and feelings	Important things in life	Values
4 Mindfulness exercise	Being aware of what is happening in the present moment without judging it	Contact with the present moment; Acceptance

Note. ACT = Acceptance and Commitment Therapy

--please insert figure 1 around here--

The (ultra-)brief intervention rational of 3 days was chosen because we wanted to provide participants with a brief possibility to do something for their mental well-being, despite their busy everyday lives. Indeed, evidence suggests that brief writing interventions of e. g. only 1 week can increase emotional well-being even 6 months after the intervention [70], particularly in case of interventions focussing on improving mental health rather than treating mental disorders.

Wait list control group

Participants of the WL get access to the writing intervention provided by SISU four weeks after randomisation. The intervention has the same content for both groups. Participants with a low WHO-5 score (< 28) in the screening receive an automatised email with further information about offers of the health care system.

Administrative and technical support

In case participants forget their individual ID or have other technical issues, they can make use of the study team via email for technical support at every point during the training.

Outcome Assessment

Screening for eligibility takes place at t0. Data for relevant outcomes will be collected prior to the intervention (t1), one day after randomisation during the intervention (t2), two days after randomisation (t3; intervention completed) and four weeks after randomisation (t4; follow-up). It is not necessary that participants have already finished the intervention to participate in the t1-survey. Demographic data and personality traits are measured once (t1). A flow chart of the study can be seen in Figure 2. The outcomes, their measurement instrument and points of assessment are shown in Table 2.

--please insert figure 2 around here--

Table 2

Constructs, measurement instruments and points of assessment

Construct	Measurement instrument	Points of assessment			
		T1	T2	T3	T4
Demographical Questionnaire		✓			
Primary endpoint					
Psychological well-being	Well-being Scale (WHO-5)	✓	✓	✓	✓
Secondary endpoints					
Emotional well-being	Flourishing Scale (FS-D)	✓	✓	✓	✓
Psychological flexibility	Acceptance and Action Questionnaire-II (FAH-II)	✓	✓	✓	✓
Quality of life	Assessment of Quality of Life (AQol 8D)	✓	-	✓	✓
Satisfaction with the intervention	Client Satisfaction Questionnaire (ZUF-8)	-	-	✓[a]	-
Side effects	Inventory for the assessment of negative effects of psychotherapy (INEP)	-	-	✓[a]	✓[b]
Manipulation-Check writing	Post Writing Questionnaire	-	✓[a,c]	✓[a]	-
Questions on content	Open questions for the interaction with SISU	-	-	✓[a]	-
Willingness to use software agents in the future	Open questions	-	-	✓[a]	-
Moderators/Mediators					
Centrality of events	Centrality of Events Scale (CES)	-	✓[a,c]	✓[a]	-
Personality	Big Five Inventory (BFI-10)	✓	-	-	-
Treatment expectancy	Credibility Expectancy Questionnaire (CEQ)	✓	-	-	-
Alexithymia	Toronto Alexithymia Scale (TAS-20)	✓	✓	✓	✓
Emotion regulation	Emotion Regulation Questionnaire (ERQ)	✓	✓	✓	✓
Technology alliance	Inventory of Technology Alliance – Online Therapy (TAI-SF)	-	✓[a]	✓[a]	-

Note. T1 = baseline; T2 = during treatment (two days post-randomisation); T3 = post-treatment (3 days post-randomisation); T4 = follow-up (four weeks after randomisation). [a] Questionnaires only used by IG; [b] adapted version for WL; [c] additionally assessed retrospective for the first contact with SISU at T2

Screening, t0

The short 5-item Well-being-Scale (WHO-5) is administered to assess the subjective well-being of participants in the last two weeks [71]. Subjects can answer on a 6-point-Likert scale (5= “All of the time”, 4 = “Most of the time”, 3 = “More than half the time”, 2 = “Less than half the time”, 1 = “Some of the time”, 0 = “At no time”). The sum of raw scores (range: 0-25) is multiplied with 4 and produces a total score (range: 0-100) with 0 representing the worst imaginable well-being to 100 representing the best imaginable well-being [71]. Scores ≤ 52 indicate a low, scores ≤ 28 indicate a very low psychological well-being. Topp and colleagues[71] mention a comparable cut-off score of ≤ 50. The WHO-5 shows a sensitivity of 0.93 and a specificity of 0.83 in the detection of depression [71]. Additionally, the screening includes age, sex, contact information and the sufficient knowledge of German language.

Demographic data

The following information will be collected from each participant at T1: sex, age, education, nationality, German speaking skills, relationship status, profession and highest educational attainment.

Primary outcome

Psychological well-being

Primary outcome is psychological well-being at t3 measured by the Well-being-Scale [71] already described in the section for screening.

Secondary outcomes and covariates

Emotional well-being.

The German version of the Flourishing Scale [FS-D; 72] is a measure of psychosocial well-being and personal growth and development (i.e., flourishing). Each of the 8 items is rated on a 7-point-Likert scale ranging from 1 = “strongly disagree” to 7 = “strongly agree”. A sum score is computed with higher scores indicating higher flourishing. With a Cronbach’s α of 0.87 the scale shows good internal consistency [72].

Psychological flexibility

The German version of the Acceptance and Action Questionnaire-II [73] is a general measure for psychological inflexibility and consists of 7 items. On a 7-point-Likert scale that ranges from 0 = “never true” to 6 = “always true”, the questionnaire assesses a person’s willingness to experience unwanted thoughts and feeling and a person’s ability to act despite the presence of undesirable thoughts and feelings. In this study items were reverse coded to assess psychological flexibility. Sum scores (range: 0-42) are computed with higher scores indicating

higher psychological flexibility. The questionnaire shows good to excellent psychometric properties in a German sample [73].

Quality of life

With the help of the inventory Assessment of Quality of Life (AQoL-8D) participants quality of life is recorded [74]. Each of 35 items loads on one of eight dimensions of quality of life and is rated on 4- to 6-point-Likert scales. For analysis there is an algorithm which can be used for quality of life in general as well as for particular sub dimensions. In total, scores between 0 and 1 are possible. Standard values are available. Reliability of AQoL-8D is very good with Cronbach's α of 0.96 [74].

Side-effects

Subjective adverse events of the intervention are recorded with the 15-item inventory for the assessment of negative effects of psychotherapy [75]. Items are rated on a 4-point-Likert scale (0 = "no agreement" to 3 = "total agreement") or a bipolar 7-point scale. Adverse effects in social life, intrapersonal factors or work-related situations are taken in consideration. The original inventory with 32 items has an internal consistency of α = 0.95 [76].

Satisfaction with the intervention

To assess the global satisfaction with the intervention a revised version of the German version of the Client Satisfaction Questionnaire [ZUF-8; 77] was used. Participants rate their satisfaction on a 4-point-Likert scale for each of the 8 items. A sum score is computed. Higher scores indicate higher satisfaction. Internal consistency of the ZUF-8 is very good with α = 0.90 [78]. A study on reliability and validity of assessing user satisfaction with internet-based interventions indicates good overall psychometric quality of the measure [79].

Post-Writing Questionnaire

To assess the paradigm of expressive writing after every writing session the participants answer four questions about their feelings and thoughts during and after the writing experience. Answers are rated on a 5-point-Likert scale (1 = "not at all", 3 = "few", 5 = "very much/extremely"). The questionnaire was adapted from the English version of Pennebaker and Beall [80].

Open questions

For the final survey (t3) four open questions inspired by the open questions from Fitzpatrick, Darcy and Vierhile [81] about the interaction with SISU are provided. The answers are individually evaluated and thematically summarised.

Questions for the future of software agents

The final survey (t3) will assess the behavioural intention to use a software agent in the future or recommend one to friends as well as the future performance expectancy of software agents providing psychological interventions to uplift psychological well-being in three open questions. Participant responses will be analysed on a qualitative basis.

Moderators/Mediators

Centrality of events

The Centrality of Event Scale [CES; 82] assesses the centrality of an event to a person, differentiating three independent characteristics. Whether the event is seen as (1) a reference point for everyday inferences, (2) a turning point in the life story and (3) as an element of the personal identity. Participants rate the 7 items of the short-term version on a 5-point-Likert scale from 1 = “totally disagree” to 5 = “totally agree”. With a Cronbach’s α of 0.88 the scale shows high internal consistency [82].

Personality

To assess the Big Five personality traits of participants the short version of the Big Five Inventory [BFI-10; 83] is used. Each of the five personality dimensions is measured with two items depicting either the positive or the negative pole of the spectrum. Participants rate the items on a 5-point-Likert scale from 1 = “fully disagree” to 5 = “fully agree”. The questionnaire shows average retest-reliabilities ranging from 0.56 to 0.60 [83].

Alexithymia

The German version of the Toronto Alexithymia Scale [TAS-20; 84] assesses alexithymia of participants. Each of the 20 items is rated on a 5-point-Likert scale ranging from 1 = “strongly disagree” to 5 = “strongly agree”. The German version assesses 3 factors [85]: “difficulties in identifying and describing feelings“, “external oriented thinking“ and “importance of emotional introspection“. For each dimension sum scores are computed with higher scores each indicating higher manifestations of alexithymia. Internal consistency of the scale is good with a α = 0.80 [85].

Emotion regulation

The Emotion Regulation Questionnaire [ERQ; 86] is a 10-item questionnaire measuring positive and negative feelings as well as their regulation. Items refer to two different emotion regulation strategies: Reappraisal and suppression. Participants rate the items on a scale from 1 = “strongly disagree” to 7 = “strongly agree”. Means show the preference for each strategy indicating higher preference at higher mean scores. Internal consistencies are acceptable to good and differ from α = 0.75 to α = 0.82 [86].

Treatment expectancy

Treatment expectancy is measured with the Credibility/Expectancy Questionnaire [CEQ; 87] with 6 items. Participants rate four items on a 9- and two items on a 10-point-Likert scale with varying descriptions. The scale can be separated in the two factors credibility and expectancy. Cronbach's α for credibility differs from 0.79 to 0.90, for expectancy from 0.81 to 0.86 and for the total scale from 0.84 to 0.85 indicating acceptable to high internal consistency [87].

Technology alliance

The Inventory of Technology Alliance – Online Therapy (TAI-SF) was used to evaluate the technological alliance between the participants and the online intervention, thus the software agent. The TAI-SF is a 12-items questionnaire developed by Labpsitec (http://www.labpsitec.uji.es/eng/index.php) that assesses the degree to which the participant perceives the online intervention as helpful. Items are rated on a 7-point-Likert scale from 1 = "never" to 7 = "always".

Data privacy and ethics

Data will be pseudonymised and analysed in the Department of Clinical Psychology and Psychotherapy of the Ulm University via individual ID and an internal participant ID for every participant to encode the individual datasets. Messages exchanged between participants and SISU are encrypted in-transit by the end-to-end encryption of the "Wire" application. Thus, only the study team will have access to the collected data. Participants will have the opportunity to have all of their collected data deleted. External researchers may get access to the final trial dataset (from HB) on request depending on to be specified data security and data exchange regulation agreements. To ensure confidentiality, data dispersed to any investigator or researcher will be blinded of any identifying participant information. Anonymised results will be published in peer-reviewed journals and presented on international conferences.

The participation in this study should not be associated with any specific risks. However, temporary changes in mood could arise directly after the writing task [88]. Therefore, participants will have the opportunity to contact the study team at every point during the trial. Additionally to the interventions, participants with a low WHO-5 score (< 28) in the screening will be sent an automatized email with further information about offers of the health care system.

Sample Size

A meta-analysis by Bolier and colleagues [60] found an effect size of d=0.34 for positive psychological interventions aiming at uplifting well-being. Riddle and colleagues [89] reported an effect size of d=0.46 for writing interventions to enhance well-being. However, for internet-

based mindfulness interventions, Spijkerman and colleagues [28] found a somewhat smaller effect of *g*=0.23.

Based on these previous findings, a small effect size of *d* = 0.30 is expected. Power analysis for an ANOVA with repeated measures with g-power (http://gpower.hhu.de/) recommends a sample size of at least 60 participants per group (N=120) on the assumption of two-tailed testing, an alpha error $\alpha = 0.05$ and power $1-\beta = 0.90$.

Statistical Analysis

Patterns of missing data will be investigated, and analyses will be adjusted accordingly (e.g., MI or FIML). All analyses will be conducted on a two-sided level of significance (α=.05). Participant characteristics will be described descriptively.

All statistical analyses will be performed based on the intention-to-treat (ITT) principle. Additional per protocol analyses will be conducted in order to examine the effects of SISU in case of patients adhering to the intervention protocol. Participants who completed at least 66% of the intervention are defined as intervention completer (=per protocol).

The primary outcome will be analysed using linear regression models at T3 as dependent variable and the baseline value as covariate, adjusting for sex and age. To analyse between-group effect sizes, standardised mean differences with 95% confidence intervals will be calculated for post-treatment (t3) and follow-up (t4). Secondary outcomes will be analysed accordingly.

Exploratory mediation and moderator analyses involving the primary and secondary outcomes as well as demographic data will be conducted. Moderator and subgroup analyses are aimed for in case of a sufficiently large sample size.

For the planned exploratory moderator analyses, regression models will be employed. Initially, each potential moderator described under “Covariates” will be analysed in a separate regression model. The primary outcome psychological well-being at t3 will be the dependent variable. Predictors will comprise group, the moderator variable and the interaction of group and moderator. In a next step, a comprising model of all identified moderators will be tested.
Mediation analyses will be conducted according to the principles of time-lagged mediation [90]. Psychological well-being at t3 will be the outcome variable. Group will be chosen as independent variable, whereas the variables defined in the section “Potentials mediators” will constitute the respective mediating variables. No interim analyses will be applied to the data.

Discussion

To the best of our knowledge, this study will be the first to investigate an intervention with the paradigm of expressive writing combined with mindfulness-based exercises provided via a software agent. It is a two-parallel arm controlled trial with the aim of evaluating SISU, a software agent as an innovative form of providing a scalable mental health interventions [44] to uplift peoples´ well-being.

The proposed study can be characterized by several strengths. First, our software agent SISU was successfully tested within a feasibility trial of Bendig and colleagues in preparation,[64] and provides elements of established approaches [69,88]. Therefore, we consider SISU to provide an eligible intervention and the potential to uplift psychological well-being in participants. To our knowledge, there are no known risks or negative effects for internet-based intervention in the context of self-help interventions to uplift psychological well-being. Still, we will systematically record via questionnaire (INEP) if and which negative effects of our IMI might appear. This will contribute to the still understudied area of research on risks and side effect [91] and therefore help make future IMIs safer.

Second, besides the relevance and necessity of our intervention, the methodical quality of our study is another strength. This is especially relevant in the relatively young field of research on therapeutic software agents, where highly qualitative studies are still sparse. First, we will use a randomised controlled design and we will apply ITT-analysis to avoid a possibly overestimated effect of the intervention. Second, the writing intervention is highly standardised due to the completely automated instructions and feedback given by SISU. Third, we will collect data on many variables and time points to enable moderator- and mediator-analysis on an explanatory level. The knowledge of how and for whom interventions work best is an important prerequisite improving their content and target groups [92].

Another strength concerns our recruitment strategy. We will be able to reach students from many different universities in Germany, Austria and Switzerland. The StudiCare website offers [68]recruitment possibilities at more than 15 cooperating colleges by sending out circular emails to all their students on a regular basis, informing them about all of their StudiCare online trainings (usually in the context of their student counselling or health management). Furthermore, recruitment takes place on various social media platforms to ensure the enrollment of a wide-ranged population of participants.

Usually, moderate to high dropout rates are a problem within online interventions, which needs to be addressed in the planning of a study [93]. In our feasibility trial 39% of the participants dropped out during study progress (assessment dropout), which could be (partly) explained by organisational effort providing informed consent and unfulfilled expectations concerning the intervention or the interaction with SISU. Nonetheless, the dropout rate of 14% during the

intervention with SISU (intervention dropout) is comparably low, which could be traced back to the responsiveness/guidance by SISU. Those have been shown to improve intervention adherence [94]. For the present trial we maintained these successfully tested techniques.

Another possible limitation is the use a waitlist control group. This can be associated with overestimation of effects compared to psychological placebo or no intervention [95]. If *SISU* shows its effectiveness compared to a waitlist control group, a next step should be to compare it with an active control group like e. g. participants receiving a pamphlet with instructions for doing mindfulness exercises at home.

Furthermore, only participants with internet-access and email-address can be included in the intervention. Whereas this is probably not relevant for younger people, it might still be a potential reason for selection and limited generalizability, especially with regard to elder generations.

Conclusion

Internet-based interventions aimed at the improvement of mental well-being have the potential to improve the general mental health care situation substantially. The proposed brief writing intervention that SISU enriches with mindfulness-based exercises and provides through a software agent could be a widely practicable, low-threshold self-help way to support users in increasing their psychological well-being with relatively little effort, when- and wherever they are in need.

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Author contributions

EB had the idea of SISU. SISU was developed by the Department of Clinical Psychology and Psychotherapy and the Institute of Distributed Systems at Ulm University (lead developer DM, BE and EB). EB and HB designed and planned the study. EB and HB supervised the study. EB and LW operatively perform the study. EB drafted the manuscript, all other authors critically revised the work for important intellectual content. All authors approved the final version to be published and agree to be accountable for all aspects of the work.

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Declaration of interest

HB reports to have received consultancy fees and fees for lectures/workshops from chambers of psychotherapists and training institutes for psychotherapists in the e-mental-health context. AK has received fees for lectures/workshops from chambers of psychotherapists and health insurance companies. DDE reports to have received consultancy fees/served in the scientific advisory board from several companies such as Minddistrict, Lantern, Schoen Kliniken and German health insurance companies. He is stakeholder of the Institute for health training online (GET.ON), which aims to implement scientific findings related to digital health interventions into routine care.

All other authors declare not to have competing interests.

Access to data and availability

All principal investigators will be given full access to the data sets. Data set will be stored on password-protected servers of university Ulm with restricted access. External researches may get access to the final trial dataset on request depending on to be specified data security and data exchange regulation agreements. To ensure confidentiality, data dispersed to any investigator or researcher will be blinded of any identifying participant information.

Patient and public involvement

Patient and public involvement (PPI) representatives provide input to the present study in several stages. Results of the feasibility trial on SISU (DRKS-ID: DRKS00014933) were used to further develop and optimise study design and procedures. PPI representatives were included in the intervention development to improve content, usability and design of SISU. However, acceptance of SISU from the participants' perspective is a crucial outcome of the study and both quantitative and qualitative methods are applied to capture acceptance and side-effects. The dissemination plan of the study results includes presentations on international conferences and publications in peer-reviewed journals.

Abbreviations

ACT	Acceptance and commitment therapy
AQoL-8D	Inventory for the Assessment of Quality of Life
BFI-10	Short version of the Big Five Inventory
CES	Centrality of Event Scale
CEQ	Credibility/Expectancy Questionnaire
DRKS	Deutsches Register Klinischer Studien
ERQ	Emotion Regulation Questionnaire
FAH-II	Acceptance and Action Questionnaire-II
FS-D	Flourishing Scale
IMI	Internet-based intervention
IG	Intervention group
INEP	Inventory for the assessment of negative effects of psychotherapy
RCT	Randomised controlled trial
TAI-SF	Inventory of Technology Alliance – Online Therapy
TAS-20	Toronto Alexithymia Scale
WHO-5	Well-being-Scale
WL	Waiting List Control Group
ZUF-8	Client Satisfaction Questionnaire

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Figures

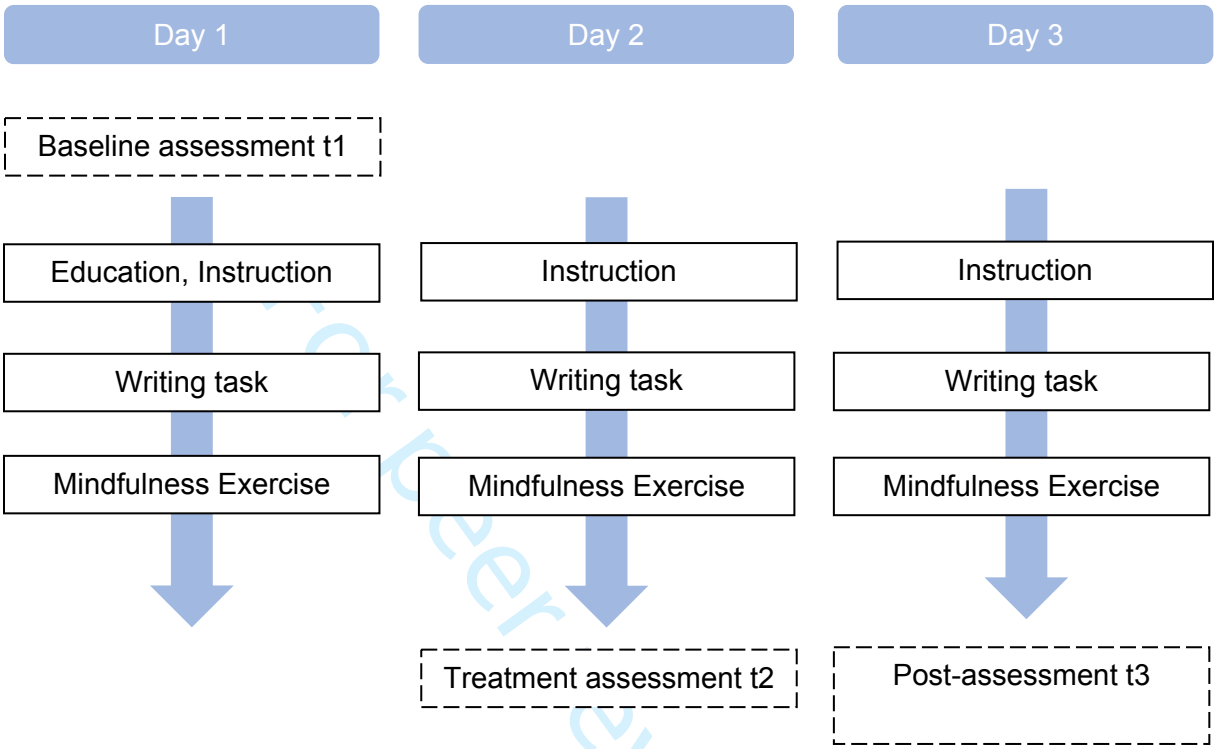

Figure 1. Content and chronological structure of the study

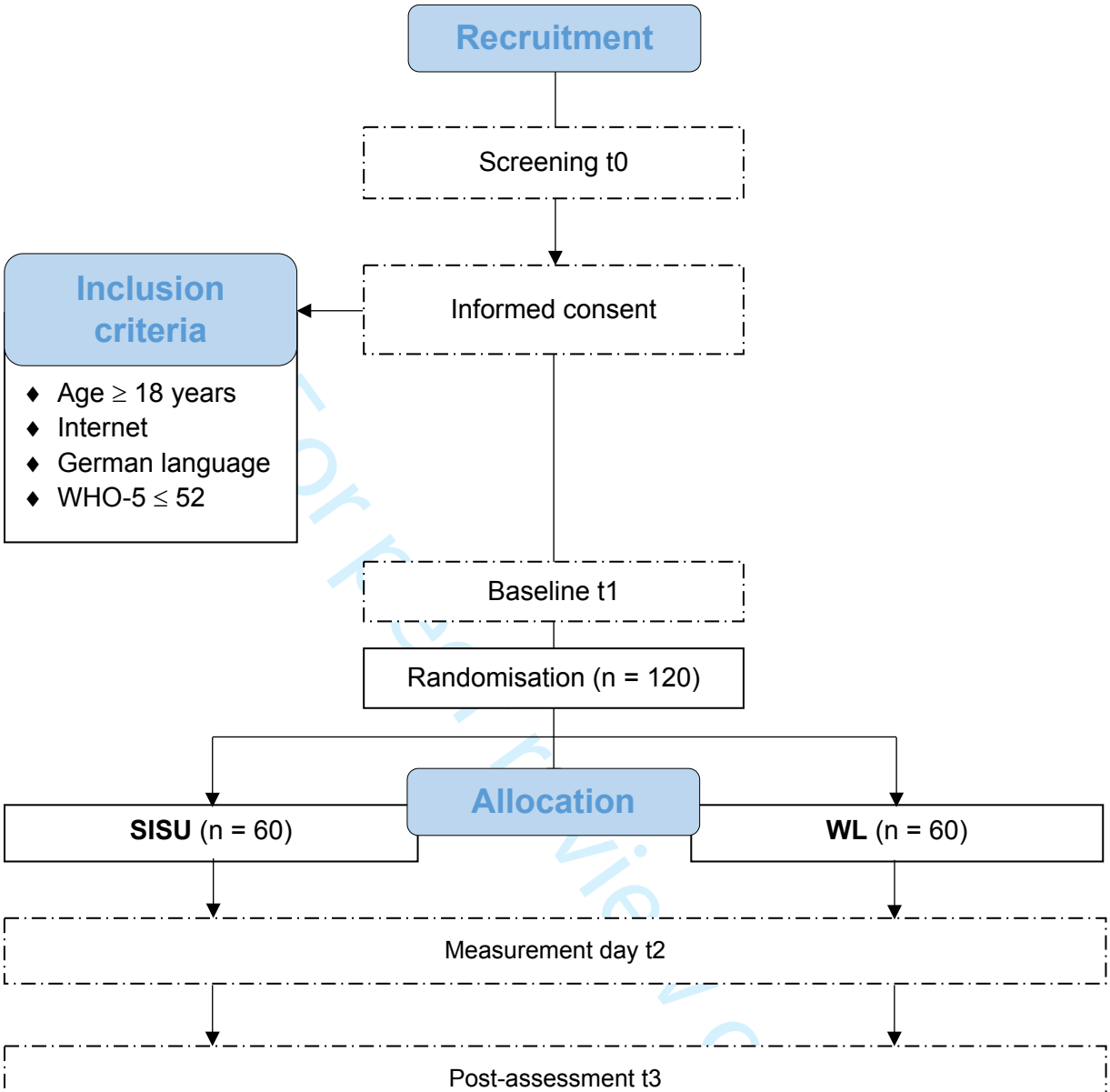

Figure 2. Flowchart of the planned study procedure.

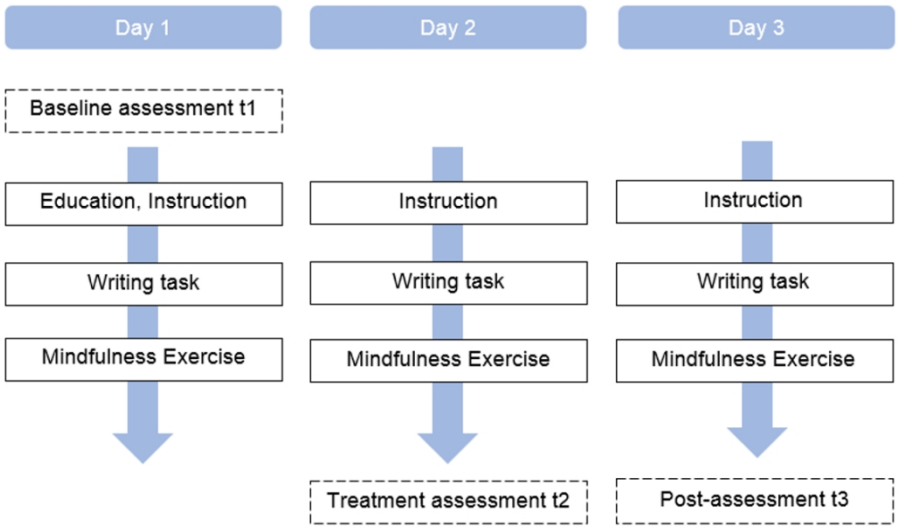

Figure 1. Content and chronological structure of the study

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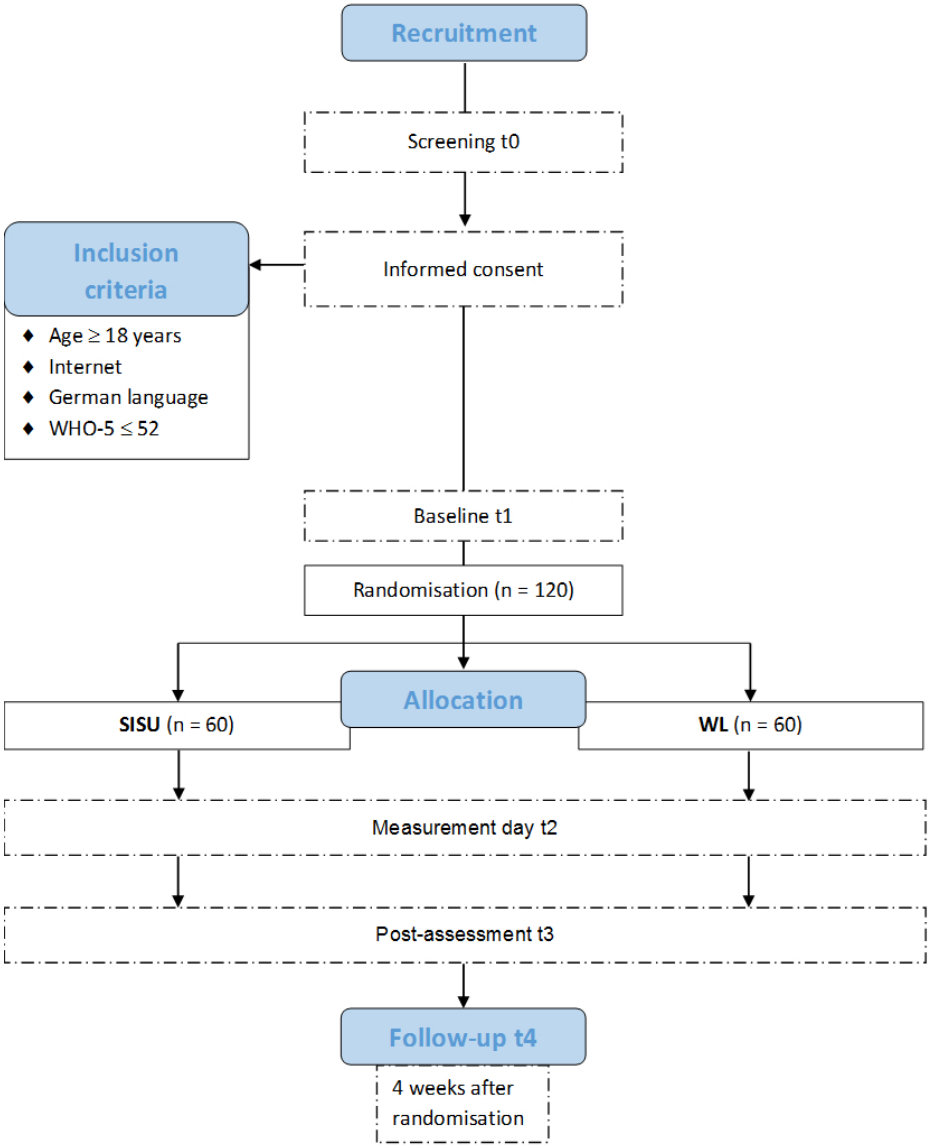

Figure 2. Flowchart of the planned study procedure.

175x226mm (120 x 120 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

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Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	0
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	16
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	0,16

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	n/a
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	16
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2-4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	8
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6f

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	6f
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5f, fig.2
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6

Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	6,7
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a

Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	14
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	5,13
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	1
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5, 15
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13,17
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13,17

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	13,17
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

Study Protocol of a randomised controlled trial on SISU, a software agent providing a brief intervention for self-help to uplift psychological well-being

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Study Protocol of a randomised controlled trial on SISU, a software agent providing a brief intervention for self-help to uplift psychological well-being.

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ABSTRACT

Introduction: Only a minority of people living with mental health problems are getting professional help. As digitalisation moves on, the possibility of providing internet- and mobile-based interventions (IMIs) arises. One type of IMIs are fully automated conversational software agents (chatbots). Software agents are computer programs that can hold conversations with a human by mimicking a human conversational style. Software agents could deliver low-threshold and cost-effective interventions aiming at promoting psychological well-being in a large number of individuals. The aim of this trial is to evaluate the clinical effectiveness and acceptance of the brief software agent-based IMI SISU in comparison to a waitlist control group (WL). **Methods and Analysis:** Within a two-group randomised controlled trail, a total of 120 adult participants living with low well-being (WHO-5) will be recruited in Germany, Austria and Switzerland. SISU is based on therapeutic writing and acceptance and commitment therapy-based principles. The brief intervention consists of three modules. Participants work through the intervention on three consecutive days. Assessment takes place before (t1), during (t2) and after (t3) the interaction with SISU, as well as 4 weeks after randomisation (t4). Primary outcome is psychological well-being (WHO-5). Secondary outcomes are emotional well-being (FS-D), psychological flexibility (FAH-II), quality of life (AQoL-8D), satisfaction with the intervention (ZUF-8) and side effects (INEP). Examined mediators and moderators are sociodemographic variables, personality (BFI-10), emotion regulation (ERQ), alexithymia (TAS-20), centrality of events (CES), treatment expectancies (CEQ) and technology alliance (TAI-SF). Data analysis will be based on intention-to-treat principles. SISU guides participants through a three-day intervention. **Ethics and Dissemination:** This trial has been approved by the ethics committee of the Ulm University (No. 448/18, 18.02.2019). Results will be submitted for publication in a peer-reviewed journal and presented at conferences.

Strengths and limitations of this study:

- ➔ To our knowledge, this is the first full-scale RCT on a chatbot delivering a brief psychological intervention to uplift psychological well-being.
- ➔ Results on user acceptance will help to gain further insights for requirements due to the fully automated presentation form of psychological internet interventions.
- ➔ Technology alliance and side effects will be monitored.
- ➔ Dropout rate is to be kept small by automated guidance and prompts.

Trial registration: The trial is registered at the WHO International Clinical Trials Registry Platform via the German Clinical Studies Trial Register (DRKS): DRKS00016799 (date of registration: 25.04.2019). In case of important protocol modifications, trial registration will be updated. This is protocol version number 1.

Keywords: Chatbot, software agent, psychological well-being, internet and mobile-based interventions, writing, positive psychology intervention, digital, conversational agent

INTRODUCTION

The global direct and indirect economic costs of mental disorders are estimated at 2.5 trillion US $ [1]. Thus, untreated mental disorders are a public health concern worldwide. However, the majority of individuals living with mental disorders do not receive any health care supply [2–4]. In Europe, only about 25% of people with mental disorders receive professional treatment [5].

On the one hand, there are societal barriers to receiving adequate mental health care offers. On the other hand, there are barriers on the side of individuals, keeping them from seeking professional help [6]. The latter aspect comprises fear of stigmatization [7,8], restrictions of time and location [9,10], negative attitudes towards pharmacological and psychotherapeutic treatments [11], negative experiences with professionals [12,13] or missing conscientiousness for diseases [14]. In order to overcome some of these barriers and to improve mental health care at a large scale, digital means are frequently discussed options.

Digitalization sets societal changes in motion in various fields [15]. Other than in the areas of work, economy, and science, new technologies slowly emerge in the field of mental health care. Internet-based and mobile-based Interventions (IMIs) can provide low-threshold, flexible interventions that are resource-, time- and location-independent [9,10] and can be as effective as traditional face-to-face psychotherapy [16]. As such, they might help to reduce societal and individual barriers to mental health care and expand supply offers [9,16,17]. At this point, their effectiveness and cost-effectiveness could be established for the prevention [18] and treatment of mental disorders [9,19–24] and chronic somatic diseases [25] as well for positive mental health promotion purposes [26–29].

IMIs are highly standardised computer programs. They are often manualised, which means that they are incorporating instructions, theory-based key elements and concepts as well as how-to approaches regarding the evidence-based implementation of a certain delimited psychological program. which can be seen as digitised therapeutic interventions [9,30]. While they have without doubt substantial merits, some limitations still restrict their scalability and widespread roll-out. As yet, for example, IMIs seem to work best if they provide any form of human guidance alongside the digital program [21,31]. However, fully unguided interventions could be a more cost-effective way of providing digital interventions (e.g.,[32]). Thereby, professional guidance does not only limit the cost-effectiveness, but also necessitates health care infrastructures that might not always be at place at a large (enough) scale. In addition to the possibility of an increased cost-effectiveness unguided fully automated interventions like mHealth interventions have shown potential to effectively targeting mental health symptoms [33].

Evidence shows that the effectiveness of IMIs might be in part attributable to other effect factors than in face-to-face therapy [34]. In comparison to face-to face therapy, the therapeutic alliance might not be as relevant as effect factor [35]. Instead, other factors, e. g. an agreement on tasks and goals [35] or the fostering of self-efficacy [36], have been discussed. Software agents could combine the best of both worlds, as they seem to have the potential to human-machine alliance [37]. Delivering IMIs by software agents could compensate for some of the disadvantages of conventional computer program-based IMIs (e.g., [31]) Amongst others, they could show human-like, immediate responses with regards to user input [38].

A software agent or "chatbot" is a computer program that can hold a fully automated text-based conversation in real-time with people via a chat-interface (e.g., smartphone application) by using a natural language style [38]. The growing interest and body of research about software agents [39,40] is realised in various populations and contexts, such as problem solving and stress [41–43]. In the context of clinical psychology and psychotherapy, research on software agents is sparse [44] but could create opportunities for the field regarding the provision of mental health services. Software agents could be used to convey therapeutic contents and brief interventions [45,46]. Establishing contact to a software agent might not be as stigmatising as using formal mental health services like starting a face-to-face therapy or asking a general practitioner for possibilities of mental health care [47]. Furthermore, they are flexible regarding location and time [48], can be used anonymously [49,50] and provide personalization through implicit customization [51]. Therefore, software agents could help to overcome barriers and provide psychological and health behaviour change interventions on a large scale in the future.

Current mental health software agents are primarily based on cognitive behavioural therapy [44]. However, other popular approaches with proven effectiveness in face-to-face settings could also readily be realized in a digital form, such as writing interventions [52] and acceptance and commitment-based approaches [53].

Writing with the aim of improving health has a long history [54]. In the current literature, the labelling of this kind of intervention varies: Terminology includes expressive writing [55,56], benefit-finding or positive writing [57,58] and therapeutic writing (e.g., [59]). Regardless of terminology, the writing intervention to be investigated in this study will refer to the process of freely and emotionally writing about a positive personal life event without paying attention to spelling or grammar. The call to write about personal life events, to tell a story, seems to go straight at the centre of subjective experiences [60], which in turn is the main medium in traditional face-to-face therapy. In that, the term therapeutic writing will be used in this context to acknowledge that the intervention refers to some kind of therapeutic work [61]. It has been shown that writing interventions can be highly time- and cost-efficient [62]. A recent meta-analysis shows that writing interventions can help to improve general psychological health

(SMD=-0.46, 95% CI -.86, -0.06) [63]. Finally, a meta-analysis from Bolier and colleagues [64] found an effect of Cohen's *d* = 0.34 (95% CI 0.22, 0.45) for positive interventions to uplift cognitive and/or affective appraisal of one´s life as a whole and d=0.20 (95% CI 0.09, 0.30) optimal functioning including mastery, hope and purpose in life.

Acceptance and Commitment Therapy (ACT) [65] aims at acceptance, mindfulness and value-based living and has been found to be effective in the prevention of stress and the increase of well-being [27,66]. The efficacy of ACT-based interventions in general and ACT-based IMIs in particular has been indicated in a number of studies and systematic reviews. Within a randomised-controlled trial, Fledderus and colleagues (2012) investigated an ACT-based IMI for people living with depression. The authors found significant reductions in depression, anxiety, fatigue, experiential avoidance and improvements in positive mental health, compared to a waitlist control condition (effect sizes Cohen´s *d* = 0.51 to 1.00) [29]. In their meta-analysis, Brown and colleagues[67] examined 10 randomised controlled trials investigating the effectiveness of ACT in the treatment of depressive or anxiety symptoms and well-being in adult populations. ACT interventions were compared to passive control groups (N=3), active control groups (N=4) or both (N=3). The authors found small effect sizes regarding the improvement of depression (*g* = 0.24, 95% CI: 0.04 - 0.45) whilst the heterogeneity of conditions and outcome measures on anxiety and well-being was too high to draw firm conclusions. Spijkerman and colleagues [28] examined 15 randomised controlled trials in adults with various mental problems and healthy populations. Mindfulness interventions, of which the authors include ACT, were compared to passive control groups (N=10), active control groups (N=5) or both (N=2). The authors found small to medium effect sizes concerning the improvement of depression (*g* = 0.29, 95% CI: 0.13 - 0.46), anxiety (*g* = 0.22, 95% CI: 0.05 - 0.39) and well-being (*g* = 0.23, 95% CI: 0.09 - 0.38) [28].

We developed a software agent gender neutrally called SISU (**S**oftware agent providing an **I**ntervention for **S**elf-help to **U**plift psychological well-being and finnish word [ˈsisu] for inner strength) with the aim to provide an easily deployable software agent that improve peoples´ well-being. Therefore, SISU combines therapeutic writing and acceptance- and commitment-based principles. Results of a feasibility trial on SISU [68] showed that SISU is feasible in terms of user acceptance and the potential of the software agent to deliver a brief writing intervention. Thus SISU is feasible to be implemented within a confirmatory clinical trial. Hence, the present study is designed to investigate the clinical effectiveness and acceptance of the Software agent SISU thereby focusing on the following specific research aims:

1. To estimate the effects of SISU on psychological well-being compared to the WL at T3 (primary outcome).

2. To estimate the effects of SISU regarding the secondary outcomes flourishing, quality of life, and psychological flexibility compared to the WL at T3.

3. Which factors are associated with, moderate or mediate the effects of SISU?

4. Is the intervention associated with measured side effects?

5. What is the level of acceptance (satisfaction, adherence) with the intervention?

METHODS

Study Design

This is a two- arm, parallel randomised controlled trial (RCT) with the intervention group SISU (IG) and a waiting list control group (WL). The IG receives the online-based intervention guided by the SISU software agent. The WL receives the intervention 4 weeks later. Primary and secondary outcomes will be assessed over a period of four weeks. Assessments will take place at screening (t0), baseline at day 1 (t1), intermediately at day 2 (t2), post-treatment at day 3 (t3) as well as four weeks follow-up (t4).

The present study is conducted and will be reported in accordance with the CONSORT 2010 guidelines for RCTs [69] and the guidelines for executing and reporting IMI research [70]. The study protocol follows recommendations of the SPIRIT 2013 Checklist for clinical trial protocols [71].

Recruitment

Recruitment has started in May 2019 and will be continued until the targeted sample size of N=120 has been reached. We recruit in German speaking countries, Germany, Austria and Switzerland. Recruitment strategies comprise a dynamic, broad on- and offline recruitment strategy. Offline recruitment will be conducted via posters and flyers at different universities, psychosocial counselling services, city libraries and other publicly accessible sites. Online recruitment strategies will comprise postings in online self-help groups on social media (e.g. facebook), displays on ebay and xing as well as the Studicare®-website. StudiCare is a project that offers a broad assortment of internet-based interventions for psychological and behavioural issues [72]. Interested persons will get access to the screening (t0) at unipark.de via QR-code, link or via email on request. Directly after the screening eligible participants will automatically receive informed consent for signing via email. Apart from the recruitment, the study will be fully conducted online.

Eligibility criteria

Participants will be eligible for inclusion in the present trial if they are (a) 18 years or older, (b) willing to take part in this study, (c) have internet access and an email address, (d) have a low psychological well-being (WHO-5 $\leq$ 52) and (e) possess sufficient German language skills.

Study Procedures

If eligibility criteria are fulfilled, applicants will receive an online information letter including detailed information about study procedure and informed consent. They will be informed that they can withdraw from the intervention and/or study at any time without any negative consequences. After signing the informed consent, participants will be randomised to the IG

or WL condition. Following, they will receive their individual ID and get an invitation for the baseline questionnaire (t1) at unipark.de via email. Afterwards, participants will learn about their group membership. The IG will get in contact with SISU and the intervention using the end-to-end encrypted online messaging app “Wire” after finishing baseline (t1). SISU guides participants through a writing intervention on three consecutive days using a standardised conversation script. Each writing intervention is automatically followed by an assessment. Participants who are part of the WL will receive access to SISU four weeks after randomisation. If participants complete questionnaires for t3 and t4 they will each time get the chance to win a 10€ gift card for Amazon as a monetary incentive to promote retention and follow-up completion. All participants with a low WHO-5 score (< 28) in the screening receive an automatised email with further information about offers of the health care system.

Randomisation and blinding

Participants will be randomised to either IG or WL. An academic assistant (JM) from the Department of Clinical Psychology and Psychotherapy at the University Ulm, not otherwise involved in the trial and blinded towards all further procedures, will perform the allocation. A permuted block randomisation with 4, 6, 8 and 12-block-size and an allocation ratio of 1:1 will be used. The randomisation list will be created by a well-accepted website (https://www.sealedenvelope.com). Whereas blinding of participants is not possible, data collectors and data analysts are blinded regarding group membership.

Intervention

The software agent (SISU) provides a brief three-day intervention. The writing instruction provided by SISU is based on the paradigm of therapeutic writing as well as acceptance and commitment therapy [ACT; 73]. The version of SISU used for this study was improved through participant feedback collected in the feasibility trial [68]. Revisions included the enrichment of the instruction for writing about positive life events with elements of ACT (more mindfulness exercises, authenticity of the dialog through reduction of repetitions, interactions on reported life events) and elements for the reconstruction of narrative identity.

SISU mimicks a human conversational style. Participants are guided to write each day at the same time for 10-20 minutes about a self-chosen autobiographical, positive life event. On day 1 there is psychoeducation in the beginning. Then, instructions for the writing tasks are followed by the narratives of the participants. Participants are instructed to write about a meaningful, outstanding positive life event on day 1 and about an outstanding positive event from adulthood on day 2. On day 3 participants are guided to write about their best possible future. After the writing task, SISU encourages participants to experience the positive emotions due to the reported event in the present moment. Mindfulness exercises are provided by an audio file right after the writing intervention, whilst ACT-metaphors are integrated into the

conversational content. Participants are encouraged to practice on a daily basis. To increase adherence, SISU reminds participants at 24 hour intervals. More details on intervention contents can be derived from Table 1. For an illustration of content and chronological structure see Figure 1.

Using the online messaging Wire Services SDK enables programmatic end-to-end encrypted communication. Thanks to this encryption, messages sent by SISU or participants are not accessible by third parties, including the service provider. We further protect participation data by hosting SISU on premises and by encrypting the data at rest, thus limiting the access to our research group. The communication logic is implemented as a finite-state machine. Our SISU implementation parses incoming messages based on a fixed set of rules and responds with an appropriate answer. In addition, SISU can react to external triggers. That is, external triggers can lead to a status change of SISU. For example, the termination of a survey at Unipark can cause a status change of SISU from "user is active" to "user finished the interaction for the day". External triggers can be (a) conversation timeouts (i.e., the participant has not responded in a set time frame), (b) Unipark events (i.e., participant has completed an external survey), and (c) scheduled events (e.g., daily participation reminder at pre-defined time frames).

Table 1

Content and techniques of the writing tasks as delivered by SISU

Module title	Module Content	Focused ACT technique
1 Introduction	Therapeutic writing, ACT	Psychoeducation
2 Writing tasks	Instructions for writing about a positive autobiographical life events	
3 Thoughts and feelings	Important things in life	Values
4 Mindfulness exercise	Being aware of what is happening in the present moment without judging it	Contact with the present moment; Acceptance

Note. ACT = Acceptance and Commitment Therapy

--please insert figure 1 around here--

The (ultra-)brief intervention rational of 3 days was chosen because we wanted to provide participants with a brief possibility to do something for their mental well-being, despite their busy everyday lives. Indeed, evidence suggests that brief writing interventions of e. g. only 1

week can increase emotional well-being even 6 months after the intervention [74], particularly in case of interventions focusing on improving mental health rather than treating mental disorders.

Wait list control group

Participants of the WL get access to the writing intervention provided by SISU four weeks after randomisation. The intervention has the same content for both groups.

Administrative and technical support

In case participants forget their individual ID or have other technical issues, they can make use of the study team via email for technical support at every point during the training.

Outcome Assessment

Screening for eligibility takes place at t0. Data for relevant outcomes will be collected prior to the intervention on day 1 (t1), on day 2 (t2), and day 3 (t3; intervention completed) and four weeks after randomisation (t4; follow-up). Demographic data and personality traits are measured once (t1). A flow chart of the study can be seen in Figure 2. The outcomes, their measurement instrument and points of assessment are shown in Table 2.

--please insert figure 2 around here--

Table 2

Constructs, measurement instruments and points of assessment

Construct	Measurement instrument	Points of assessment				
		T0	T1	T2	T3	T4
Demographical Questionnaire		✓	✓			
Primary endpoint						
Psychological well-being	Well-being Scale (WHO-5)	✓	✓	✓	✓	✓
Secondary endpoints						
Emotional well-being	Flourishing Scale (FS-D)	-	✓	✓	✓	✓
Psychological flexibility	Acceptance and Action Questionnaire-II (FAH-II)	-	✓	✓	✓	✓
Quality of life	Assessment of Quality of Life (AQol 8D)	-	✓	-	✓	✓
Satisfaction with the intervention	Client Satisfaction Questionnaire (ZUF-8)	-	-	-	✓[a]	-
Side effects	Inventory for the assessment of negative effects of psychotherapy (INEP)	-	-	-	✓[a]	✓[b]
Manipulation-Check writing	Post Writing Questionnaire	-	-	✓[a,c]	✓[a]	-
Questions on content	Open questions for the interaction with SISU	-	-	-	✓[a]	-
Willingness to use software agents in the future	Open questions	-	-	-	✓[a]	-
Moderators/Mediators						
Centrality of events	Centrality of Events Scale (CES)	-	-	✓[a,c]	✓[a]	-
Personality	Big Five Inventory (BFI-10)	-	✓	-	-	-
Treatment expectancy	Credibility Expectancy Questionnaire (CEQ)	-	✓	-	-	-
Alexithymia	Toronto Alexithymia Scale (TAS-20)	-	✓	✓	✓	✓
Emotion regulation	Emotion Regulation Questionnaire (ERQ)	-	✓	✓	✓	✓
Technology alliance	Inventory of Technology Alliance – Online Therapy (TAI-SF)	-	-	✓[a]	✓[a]	-

Note. t1 = baseline; t2 = during treatment (two days post-randomisation); t3 = post-treatment (3 days post-randomisation); t4 = follow-up (four weeks after randomisation). [a] Questionnaires only used by IG; [b] adapted version for WL; [c] additionally assessed retrospective for the first contact with SISU at t2

Screening, t0

The short 5-item Well-being-Scale (WHO-5) is administered to assess the subjective psychological well-being of participants in the last two weeks [75]. Participants can answer on a 6-point-Likert scale (5= “All of the time”, 4 = “Most of the time”, 3 = “More than half the time”, 2 = “Less than half the time”, 1 = “Some of the time”, 0 = “At no time”). The sum of raw scores (range: 0-25) is multiplied with 4 and produces a total score (range: 0-100) with 0 representing the worst imaginable well-being to 100 representing the best imaginable well-being [75]. Scores ≤ 52 indicate a low, scores ≤ 28 indicate a very low psychological well-being. Topp and colleagues[75] mention a comparable cut-off score of ≤ 50. The WHO-5 shows a sensitivity of 0.93 and a specificity of 0.83 in the detection of depression [75]. Additionally, the screening includes age, sex, contact information and the sufficient knowledge of German language.

Demographic data

The following information will be collected from each participant at T1: sex, age, education, nationality, German speaking skills, relationship status, profession and highest educational attainment.

Primary outcome

Psychological well-being

Primary outcome is psychological well-being at t3 measured by the Well-being-Scale [75] already described in the section for screening.

Secondary outcomes and covariates

Emotional well-being.

The German version of the Flourishing Scale [FS-D; 76] is a measure of psychosocial well-being and personal growth and development (i.e., flourishing). Each of the 8 items is rated on a 7-point-Likert scale ranging from 1 = “strongly disagree” to 7 = “strongly agree”. A sum score is computed with higher scores indicating higher flourishing. With a Cronbach’s α of 0.87 the scale shows good internal consistency [76].

Psychological flexibility

The German version of the Acceptance and Action Questionnaire-II [77] is a general measure for psychological inflexibility and consists of 7 items. On a 7-point-Likert scale that ranges from 0 = “never true” to 6 = “always true”, the questionnaire assesses a person’s willingness to experience unwanted thoughts and feeling and a person’s ability to act despite the presence of undesirable thoughts and feelings. In this study items were reverse coded to assess psychological flexibility. Sum scores (range: 0-42) are computed with higher scores indicating

higher psychological flexibility. The questionnaire shows good to excellent psychometric properties in a German sample [77].

Quality of life

With the help of the inventory Assessment of Quality of Life (AQoL-8D) participants quality of life is recorded [78]. Each of 35 items loads on one of eight dimensions of quality of life and is rated on 4- to 6-point-Likert scales. For analysis there is an algorithm which can be used for quality of life in general as well as for particular sub dimensions. In total, scores between 0 and 1 are possible. Standard values are available. Reliability of AQoL-8D is very good with Cronbach's α of 0.96 [78].

Side-effects

Subjective adverse events of the intervention are recorded with the 15-item inventory for the assessment of negative effects of psychotherapy [79]. Items are rated on a 4-point-Likert scale (0 = "no agreement" to 3 = "total agreement") or a bipolar 7-point scale. Adverse effects in social life, intrapersonal factors or work-related situations are taken in consideration. The original inventory with 32 items has an internal consistency of α = 0.95 [80].

Satisfaction with the intervention

To assess the global satisfaction with the intervention a revised version of the German version of the Client Satisfaction Questionnaire [ZUF-8; 81] was used. Participants rate their satisfaction on a 4-point-Likert scale for each of the 8 items. A sum score is computed. Higher scores indicate higher satisfaction. Internal consistency of the ZUF-8 is very good with α = 0.90 [82]. A study on reliability and validity of assessing user satisfaction with internet-based interventions indicates good overall psychometric quality of the measure [83].

Post-Writing Questionnaire

To assess therapeuticwriting after every writing session the participants answer four questions about their feelings and thoughts during and after the writing experience. Answers are rated on a 5-point-Likert scale (1 = "not at all", 3 = "few", 5 = "very much/extremely"). The questionnaire was adapted from the English version of Pennebaker and Beall [56].

Open questions

For the final survey (t3) four open questions inspired by the open questions from Fitzpatrick, Darcy and Vierhile [84] about the interaction with SISU are provided. The answers are individually evaluated and thematically summarised.

Questions for the future of software agents

The final survey (t3) will assess the behavioural intention to use a software agent in the future or recommend one to friends as well as the future performance expectancy of software

agents providing psychological interventions to uplift psychological well-being in three open questions. Participant responses will be analysed on a qualitative basis.

Moderators/Mediators

Centrality of events

The Centrality of Event Scale [CES; 85] assesses the centrality of an event to a person, differentiating three independent characteristics. Whether the event is seen as (1) a reference point for everyday inferences, (2) a turning point in the life story and (3) as an element of the personal identity. Participants rate the 7 items of the short version on a 5-point-Likert scale from 1 = “totally disagree” to 5 = “totally agree”. With a Cronbach’s α of 0.88 the scale shows high internal consistency [85].

Personality

To assess the Big Five personality traits of participants the short version of the Big Five Inventory [BFI-10; 86] is used. Each of the five personality dimensions is measured with two items depicting either the positive or the negative pole of the spectrum. Participants rate the items on a 5-point-Likert scale from 1 = “fully disagree” to 5 = “fully agree”. The questionnaire shows average retest-reliabilities ranging from 0.56 to 0.60 [86].

Alexithymia

The German version of the Toronto Alexithymia Scale [TAS-20; 87] assesses alexithymia of participants. Each of the 20 items is rated on a 5-point-Likert scale ranging from 1 = “strongly disagree” to 5 = “strongly agree”. The German version assesses 3 factors [88]: “difficulties in identifying and describing feelings“, “external oriented thinking“ and “importance of emotional introspection“. For each dimension sum scores are computed with higher scores each indicating higher manifestations of alexithymia. Internal consistency of the scale is good with a α = 0.80 [88].

Emotion regulation

The Emotion Regulation Questionnaire [ERQ; 89] is a 10-item questionnaire measuring positive and negative feelings as well as their regulation. Items refer to two different emotion regulation strategies: Reappraisal and suppression. Participants rate the items on a scale from 1 = “strongly disagree” to 7 = “strongly agree”. Means show the preference for each strategy indicating higher preference at higher mean scores. Internal consistencies are acceptable to good and differ from α = 0.75 to α = 0.82 [89].

Treatment expectancy

Treatment expectancy is measured with the Credibility/Expectancy Questionnaire [CEQ; 90] with 6 items. Participants rate four items on a 9- and two items on a 10-point-Likert scale with varying descriptions. The scale can be separated in the two factors credibility and expectancy.

Cronbach's α for credibility differs from 0.79 to 0.90, for expectancy from 0.81 to 0.86 and for the total scale from 0.84 to 0.85 indicating acceptable to high internal consistency [90].

Technology alliance

The Inventory of Technology Alliance – Online Therapy (TAI-SF) was used to evaluate the technological alliance between the participants and the online intervention, thus the software agent. The TAI-SF is a 12-items questionnaire developed by Labpsitec (http://www.labpsitec.uji.es/eng/index.php) that assesses the degree to which the participant perceives the online intervention as helpful. Items are rated on a 7-point-Likert scale from 1 = "never" to 7 = "always".

Data privacy and ethics

Data will be pseudonymised and analysed in the Department of Clinical Psychology and Psychotherapy of the Ulm University via individual ID and an internal participant ID for every participant to encode the individual datasets. Messages exchanged between participants and SISU are encrypted in-transit by the end-to-end encryption of the "Wire" application. Thus, only the study team will have access to the collected data. Participants will have the opportunity to have all of their collected data deleted. External researchers may get access to the final trial dataset (from HB) on request depending on to be specified data security and data exchange regulation agreements. To ensure confidentiality, data dispersed to any investigator or researcher will be blinded of any identifying participant information. Anonymised results will be published in peer-reviewed journals and presented on international conferences.

The participation in this study should not be associated with any specific risks. However, temporary changes in mood could arise directly after the writing task [91]. Furthermore, therapeutic writing can lead to emotional-cognitive (change) processes [61] with which the participants could have difficulties in dealing with. Therefore, participants will have the opportunity to contact the study team at every point during the trial. Additionally to the interventions, participants with a very low WHO-5 score (< 28) in the screening will be sent an automatised email with further information about offers of the health care system.

Sample Size

A meta-analysis by Bolier and colleagues [64] found an effect size of d=0.34 for positive psychological interventions aiming at uplifting well-being. Riddle and colleagues [92] reported an effect size of d=0.46 for writing interventions to enhance well-being. However, for internet-based mindfulness interventions, Spijkerman and colleagues [28] found a somewhat smaller effect of g=0.23.

Based on these previous findings, a small effect size of d = 0.30 is expected. Power analysis for an ANOVA with repeated measures with g-power (http://gpower.hhu.de/) recommends a

sample size of at least 60 participants per group (N=120) on the assumption of two-tailed testing, an alpha error $\alpha = 0.05$ and power $1-\beta = 0.90$.

Statistical Analysis

Patterns of missing data will be investigated, and analyses will be adjusted accordingly (multiple imputation). Regarding the imputation method and predictor selection we will follow the recommendations of van Buuren and colleagues [93]. It will be assumed that missing values are missing at random. Analyses will be conducted on a two-sided level of significance (α=.05). Participant characteristics will be described descriptively.

All statistical analyses will be performed based on the intention-to-treat (ITT) principle. Additional per protocol analyses will be conducted in order to examine associations in case of patients adhering to the intervention protocol. Participants who completed at least 66% of the intervention are defined as intervention completer (=per protocol).

The primary outcome will be analysed using linear regression models at T3 as dependent variable and the baseline value as covariate, adjusting for sex and age. The necessity of multilevel models will be explored by interclass correlations. On substantial ICC (>.05) the use of multilevel models will be considered or other adjustments of standard errors will be used. To analyse between-group effect sizes, standardised mean differences with 95% confidence intervals will be calculated for post-treatment (t3) and follow-up (t4). Secondary outcomes will be analysed accordingly.

Exploratory mediation and moderator analyses involving the primary and secondary outcomes as well as demographic data will be conducted. Moderator and subgroup analyses are aimed for in case of a sufficiently large sample size.

For the planned exploratory moderator analyses, regression models will be employed. Initially, each potential moderator described under “Covariates” will be analysed in a separate regression model. The primary outcome psychological well-being at t3 will be the dependent variable. Predictors will comprise group, the moderator variable and the interaction of group and moderator. In a next step, a comprising model of all identified moderators will be tested.
Mediation analyses will be conducted according to the principles of time-lagged mediation [94]. Psychological well-being at t3 will be the outcome variable. Group will be chosen as independent variable, whereas the variables defined in the section “Potentials mediators” will constitute the respective mediating variables. No interim analyses will be applied to the data.

Patient and public involvement

Patient and public involvement (PPI) representatives provide input to the present study in several stages. Results of the feasibility trial on SISU (DRKS-ID: DRKS00014933) were used

to further develop and optimise study design and procedures. PPI representatives were included in the intervention development to improve content, usability and design of SISU. However, acceptance of SISU from the participants' perspective is a crucial outcome of the study and both quantitative and qualitative methods are applied to capture acceptance and side-effects. The dissemination plan of the study results includes presentations on international conferences and publications in peer-reviewed journals.

Discussion

To the best of our knowledge, this study will be the first to investigate an intervention on therapeutic writing combined with mindfulness-based exercises provided via a software agent. It is a two-parallel arm controlled trial with the aim of evaluating SISU, a software agent as an innovative form of providing a scalable mental health interventions [44] to uplift peoples´ well-being.

The proposed study can be characterized by several strengths. First, our software agent SISU was successfully tested within a feasibility trial of Bendig and colleagues in preparation [68] and provides elements of established approaches [73,91]. Therefore, we consider SISU to provide an eligible intervention and the potential to uplift psychological well-being in participants. To our knowledge, there are no known risks or negative effects for internet- and mobile-based interventions in the context of self-help interventions to uplift psychological well-being. Still, we will systematically record via questionnaire (INEP) if and which negative effects of SISU might appear. This will contribute to the still understudied area of research on risks and side effect [95] and therefore help make future Internet- and mobile-based interventions safer.

Second, besides the relevance and necessity of our intervention, the methodical quality of our study is another strength. This is especially relevant in the relatively young field of research on therapeutic software agents, where highly qualitative studies are still sparse. First, we will use a randomised controlled design and we will apply ITT-analysis to avoid a possibly overestimated effect of the intervention. Second, the writing intervention is highly standardised due to the completely automated instructions and feedback given by SISU. Third, we will collect data on many variables and time points to enable moderator- and mediator-analysis on an explanatory level. The knowledge of how and for whom interventions work best is an important prerequisite improving their content and target groups [96].

Third, although effectiveness with the same range of expected effect size (and at the same cost) can be expected from other fully automated unguided intervention formats (e.g., [97]), this is the very first study to evaluate a software agent-delivered intervention. As it can be assumed that not everybody or every population prefers the same kind of delivery-format, it is important to evaluate a broad variety of formats to enable adaptability. In this respect, the present study makes an important contribution.

Another strength concerns our recruitment strategy. We will be able to reach a wide-range of participants by broad online and offline recruitment in Germany, Austria and Switzerland. Recruitment strategies might help to gain knowledge on feasibility and effectiveness of SISU in a broad range of adult people living with low psychological well-being. However, people living with high psychological well-being which e.g. want to further invest in their mental health

will be excluded. Thus, it is not possible to say whether SISU is useful in people with already high psychological well-being. Furthermore, new technologies like chatbots could be especially attractive to the youth, which were excluded as a population. Thus it remains unclear if SISU could be useful in younger people living with low psychological well-being. Self-selection bias could lead to a population which has an internet affinity. Only participants with internet-access and email-address can be included in the intervention. Whereas this is probably not relevant for younger people, it might still be a potential reason for selection and limited generalizability, especially with regard to elder people. To rule out a potential gender bias due to a male or female software agent, SISU was conceptualised gender neutral so that members of all sexes feel equally addressed.

Usually, moderate to high dropout rates are a problem within online interventions, which needs to be addressed in the planning of a study [98]. In our feasibility trial 39% of the participants dropped out during study progress (assessment dropout), which could be (partly) explained by organisational effort providing informed consent and unfulfilled expectations concerning the intervention or the interaction with SISU. Nonetheless, the dropout rate of 14% during the intervention with SISU (intervention dropout) is comparably low, which could be traced back to the responsiveness/guidance by SISU. Those have been shown to improve intervention adherence [99]. For the present trial we maintained these successfully tested techniques.

Another possible limitation is the use a waitlist control group. This can be associated with overestimation of effects compared to psychological placebo or no intervention [100]. If SISU shows its effectiveness compared to a waitlist control group, a next step should be to compare it with an active control group like e. g. participants receiving a pamphlet with instructions for doing mindfulness exercises at home. Furthermore, a potential methodological confound concerns blinding. Participants are not blinded towards the primary outcome and could possibly answer in a socially desirable way. However, as participants are unlikely to know the study team personally, test manager effects might be low. Another methodological problem could arise from assessment reactivity. Frequent assessments can trigger self-reflection which can lead to an incremental effect regardless of the intervention [101]. However, this is a general problem which can be particularly noticeable in control groups and in groups which receive low-threshold intervention offers.

Last but not least, the planned analyses are based on classic inferential statistics to test the significance of group differences. A sample size calculation (g*power) was performed to plan the sample size accordingly. However, recent evidence emphasises, that it might be fruitful not to test for differences from zero. Instead, Bayesian methods could be used. They allow discovering uncertainties of the effects of treatments instead of solemnly focusing on dichotomising evidence into significant and not significant [102]. If this trial points towards the

usefulness / effectiveness of SISU, future trials could substantiate results using Bayesian methods.

Ethics and Dissemination: This trial has been approved by the ethics committee of the University of Ulm (No. 448/18, 18.02.2019) and registered in the German Clinical Trials Register (DRKS-ID: DRKS00014933) on 25 April 2019. Written informed consent for participation in the study will be obtained from all participants prior to their involvement. Participants will receive written information on study conditions, data security, publication of anonymised results, voluntariness of participation and the right to leave the study at all times. They will also be informed that in case of study withdrawal, they will be able to decide whether they want their data to be included in the analysis or to be deleted. Additionally, participants will be asked for permission for the research team to share relevant data with people from regulatory authorities, where necessary. This trial will only involve the collection and storage of self-report data, not of biological specimens. Data collection will be pseudonymised and data will only be accessed by authorized study personnel obliged to secrecy. After data collection is completed, personalised information will be deleted and all data will be completely anonymised. All participant information will be stored securely in locked file cabinets and/or password-protected in a secured cloud storage with restricted acess. All reports, data collection, and administrated forms will be identified by a coded ID number only to maintain participant confidentiality. All records that contain names or other personal identifiers, such as informed consent forms will be stored separately from study records identified by ID number. Listings that link participant ID numbers to other identifying information will be stored in separate password-protected files with limited access. According to German law, data will only be shared with parties outside the project team in anonymised form. Trial results will be submitted for publication in a peer-reviewed journal and presented at conferences.

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Author contributions

EB had the idea of SISU. SISU was developed by the Department of Clinical Psychology and Psychotherapy and the Institute of Distributed Systems at Ulm University (lead developer DM, BE and EB). EB and HB designed and planned the study. EB and HB supervised the study. EB and LW operatively perform the study. EB drafted the manuscript, all other authors critically revised the work for important intellectual content. All authors (HB, BE, DE, A-MK,

NB, LW) approved the final version to be published and agree to be accountable for all aspects of the work.

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Declaration of interest

HB reports to have received consultancy fees and fees for lectures/workshops from chambers of psychotherapists and training institutes for psychotherapists in the e-mental-health context. A-MK has received fees for lectures/workshops from chambers of psychotherapists and health insurance companies. DE reports to have received consultancy fees/served in the scientific advisory board from several companies such as Minddistrict, Lantern, Schoen Kliniken and German health insurance companies. He is stakeholder of the Institute for health training online (GET.ON), which aims to implement scientific findings related to digital health interventions into routine care.

All other authors declare not to have competing interests.

Access to data and availability

All principal investigators will be given full access to the data sets. Data set will be stored on password-protected servers of university Ulm with restricted access. External researches may get access to the final trial dataset on request depending on to be specified data security and data exchange regulation agreements. To ensure confidentiality, data dispersed to any investigator or researcher will be blinded of any identifying participant information.

Abbreviations

ACT	Acceptance and commitment therapy
AQoL-8D	Inventory for the Assessment of Quality of Life
BFI-10	Short version of the Big Five Inventory
CES	Centrality of Event Scale
CEQ	Credibility/Expectancy Questionnaire
DRKS	Deutsches Register Klinischer Studien
ERQ	Emotion Regulation Questionnaire
FAH-II	Acceptance and Action Questionnaire-II
FS-D	Flourishing Scale
IMI	Internet-based intervention
IG	Intervention group
INEP	Inventory for the assessment of negative effects of psychotherapy
RCT	Randomised controlled trial
TAI-SF	Inventory of Technology Alliance – Online Therapy
TAS-20	Toronto Alexithymia Scale
WHO-5	Well-being-Scale
WL	Waiting List Control Group
ZUF-8	Client Satisfaction Questionnaire

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Figure Legends

Figure 1. Content and chronological structure of the study

Figure 2. Flowchart of the planned study procedure.

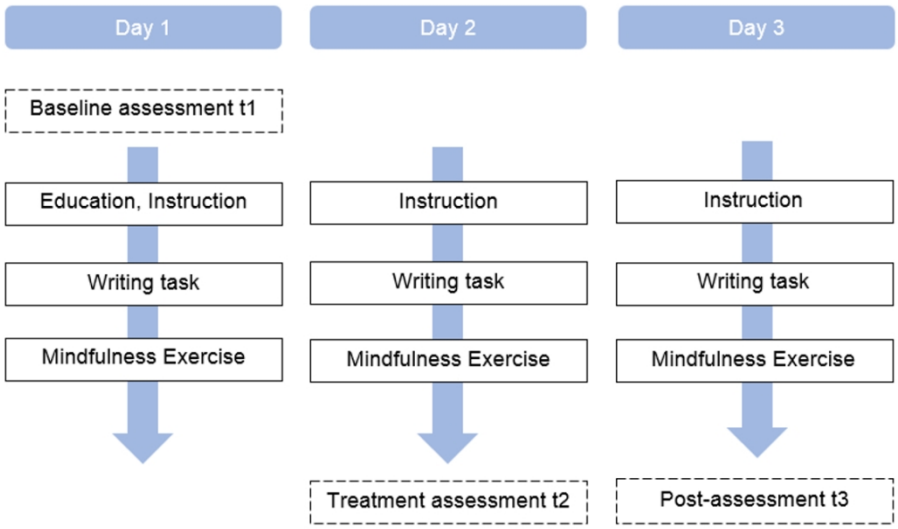

Figure 1. Content and chronological structure of the study

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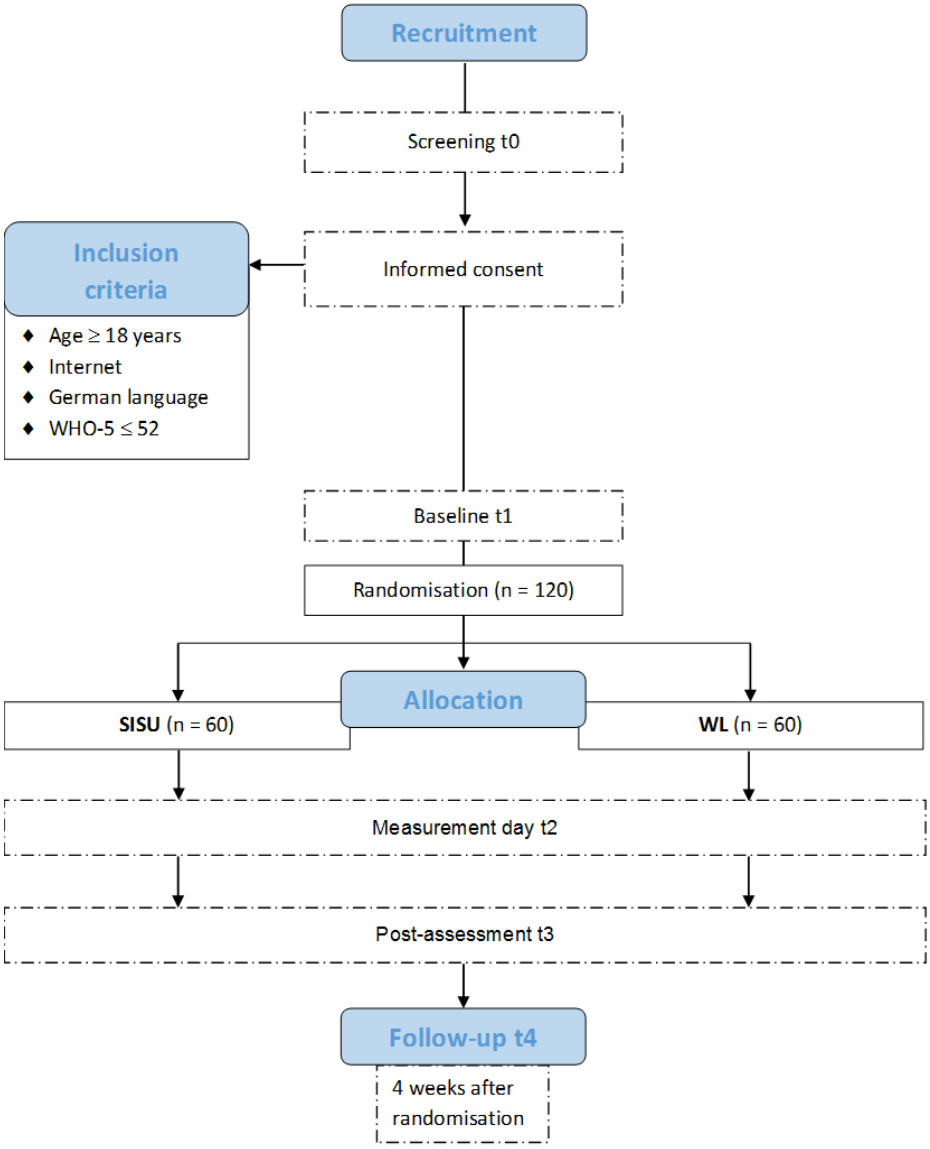

Figure 2. Flowchart of the planned study procedure.

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Teilnehmendeninformation

» SISU – Eine randomisiert-kontrollierte Pilotstudie zur Evaluation eines Chatbots zur Darbietung einer Schreibintervention zur Steigerung des psychischen Wohlbefindens.«

Sehr geehrte Teilnehmerin, sehr geehrter Teilnehmer,

Wir möchten Sie einladen, an der folgenden Studie teilzunehmen. Die Universität Ulm führt ein Forschungsprojekt durch, in dessen Rahmen ein an der Universität Ulm entwickelter Chatbot überprüft werden soll. Wir möchten Sie einladen, einen innovativen Chatbot zur Steigerung psychischen Wohlbefindens zu testen und an vier kurzen Befragungen teilzunehmen.

WORUM GEHT ES IN DER STUDIE UND WELCHES ZIEL WIRD MIT DER DURCHFÜHRUNG DER STUDIE VERFOLGT?

Ein Chatbot ist ein Computer-Programm, das eine Konversation über ein Chat-Interface (Chat: Onlinekommunikation mit Hilfe eines Chats, Interface: Schnittstelle, an der der Austausch von Daten oder Steuersignalen erfolgt) mit einem Menschen hält. Der Chatbot leitet Sie dazu an, an drei aufeinanderfolgenden Tagen über ein emotional positives Lebensereignis zu schreiben. Das Schreiben über positive, autobiographische Lebensereignisse ist eine Form therapeutischen Schreibens und zielt darauf ab, emotionales Wohlbefinden zu steigern. Das Schreiben über emotionale Lebensereignisse wurde in zahlreichen Studien wissenschaftlich überprüft. Ziel der Studie ist die Untersuchung der Wirksamkeit und Akzeptanz des Chatbots. Durch Ihre Teilnahme leisten Sie einen entscheidenden Beitrag zur Weiterentwicklung eines Chatbots.

VORAUSSETZUNGEN FÜR DIE TEILNAHME:

- Sie sind mindestens 18 Jahre alt.
- Sie sind motiviert, einen Chatbot zum Schreiben über positive Lebensereignisse auszuprobieren und an drei aufeinanderfolgenden Tagen über ein autobiographisches, positives Lebensereignis zu schreiben.
- Sie sind bereit, an 4 Befragungen teilzunehmen.
- Sie verfügen über ein Smartphone und sind bereit, eine Ende-zu-Ende verschlüsselte Instant-Messaging Anwendung zu installieren.

STUDIENABLAUF:

Die erste Befragung enthält Angaben zu Ihrer Person (Geschlecht, Alter, etc.). Die drei nachfolgenden Befragungen bestehen aus Fragen zur Akzeptanz des Chatbots und zum Verbesserungspotenzial sowie aus Fragen zu Ihrem emotionalen und psychischen Wohlbefinden. Eine Befragung dauert ca. 10-15 Minuten.

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Wenn Sie sich bereit erklären, an der Studie teilzunehmen, senden Sie bitte die unterschriebene Einverständniserklärung zeitnah unterschrieben an uns zurück (z.B. postalisch oder eingescannt per Email an chatbot-studie@uni-ulm.de). Weitere Schritte:

Tag 1

Schritt 1: Nachdem wir die Einverständniserklärung erhalten haben, können Sie sich die Ende-zu-Ende verschlüsselte Instant-Messaging Anwendung installieren. Zusätzlich erhalten Sie einen Link zur ersten Befragung.

Schritt 2: Sobald Sie die Online-Befragung durchlaufen haben, können Sie über die Instant-Messaging Anwendung Kontakt zum Chatbot „SISU“ aufnehmen.

Tag 2 und Tag 3

Schritt 3: Sie nehmen Kontakt zum Chatbot auf und füllen eine anschließende Befragung aus.

Follow-up

Schritt 4: Etwa 4 Wochen später bitten wir Sie per E-Mail, die letzte Befragung auszufüllen.

FREIWILLIGKEIT:
An diesem Forschungsprojekt nehmen Sie freiwillig teil. Ihr Einverständnis können Sie jederzeit und ohne Angabe von Gründen widerrufen, dann werden alle bis dahin studienbedingt erhobenen Daten gelöscht. Dieser eventuelle Widerruf hat keinerlei Auswirkungen für Sie.

ERREICHBARKEIT DES STUDIENTHERAPEUTEN:
Sollten während des Verlaufes des Forschungsprojektes Fragen auftauchen, so können Sie diese jederzeit an das Studienteam richten (E-Mail an: chatbot-studie@uni-ulm.de). Als Ansprechpartner können Sie jederzeit den Studienleiter Prof. Dr. Harald Baumeister (0731-50-32800) oder die Studienmitarbeiterin Eileen Bendig (M.Sc.) (0731-50-32807) erreichen. In Notfällen gilt folgende Nummer: 116 117.

VERSICHERUNG:
Während der Teilnahme an dem Forschungsprojekt genießen Sie Versicherungsschutz. Die an der Studie mitwirkenden Mitarbeiter sind über die Universität Ulm beim Land Baden-Württemberg haftpflichtversichert für den Fall, dass Sie durch deren Verschulden einen Schaden erleiden. Gleichzeitig weisen wir darauf hin, dass Sie für die direkten Wege zum und vom Studienzentrum nicht unfallversichert sind. Einen Schaden, der Ihrer Meinung nach auf dieses Forschungsprojekt zurückzuführen ist, melden Sie bitte unverzüglich dem Studienleiter.

SCHWEIGEPFLICHT/DATENSCHUTZ:
Alle Personen, welche Sie im Rahmen dieses Projektes betreuen, unterliegen der Schweigepflicht und sind auf das Datengeheimnis verpflichtet. Die studienbezogenen Untersuchungsergebnisse sollen in anonymisierter Form in wissenschaftlichen Veröffentlichungen verwendet werden.
Soweit es zur Kontrolle der korrekten Datenerhebung erforderlich ist, dürfen autorisierte Personen (z.B.: des Auftraggebers, der Universität) Einsicht in die studienrelevanten Teile der Krankenakte nehmen. Sofern zur Einsichtnahme autorisierte Personen nicht der obengenannten ärztlichen Schweigepflicht unterliegen, stellen personenbezogene Daten, von denen sie bei der Kontrolle Kenntnis erlangen, Betriebsgeheimnisse dar, die geheim zu halten sind.

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Die in diesem Projekt für die Datenverarbeitung verantwortliche Person ist: Prof. Dr. Harald Baumeister, Leiter der Abteilung Klinische Psychologie und Psychotherapie, Universität Ulm, Albert-Einstein-Allee 47, 89091 Ulm, 0049 731-50-32800, E-Mail: Harald.Baumeister@uni-ulm.de. Bei Fragen zur Nutzung oder Verarbeitung Ihrer Daten wenden Sie sich bitte an den/die:

Datenschutzbeauftragte/n des lokalen Studienzentrums Universität Ulm:
Universität Ulm, Helmholtzstr. 16, 89081 Ulm, Telefonnummer.: 0731 50 - 25056,
E-Mail: datenschutz@uni-ulm.de

Falls Sie Bedenken oder Beschwerden hinsichtlich der Verarbeitung Ihrer Daten haben, wenden Sie sich bitte an die Datenschutz-Aufsichtsbehörde Ihres Studienzentrums: Die entsprechenden Kontaktdaten finden Sie auf der Internetseite des Landesbeauftragten für Datenschutz und Informationsfreiheit Baden-Württemberg:
https://www.baden-wuerttemberg.datenschutz.de/dsb-online-melden/

..... ……..

Ort, Datum Name der aufklärenden Mitarbeiters/in

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EINWILLIGUNGSERKLÄRUNG

» SISU – Eine randomisiert-kontrollierte Pilotstudie zur Evaluation eines Chatbots zur Darbietung einer Schreibintervention zur Steigerung des psychischen Wohlbefindens.«

Inhalt, Vorgehensweise, Risiken und Ziel des obengenannten Forschungsprojektes sowie die Befugnis zur Einsichtnahme in die erhobenen Daten hat mir …….ausreichend erklärt.

Ich hatte zusätzliche Fragen:
……

……

Ich hatte Gelegenheit Fragen zu stellen und habe hierauf Antwort erhalten.

Ich hatte ausreichend Zeit, mich für oder gegen die Teilnahme am Projekt zu entscheiden.

Eine Kopie der Patienteninformation und Einwilligungserklärung habe ich erhalten.

Ich willige in die Teilnahme am Forschungsprojekt ein.

.....
(Name Teilnehmer/in)

....
Ort, Datum (Unterschrift Teilnehmer/in)

INFORMATION UND EINWILLIGUNGSERKLÄRUNG ZUM DATENSCHUTZ

Bei wissenschaftlichen Studien werden persönliche Daten und medizinische Befunde über Sie erhoben. Die Speicherung, Auswertung und Weitergabe dieser studienbezogenen Daten erfolgt nach gesetzlichen Bestimmungen und setzt vor Teilnahme an der Studie folgende freiwillige Einwilligung voraus:

1. Ich erkläre mich damit einverstanden, dass im Rahmen dieser Studie erhobene Daten/ Krankheitsdaten auf Fragebögen und elektronischen Datenträgern aufgezeichnet und ohne Namensnennung verarbeitet werden
2) Außerdem erkläre ich mich damit einverstanden, dass eine autorisierte und zur Verschwiegenheit verpflichtete Person (z.B.: des Auftraggebers, der Universität) in meine erhobenen personenbezogenen Daten Einsicht nimmt, soweit dies für die Überprüfung des Projektes notwendig ist. Für diese Maßnahme entbinde ich den Arzt von der ärztlichen Schweigepflicht.
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interventions, and outcomes			
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Study Protocol of a randomised controlled trial on SISU, a software agent providing a brief self-help intervention for adults with low psychological well-being.

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Manuscript ID	bmjopen-2020-041573.R2
Article Type:	Protocol
Date Submitted by the Author:	23-Dec-2020
Complete List of Authors:	Bendig, Eileen; Ulm University, Institute of Psychology and Education, Department of Clinical Psychology and Psychotherapy Meißner, Dominik; Universitat Ulm, Institute of Distributed Systems, Department of Computer Science Erb, Benjamin; Universitat Ulm, Institute of Distributed Systems, Department of Computer Science Weger, Lena; Ulm University, Institute of Psychology and Education, Department of Clinical Psychology and Psychotherapy Küchler, Ann-Marie; Ulm University, Institute of Psychology and Education, Department of Clinical Psychology and Psychotherapy Bauereiss, Natalie; Institut of Psychology and Education, Department of Clinical Psychology and Psychotherapy Ebert, David ; Vrije Universiteit Amsterdam, Baumeister, Harald; Ulm University, Institute of Psychology and Education, Department of Clinical Psychology and Psychotherapy
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Mental health
Keywords:	MENTAL HEALTH, Telemedicine < BIOTECHNOLOGY & BIOINFORMATICS, PUBLIC HEALTH, Depression & mood disorders < PSYCHIATRY

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Study Protocol of a randomised controlled trial on SISU, a software agent providing a brief self-help intervention for adults with low psychological well-being.

Bendig, Eileen[1], Meißner, Dominik [2,] Erb, Benjamin [2], Weger, Lena [1], Küchler Ann-Marie [1], Bauereiss, Natalie [1], Ebert, David [3] & Baumeister, Harald [1]

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ABSTRACT

Introduction: Only a minority of people living with mental health problems are getting professional help. As digitalisation moves on, the possibility of providing internet- and mobile-based interventions (IMIs) arises. One type of IMIs are fully automated conversational software agents (chatbots). Software agents are computer programs that can hold conversations with a human by mimicking a human conversational style. Software agents could deliver low-threshold and cost-effective interventions aiming at promoting psychological well-being in a large number of individuals. The aim of this trial is to evaluate the clinical effectiveness and acceptance of the brief software agent-based IMI SISU in comparison to a waitlist control group (WL). **Methods and Analysis:** Within a two-group randomised controlled trail, a total of 120 adult participants living with low well-being (WHO-5) will be recruited in Germany, Austria and Switzerland. SISU is based on therapeutic writing and acceptance and commitment therapy-based principles. The brief intervention consists of three modules. Participants work through the intervention on three consecutive days. Assessment takes place before (t1), during (t2) and after (t3) the interaction with SISU, as well as 4 weeks after randomisation (t4). Primary outcome is psychological well-being (WHO-5). Secondary outcomes are emotional well-being (FS-D), psychological flexibility (FAH-II), quality of life (AQoL-8D), satisfaction with the intervention (ZUF-8) and side effects (INEP). Examined mediators and moderators are sociodemographic variables, personality (BFI-10), emotion regulation (ERQ), alexithymia (TAS-20), centrality of events (CES), treatment expectancies (CEQ) and technology alliance (TAI-SF). Data analysis will be based on intention-to-treat principles. SISU guides participants through a three-day intervention. **Ethics and Dissemination:** This trial has been approved by the ethics committee of the Ulm University (No. 448/18, 18.02.2019). Results will be submitted for publication in a peer-reviewed journal and presented at conferences.

Strengths and limitations of this study:

- ➔ To our knowledge, this is the first full-scale RCT on a chatbot delivering a brief psychological intervention to uplift psychological well-being.
- ➔ Results on user acceptance will help to gain further insights for requirements due to the fully automated presentation form of psychological internet interventions.
- ➔ Technology alliance and side effects will be monitored.
- ➔ Dropout rate is to be kept small by automated guidance and prompts.

Trial registration: The trial is registered at the WHO International Clinical Trials Registry Platform via the German Clinical Studies Trial Register (DRKS): DRKS00016799 (date of registration: 25.04.2019). In case of important protocol modifications, trial registration will be updated. This is protocol version number 1.

Keywords: Chatbot, software agent, psychological well-being, internet and mobile-based interventions, writing, positive psychology intervention, digital, conversational agent

INTRODUCTION

The global direct and indirect economic costs of mental disorders are estimated at 2.5 trillion US $ [1]. Thus, untreated mental disorders are a public health concern worldwide. However, the majority of individuals living with mental disorders do not receive any health care supply [2–4]. In Europe, only about 25% of people with mental disorders receive professional treatment [5].

On the one hand, there are societal barriers to receiving adequate mental health care offers. On the other hand, there are barriers on the side of individuals, keeping them from seeking professional help [6]. The latter aspect comprises fear of stigmatization [7,8], restrictions of time and location [9,10], negative attitudes towards pharmacological and psychotherapeutic treatments [11], negative experiences with professionals [12,13] or missing conscientiousness for diseases [14]. In order to overcome some of these barriers and to improve mental health care at a large scale, digital means are frequently discussed options.

Digitalization sets societal changes in motion in various fields [15]. Other than in the areas of work, economy, and science, new technologies slowly emerge in the field of mental health care. Internet-based and mobile-based Interventions (IMIs) can provide low-threshold, flexible interventions that are resource-, time- and location-independent [9,10] and can be as effective as traditional face-to-face psychotherapy [16]. As such, they might help to reduce societal and individual barriers to mental health care and expand supply offers [9,16,17]. At this point, their effectiveness and cost-effectiveness could be established for the prevention [18] and treatment of mental disorders [9,19–24] and chronic somatic diseases [25] as well for positive mental health promotion purposes [26–29].

IMIs are highly standardised computer programs. They are often manualised, which means that they are incorporating instructions, theory-based key elements and concepts as well as how-to approaches regarding the evidence-based implementation of a certain delimited psychological program. which can be seen as digitised therapeutic interventions [9,30]. While they have without doubt substantial merits, some limitations still restrict their scalability and widespread roll-out. As yet, for example, IMIs seem to work best if they provide any form of human guidance alongside the digital program [21,31]. However, fully unguided interventions could be a more cost-effective way of providing digital interventions (e.g.,[32]). Thereby, professional guidance does not only limit the cost-effectiveness, but also necessitates health care infrastructures that might not always be at place at a large (enough) scale. In addition to the possibility of an increased cost-effectiveness unguided fully automated interventions like mHealth interventions have shown potential to effectively targeting mental health symptoms [33].

Evidence shows that the effectiveness of IMIs might be in part attributable to other effect factors than in face-to-face therapy [34]. In comparison to face-to face therapy, the therapeutic alliance might not be as relevant as effect factor [35]. Instead, other factors, e. g. an agreement on tasks and goals [35] or the fostering of self-efficacy [36], have been discussed. Software agents could combine the best of both worlds, as they seem to have the potential to human-machine alliance [37]. Delivering IMIs by software agents could compensate for some of the disadvantages of conventional computer program-based IMIs (e.g., [31]) Amongst others, they could show human-like, immediate responses with regards to user input [38].

A software agent or "chatbot" is a computer program that can hold a fully automated text-based conversation in real-time with people via a chat-interface (e.g., smartphone application) by using a natural language style [38]. The growing interest and body of research about software agents [39,40] is realised in various populations and contexts, such as problem solving and stress [41–43]. In the context of clinical psychology and psychotherapy, research on software agents is sparse [44] but could create opportunities for the field regarding the provision of mental health services. Software agents could be used to convey therapeutic contents and brief interventions [45,46]. Establishing contact to a software agent might not be as stigmatising as using formal mental health services like starting a face-to-face therapy or asking a general practitioner for possibilities of mental health care [47]. Furthermore, they are flexible regarding location and time [48], can be used anonymously [49,50] and provide personalization through implicit customization [51]. Therefore, software agents could help to overcome barriers and provide psychological and health behaviour change interventions on a large scale in the future.

Current mental health software agents are primarily based on cognitive behavioural therapy [44]. However, other popular approaches with proven effectiveness in face-to-face settings could also readily be realized in a digital form, such as writing interventions [52] and acceptance and commitment-based approaches [53].

Writing with the aim of improving health has a long history [54]. In the current literature, the labelling of this kind of intervention varies: Terminology includes expressive writing [55,56], benefit-finding or positive writing [57,58] and therapeutic writing (e.g., [59]). Regardless of terminology, the writing intervention to be investigated in this study will refer to the process of freely and emotionally writing about a positive personal life event without paying attention to spelling or grammar. The call to write about personal life events, to tell a story, seems to go straight at the centre of subjective experiences [60], which in turn is the main medium in traditional face-to-face therapy. In that, the term therapeutic writing will be used in this context to acknowledge that the intervention refers to some kind of therapeutic work [61]. It has been shown that writing interventions can be highly time- and cost-efficient [62]. A recent meta-analysis shows that writing interventions can help to improve general psychological health

(SMD=-0.46, 95% CI -.86, -0.06) [63]. Finally, a meta-analysis from Bolier and colleagues [64] found an effect of Cohen's *d* = 0.34 (95% CI 0.22, 0.45) for positive interventions to uplift cognitive and/or affective appraisal of one´s life as a whole and d=0.20 (95% CI 0.09, 0.30) optimal functioning including mastery, hope and purpose in life.

Acceptance and Commitment Therapy (ACT) [65] aims at acceptance, mindfulness and value-based living and has been found to be effective in the prevention of stress and the increase of well-being [27,66]. The efficacy of ACT-based interventions in general and ACT-based IMIs in particular has been indicated in a number of studies and systematic reviews. Within a randomised-controlled trial, Fledderus and colleagues (2012) investigated an ACT-based IMI for people living with depression. The authors found significant reductions in depression, anxiety, fatigue, experiential avoidance and improvements in positive mental health, compared to a waitlist control condition (effect sizes Cohen´s *d* = 0.51 to 1.00) [29]. In their meta-analysis, Brown and colleagues[67] examined 10 randomised controlled trials investigating the effectiveness of ACT in the treatment of depressive or anxiety symptoms and well-being in adult populations. ACT interventions were compared to passive control groups (N=3), active control groups (N=4) or both (N=3). The authors found small effect sizes regarding the improvement of depression (*g* = 0.24, 95% CI: 0.04 - 0.45) whilst the heterogeneity of conditions and outcome measures on anxiety and well-being was too high to draw firm conclusions. Spijkerman and colleagues [28] examined 15 randomised controlled trials in adults with various mental problems and healthy populations. Mindfulness interventions, of which the authors include ACT, were compared to passive control groups (N=10), active control groups (N=5) or both (N=2). The authors found small to medium effect sizes concerning the improvement of depression (*g* = 0.29, 95% CI: 0.13 - 0.46), anxiety (*g* = 0.22, 95% CI: 0.05 - 0.39) and well-being (*g* = 0.23, 95% CI: 0.09 - 0.38) [28].

We developed a gender neutral software agent called SISU (**S**oftware agent providing an **I**ntervention for **S**elf-help to **U**plift psychological well-being and finnish word [ˈsisu] for inner strength) with the aim to provide an easily deployable software agent that improve peoples´ well-being. Therefore, SISU combines therapeutic writing and acceptance- and commitment-based principles. Results of a feasibility trial on SISU [68] showed that SISU is feasible in terms of user acceptance and the potential of the software agent to deliver a brief writing intervention. Thus SISU is feasible to be implemented within a confirmatory clinical trial. Hence, the present study is designed to investigate the clinical effectiveness and acceptance of the Software agent SISU thereby focusing on the following specific research aims:

1. To estimate the effects of SISU on psychological well-being compared to the WL at T3 (primary outcome).

2. To estimate the effects of SISU regarding the secondary outcomes flourishing, quality of life, and psychological flexibility compared to the WL at T3.

3. To explore, which factors are associated with, moderate or mediate the effects of SISU.

4. To investigate if the intervention is associated with measured side effects.

5. To investigate the level of acceptance (satisfaction, adherence) with the intervention.

METHODS

Study Design

This is a two- arm, parallel randomised controlled trial (RCT) with the intervention group SISU (IG) and a waiting list control group (WL). The IG receives the online-based intervention guided by the SISU software agent. The WL receives the intervention 4 weeks later. Primary and secondary outcomes will be assessed over a period of four weeks. Assessments will take place at screening (t0), baseline at day 1 (t1), intermediately at day 2 (t2), post-treatment at day 3 (t3) as well as four weeks follow-up (t4).

The present study is conducted and will be reported in accordance with the CONSORT 2010 guidelines for RCTs [69] and the guidelines for executing and reporting IMI research [70]. The study protocol follows recommendations of the SPIRIT 2013 Checklist for clinical trial protocols [71].

Recruitment

Recruitment has started in May 2019 and will be continued until the targeted sample size of N=120 has been reached. We recruit in German speaking countries, Germany, Austria and Switzerland. Recruitment strategies comprise a dynamic, broad on- and offline recruitment strategy. Offline recruitment will be conducted via posters and flyers at different universities, psychosocial counselling services, city libraries and other publicly accessible sites. Online recruitment strategies will comprise postings in online self-help groups on social media (e.g. facebook), displays on ebay and xing as well as the Studicare®-website. StudiCare is a project that offers a broad assortment of internet-based interventions for psychological and behavioural issues [72]. Interested persons will get access to the screening (t0) at an online survey tool (unipark.com) via QR-code, link or via email on request. Directly after the screening eligible participants will automatically receive informed consent for signing via email. Apart from the recruitment, the study will be fully conducted online.

Eligibility criteria

Participants will be eligible for inclusion in the present trial if they are (a) 18 years or older, (b) willing to take part in this study, (c) have internet access and an email address, (d) have a low psychological well-being (WHO-5 $\leq$ 52) and (e) possess sufficient German language skills.

Study Procedures

If eligibility criteria are fulfilled, applicants will receive an online information letter including detailed information about study procedure and informed consent. They will be informed that they can withdraw from the intervention and/or study at any time without any negative consequences. After signing the informed consent, participants will be randomised to the IG

or WL condition. Following, they will receive their individual ID and get an invitation for the baseline questionnaire (t1) at unipark.de via email. Afterwards, participants will learn about their group membership. The IG will get in contact with SISU and the intervention using the end-to-end encrypted online messaging app “Wire” after finishing baseline (t1). SISU guides participants through a writing intervention on three consecutive days using a standardised conversation script. Each writing intervention is automatically followed by an assessment. Participants who are part of the WL will receive access to SISU four weeks after randomisation. If participants complete questionnaires for t3 and t4 they will each time get the chance to win a 10€ gift card for Amazon as a monetary incentive to promote retention and follow-up completion. All participants with a low WHO-5 score (< 28) in the screening receive an automatised email with further information about offers of the health care system.

Randomisation and blinding

Participants will be randomised to either IG or WL. An academic assistant (JM) from the Department of Clinical Psychology and Psychotherapy at the University Ulm, not otherwise involved in the trial and blinded towards all further procedures, will perform the allocation. A permuted block randomisation with 4, 6, 8 and 12-block-size and an allocation ratio of 1:1 will be used. The randomisation list will be created by a well-accepted website (https://www.sealedenvelope.com). Whereas blinding of participants is not possible, data collectors and data analysts are blinded regarding group membership.

Intervention

The software agent (SISU) provides a brief three-day intervention. The writing instruction provided by SISU is based on the paradigm of therapeutic writing as well as acceptance and commitment therapy [ACT; 73]. The version of SISU used for this study was improved through participant feedback collected in the feasibility trial [68]. Revisions included the enrichment of the instruction for writing about positive life events with elements of ACT (more mindfulness exercises, authenticity of the dialog through reduction of repetitions, interactions on reported life events) and elements for the reconstruction of narrative identity.

SISU mimics a human conversational style. Participants are guided to write each day at the same time for 10-20 minutes about a self-chosen autobiographical, positive life event. On day 1 there is psychoeducation in the beginning. Then, instructions for the writing tasks are followed by the narratives of the participants. Participants are instructed to write about a meaningful, outstanding positive life event on day 1 and about an outstanding positive event from adulthood on day 2. On day 3 participants are guided to write about their best possible future. After the writing task, SISU encourages participants to experience the positive emotions due to the reported event in the present moment. Mindfulness exercises are provided by an audio file right after the writing intervention, whilst ACT-metaphors are integrated into the

conversational content. Participants are encouraged to practice on a daily basis. To increase adherence, SISU reminds participants at 24 hour intervals. More details on intervention contents can be derived from Table 1. For an illustration of content and chronological structure see Figure 1.

Using the online messaging Wire Services SDK enables programmatic end-to-end encrypted communication. Thanks to this encryption, messages sent by SISU or participants are not accessible by third parties, including the service provider. We further protect participation data by hosting SISU on premises and by encrypting the data at rest, thus limiting the access to our research group. The communication logic is implemented as a finite-state machine. Our SISU implementation parses incoming messages based on a fixed set of rules and responds with an appropriate answer. In addition, SISU can react to external triggers. That is, external triggers can lead to a status change of SISU. For example, the termination of a survey at Unipark can cause a status change of SISU from "user is active" to "user finished the interaction for the day". External triggers can be (a) conversation timeouts (i.e., the participant has not responded in a set time frame), (b) Unipark events (i.e., participant has completed an external survey), and (c) scheduled events (e.g., daily participation reminder at pre-defined time frames).

Table 1

Content and techniques of the writing tasks as delivered by SISU

Module title	Module Content	Focused ACT technique
1 Introduction	Therapeutic writing, ACT	Psychoeducation
2 Writing tasks	Instructions for writing about a positive autobiographical life events	
3 Thoughts and feelings	Important things in life	Values
4 Mindfulness exercise	Being aware of what is happening in the present moment without judging it	Contact with the present moment; Acceptance

Note. ACT = Acceptance and Commitment Therapy

--please insert figure 1 around here--

The (ultra-)brief intervention rational of 3 days was chosen because we wanted to provide participants with a brief possibility to do something for their mental well-being, despite their busy everyday lives. Indeed, evidence suggests that brief writing interventions of e. g. only 1

week can increase emotional well-being even 6 months after the intervention [74], particularly in case of interventions focusing on improving mental health rather than treating mental disorders.

Wait list control group

Participants of the WL get access to the writing intervention provided by SISU four weeks after randomisation. The intervention has the same content for both groups.

Administrative and technical support

In case participants forget their individual ID or have other technical issues, they can make use of the study team via email for technical support at every point during the training.

Outcome Assessment

Screening for eligibility takes place at t0. Data for relevant outcomes will be collected prior to the intervention on day 1 (t1), on day 2 (t2), and day 3 (t3; intervention completed) and four weeks after randomisation (t4; follow-up). Demographic data and personality traits are measured once (t1). A flow chart of the study can be seen in Figure 2. The outcomes, their measurement instrument and points of assessment are shown in Table 2.

--please insert figure 2 around here--

Table 2

Constructs, measurement instruments and points of assessment

Construct	Measurement instrument	Points of assessment				
		T0	T1	T2	T3	T4
Demographical Questionnaire		✓	✓			
Primary endpoint						
Psychological well-being	Well-being Scale (WHO-5)	✓	✓	✓	✓	✓
Secondary endpoints						
Emotional well-being	Flourishing Scale (FS-D)	-	✓	✓	✓	✓
Psychological flexibility	Acceptance and Action Questionnaire-II (FAH-II)	-	✓	✓	✓	✓
Quality of life	Assessment of Quality of Life (AQol 8D)	-	✓	-	✓	✓
Satisfaction with the intervention	Client Satisfaction Questionnaire (ZUF-8)	-	-	-	✓[a]	-
Side effects	Inventory for the assessment of negative effects of psychotherapy (INEP)	-	-	-	✓[a]	✓[b]
Manipulation-Check writing	Post Writing Questionnaire	-	-	✓[a,c]	✓[a]	-
Questions on content	Open questions for the interaction with SISU	-	-	-	✓[a]	-
Willingness to use software agents in the future	Open questions	-	-	-	✓[a]	-
Moderators/Mediators						
Centrality of events	Centrality of Events Scale (CES)	-	-	✓[a,c]	✓[a]	-
Personality	Big Five Inventory (BFI-10)	-	✓	-	-	-
Treatment expectancy	Credibility Expectancy Questionnaire (CEQ)	-	✓	-	-	-
Alexithymia	Toronto Alexithymia Scale (TAS-20)	-	✓	✓	✓	✓
Emotion regulation	Emotion Regulation Questionnaire (ERQ)	-	✓	✓	✓	✓
Technology alliance	Inventory of Technology Alliance – Online Therapy (TAI-SF)	-	-	✓[a]	✓[a]	-

Note. t1 = baseline; t2 = during treatment (two days post-randomisation); t3 = post-treatment (3 days post-randomisation); t4 = follow-up (four weeks after randomisation). [a] Questionnaires only used by IG; [b] adapted version for WL; [c] additionally assessed retrospective for the first contact with SISU at t2

Screening, t0

The short 5-item Well-being-Scale (WHO-5) is administered to assess the subjective psychological well-being of participants in the last two weeks [75]. Participants can answer on a 6-point-Likert scale (5= “All of the time”, 4 = “Most of the time”, 3 = “More than half the time”, 2 = “Less than half the time”, 1 = “Some of the time”, 0 = “At no time”). The sum of raw scores (range: 0-25) is multiplied with 4 and produces a total score (range: 0-100) with 0 representing the worst imaginable well-being to 100 representing the best imaginable well-being [75]. Scores ≤ 52 indicate a low, scores ≤ 28 indicate a very low psychological well-being. Topp and colleagues[75] mention a comparable cut-off score of ≤ 50. The WHO-5 shows a sensitivity of 0.93 and a specificity of 0.83 in the detection of depression [75]. Additionally, the screening includes age, sex, contact information and the sufficient knowledge of German language.

Demographic data

The following information will be collected from each participant at T1: sex, age, education, nationality, German speaking skills, relationship status, profession and highest educational attainment.

Primary outcome

Psychological well-being

Primary outcome is psychological well-being at t3 measured by the Well-being-Scale [75] already described in the section for screening.

Secondary outcomes and covariates

Emotional well-being.

The German version of the Flourishing Scale [FS-D; 76] is a measure of psychosocial well-being and personal growth and development (i.e., flourishing). Each of the 8 items is rated on a 7-point-Likert scale ranging from 1 = “strongly disagree” to 7 = “strongly agree”. A sum score is computed with higher scores indicating higher flourishing. With a Cronbach’s α of 0.87 the scale shows good internal consistency [76].

Psychological flexibility

The German version of the Acceptance and Action Questionnaire-II [77] is a general measure for psychological inflexibility and consists of 7 items. On a 7-point-Likert scale that ranges from 0 = “never true” to 6 = “always true”, the questionnaire assesses a person’s willingness to experience unwanted thoughts and feeling and a person’s ability to act despite the presence of undesirable thoughts and feelings. In this study items were reverse coded to assess psychological flexibility. Sum scores (range: 0-42) are computed with higher scores indicating

higher psychological flexibility. The questionnaire shows good to excellent psychometric properties in a German sample [77].

Quality of life

With the help of the inventory Assessment of Quality of Life (AQoL-8D) participants quality of life is recorded [78]. Each of 35 items loads on one of eight dimensions of quality of life and is rated on 4- to 6-point-Likert scales. For analysis there is an algorithm which can be used for quality of life in general as well as for particular sub dimensions. In total, scores between 0 and 1 are possible. Standard values are available. Reliability of AQoL-8D is very good with Cronbach's α of 0.96 [78].

Side-effects

Subjective adverse events of the intervention are recorded with the 15-item inventory for the assessment of negative effects of psychotherapy [79]. Items are rated on a 4-point-Likert scale (0 = "no agreement" to 3 = "total agreement") or a bipolar 7-point scale. Adverse effects in social life, intrapersonal factors or work-related situations are taken in consideration. The original inventory with 32 items has an internal consistency of α = 0.95 [80].

Satisfaction with the intervention

To assess the global satisfaction with the intervention a revised version of the German version of the Client Satisfaction Questionnaire [ZUF-8; 81] was used. Participants rate their satisfaction on a 4-point-Likert scale for each of the 8 items. A sum score is computed. Higher scores indicate higher satisfaction. Internal consistency of the ZUF-8 is very good with α = 0.90 [82]. A study on reliability and validity of assessing user satisfaction with internet-based interventions indicates good overall psychometric quality of the measure [83].

Post-Writing Questionnaire

To assess therapeutic writing after every writing session the participants answer four questions about their feelings and thoughts during and after the writing experience. Answers are rated on a 5-point-Likert scale (1 = "not at all", 3 = "few", 5 = "very much/extremely"). The questionnaire was adapted from the English version of Pennebaker and Beall [56].

Open questions

For the final survey (t3) four open questions inspired by the open questions from Fitzpatrick, Darcy and Vierhile [84] about the interaction with SISU are provided. The answers are individually evaluated and thematically summarised.

Questions for the future of software agents

The final survey (t3) will assess the behavioural intention to use a software agent in the future or recommend one to friends as well as the future performance expectancy of software

agents providing psychological interventions to uplift psychological well-being in three open questions. Participant responses will be analysed on a qualitative basis.

Moderators/Mediators

Centrality of events

The Centrality of Event Scale [CES; 85] assesses the centrality of an event to a person, differentiating three independent characteristics. Whether the event is seen as (1) a reference point for everyday inferences, (2) a turning point in the life story and (3) as an element of the personal identity. Participants rate the 7 items of the short version on a 5-point-Likert scale from 1 = “totally disagree” to 5 = “totally agree”. With a Cronbach’s α of 0.88 the scale shows high internal consistency [85].

Personality

To assess the Big Five personality traits of participants the short version of the Big Five Inventory [BFI-10; 86] is used. Each of the five personality dimensions is measured with two items depicting either the positive or the negative pole of the spectrum. Participants rate the items on a 5-point-Likert scale from 1 = “fully disagree” to 5 = “fully agree”. The questionnaire shows average retest-reliabilities ranging from 0.56 to 0.60 [86].

Alexithymia

The German version of the Toronto Alexithymia Scale [TAS-20; 87] assesses alexithymia of participants. Each of the 20 items is rated on a 5-point-Likert scale ranging from 1 = “strongly disagree” to 5 = “strongly agree”. The German version assesses 3 factors [88]: “difficulties in identifying and describing feelings“, “external oriented thinking“ and “importance of emotional introspection“. For each dimension sum scores are computed with higher scores each indicating higher manifestations of alexithymia. Internal consistency of the scale is good with a α = 0.80 [88].

Emotion regulation

The Emotion Regulation Questionnaire [ERQ; 89] is a 10-item questionnaire measuring positive and negative feelings as well as their regulation. Items refer to two different emotion regulation strategies: Reappraisal and suppression. Participants rate the items on a scale from 1 = “strongly disagree” to 7 = “strongly agree”. Means show the preference for each strategy indicating higher preference at higher mean scores. Internal consistencies are acceptable to good and differ from α = 0.75 to α = 0.82 [89].

Treatment expectancy

Treatment expectancy is measured with the Credibility/Expectancy Questionnaire [CEQ; 90] with 6 items. Participants rate four items on a 9- and two items on a 10-point-Likert scale with varying descriptions. The scale can be separated in the two factors credibility and expectancy.

Cronbach's α for credibility differs from 0.79 to 0.90, for expectancy from 0.81 to 0.86 and for the total scale from 0.84 to 0.85 indicating acceptable to high internal consistency [90].

Technology alliance

The Inventory of Technology Alliance – Online Therapy (TAI-SF) was used to evaluate the technological alliance between the participants and the online intervention, thus the software agent. The TAI-SF is a 12-items questionnaire developed by Labpsitec (http://www.labpsitec.uji.es/eng/index.php) that assesses the degree to which the participant perceives the online intervention as helpful. Items are rated on a 7-point-Likert scale from 1 = "never" to 7 = "always".

Data privacy and ethics

Data will be pseudonymised and analysed in the Department of Clinical Psychology and Psychotherapy of the Ulm University via individual ID and an internal participant ID for every participant to encode the individual datasets. Messages exchanged between participants and SISU are encrypted in-transit by the end-to-end encryption of the "Wire" application. Thus, only the study team will have access to the collected data. Participants will have the opportunity to have all of their collected data deleted. External researchers may get access to the final trial dataset (from HB) on request depending on to be specified data security and data exchange regulation agreements. To ensure confidentiality, data dispersed to any investigator or researcher will be blinded of any identifying participant information. Anonymised results will be published in peer-reviewed journals and presented on international conferences.

The participation in this study should not be associated with any specific risks. However, temporary changes in mood could arise directly after the writing task [91]. Furthermore, therapeutic writing can lead to emotional-cognitive (change) processes [61] with which the participants could have difficulties in dealing with. Therefore, participants will have the opportunity to contact the study team at every point during the trial. Additionally to the interventions, participants with a very low WHO-5 score (< 28) in the screening will be sent an automatised email with further information about offers of the health care system.

Sample Size

A meta-analysis by Bolier and colleagues [64] found an effect size of d=0.34 for positive psychological interventions aiming at uplifting well-being. Riddle and colleagues [92] reported an effect size of d=0.46 for writing interventions to enhance well-being. However, for internet-based mindfulness interventions, Spijkerman and colleagues [28] found a somewhat smaller effect of g=0.23.

Based on these previous findings, a small effect size of d = 0.30 is expected. Power analysis for an ANOVA with repeated measures with g-power (http://gpower.hhu.de/) recommends a

sample size of at least 60 participants per group (N=120) on the assumption of two-tailed testing, an alpha error $\alpha = 0.05$ and power $1-\beta = 0.90$.

Statistical Analysis

Patterns of missing data will be investigated, and analyses will be adjusted accordingly (multiple imputation). Regarding the imputation method and predictor selection we will follow the recommendations of van Buuren and colleagues [93]. It will be assumed that missing values are missing at random. Analyses will be conducted on a two-sided level of significance (α=.05). Participant characteristics will be described descriptively.

All statistical analyses will be performed based on the intention-to-treat (ITT) principle. Additional per protocol analyses will be conducted in order to examine associations in case of patients adhering to the intervention protocol. Participants who completed at least 66% of the intervention are defined as intervention completer (=per protocol).

The primary outcome will be analysed using linear regression models at T3 as dependent variable and the baseline value as covariate, adjusting for sex and age. The necessity of multilevel models will be explored by interclass correlations (ICC). On substantial ICC (>.10) multilevel models will be specified to account for the dependency in the data [94]. To analyse between-group effect sizes, standardised mean differences with 95% confidence intervals will be calculated for post-treatment (t3) and follow-up (t4). Secondary outcomes will be analysed accordingly.

Exploratory mediation and moderator analyses involving the primary and secondary outcomes as well as demographic data will be conducted. Moderator and subgroup analyses are aimed for in case of a sufficiently large sample size.

For the planned exploratory moderator analyses, regression models will be employed. Initially, each potential moderator described under “Covariates” will be analysed in a separate regression model. The primary outcome psychological well-being at t3 will be the dependent variable. Predictors will comprise group, the moderator variable and the interaction of group and moderator. In a next step, a comprising model of all identified moderators will be tested.
Mediation analyses will be conducted according to the principles of time-lagged mediation [95]. Psychological well-being at t3 will be the outcome variable. Group will be chosen as independent variable, whereas the variables defined in the section “Potentials mediators” will constitute the respective mediating variables. No interim analyses will be applied to the data.

Patient and public involvement

Patient and public involvement (PPI) representatives provide input to the present study in several stages. Results of the feasibility trial on SISU (DRKS-ID: DRKS00014933) were used

to further develop and optimise study design and procedures. PPI representatives were included in the intervention development to improve content, usability and design of SISU. However, acceptance of SISU from the participants' perspective is a crucial outcome of the study and both quantitative and qualitative methods are applied to capture acceptance and side-effects. The dissemination plan of the study results includes presentations on international conferences and publications in peer-reviewed journals.

Discussion

To the best of our knowledge, this study will be the first to investigate an intervention on therapeutic writing combined with mindfulness-based exercises provided via a software agent. It is a two-parallel arm controlled trial with the aim of evaluating SISU, a software agent as an innovative form of providing a scalable mental health interventions [44] to uplift peoples´ well-being.

The proposed study can be characterized by several strengths. First, our software agent SISU was successfully tested within a feasibility trial of Bendig and colleagues in preparation [68] and provides elements of established approaches [73,91]. Therefore, we consider SISU to provide an eligible intervention and the potential to uplift psychological well-being in participants. To our knowledge, there are no known risks or negative effects for internet- and mobile-based interventions in the context of self-help interventions to uplift psychological well-being. Still, we will systematically record via questionnaire (INEP) if and which negative effects of SISU might appear. This will contribute to the still understudied area of research on risks and side effect [96] and therefore help make future Internet- and mobile-based interventions safer.

Second, besides the relevance and necessity of our intervention, the methodical quality of our study is another strength. This is especially relevant in the relatively young field of research on therapeutic software agents, where highly qualitative studies are still sparse. First, we will use a randomised controlled design and we will apply ITT-analysis to avoid a possibly overestimated effect of the intervention. Second, the writing intervention is highly standardised due to the completely automated instructions and feedback given by SISU. Third, we will collect data on many variables and time points to enable moderator- and mediator-analysis on an explanatory level. The knowledge of how and for whom interventions work best is an important prerequisite improving their content and target groups [97].

Third, although effectiveness with the same range of expected effect size (and at the same cost) can be expected from other fully automated unguided intervention formats (e.g., [98]), this is the very first study to evaluate a software agent-delivered intervention. As it can be assumed that not everybody or every population prefers the same kind of delivery-format, it is important to evaluate a broad variety of formats to enable adaptability. In this respect, the present study makes an important contribution.

Another strength concerns our recruitment strategy. We will be able to reach a wide-range of participants by broad online and offline recruitment in Germany, Austria and Switzerland. Recruitment strategies might help to gain knowledge on feasibility and effectiveness of SISU in a broad range of adult people living with low psychological well-being. However, people living with high psychological well-being which e.g. want to further invest in their mental health

will be excluded. Thus, it is not possible to say whether SISU is useful in people with already high psychological well-being. Furthermore, new technologies like chatbots could be especially attractive to the youth, which were excluded as a population. Thus it remains unclear if SISU could be useful in younger people living with low psychological well-being. Self-selection bias could lead to a population which has an internet affinity. Only participants with internet-access and email-address can be included in the intervention. Whereas this is probably not relevant for younger people, it might still be a potential reason for selection and limited generalizability, especially with regard to elder people. To rule out a potential gender bias due to a male or female software agent, SISU was conceptualised gender neutral so that members of all sexes feel equally addressed.

Usually, moderate to high dropout rates are a problem within online interventions, which needs to be addressed in the planning of a study [99]. In our feasibility trial 39% of the participants dropped out during study progress (assessment dropout), which could be (partly) explained by organisational effort providing informed consent and unfulfilled expectations concerning the intervention or the interaction with SISU. Nonetheless, the dropout rate of 14% during the intervention with SISU (intervention dropout) is comparably low, which could be traced back to the responsiveness/guidance by SISU. Those have been shown to improve intervention adherence [100]. For the present trial we maintained these successfully tested techniques.

Another possible limitation is the use a waitlist control group. This can be associated with overestimation of effects compared to psychological placebo or no intervention [101]. If SISU shows its effectiveness compared to a waitlist control group, a next step should be to compare it with an active control group like e. g. participants receiving a pamphlet with instructions for doing mindfulness exercises at home. Furthermore, a potential methodological confound concerns blinding. Participants are not blinded towards the primary outcome and could possibly answer in a socially desirable way. However, as participants are unlikely to know the study team personally, test manager effects might be low. Another methodological problem could arise from assessment reactivity. Frequent assessments can trigger self-reflection which can lead to an incremental effect regardless of the intervention [102]. However, this is a general problem which can be particularly noticeable in control groups and in groups which receive low-threshold intervention offers.

Last but not least, the planned analyses are based on classic inferential statistics to test the significance of group differences. A sample size calculation (g*power) was performed to plan the sample size accordingly. However, recent evidence emphasises, that it might be fruitful not to test for differences from zero. Instead, Bayesian methods could be used. They allow discovering uncertainties of the effects of treatments instead of solemnly focusing on dichotomising evidence into significant and not significant [103]. If this trial points towards the

usefulness / effectiveness of SISU, future trials could substantiate results using Bayesian methods.

Ethics and Dissemination: This trial has been approved by the ethics committee of the University of Ulm (No. 448/18, 18.02.2019) and registered in the German Clinical Trials Register (DRKS-ID: DRKS00014933) on 25 April 2019. Written informed consent for participation in the study will be obtained from all participants prior to their involvement. Participants will receive written information on study conditions, data security, publication of anonymised results, voluntariness of participation and the right to leave the study at all times. They will also be informed that in case of study withdrawal, they will be able to decide whether they want their data to be included in the analysis or to be deleted. Additionally, participants will be asked for permission for the research team to share relevant data with people from regulatory authorities, where necessary. This trial will only involve the collection and storage of self-report data, not of biological specimens. Data collection will be pseudonymised and data will only be accessed by authorized study personnel obliged to secrecy. After data collection is completed, personalised information will be deleted and all data will be completely anonymised. All participant information will be stored securely in locked file cabinets and/or password-protected in a secured cloud storage with restricted access. All reports, data collection, and administrated forms will be identified by a coded ID number only to maintain participant confidentiality. All records that contain names or other personal identifiers, such as informed consent forms (supplementary file) will be stored separately from study records identified by ID number. Listings that link participant ID numbers to other identifying information will be stored in separate password-protected files with limited access. According to German law, data will only be shared with parties outside the project team in anonymised form. Trial results will be submitted for publication in a peer-reviewed journal and presented at conferences.

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Author contributions

EB had the idea of SISU. SISU was developed by the Department of Clinical Psychology and Psychotherapy and the Institute of Distributed Systems at Ulm University (lead developer DM, BE and EB). EB and HB designed and planned the study. EB and HB supervised the study. EB and LW operatively perform the study. EB drafted the manuscript, all other authors

critically revised the work for important intellectual content. All authors (HB, BE, DE, A-MK, NB, LW) approved the final version to be published and agree to be accountable for all aspects of the work.

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Declaration of interest

HB reports to have received consultancy fees and fees for lectures/workshops from chambers of psychotherapists and training institutes for psychotherapists in the e-mental-health context. A-MK has received fees for lectures/workshops from chambers of psychotherapists and health insurance companies. DE reports to have received consultancy fees/served in the scientific advisory board from several companies such as Minddistrict, Lantern, Schoen Kliniken and German health insurance companies. He is stakeholder of the Institute for health training online (GET.ON), which aims to implement scientific findings related to digital health interventions into routine care.

All other authors declare not to have competing interests.

Access to data and availability

All principal investigators will be given full access to the data sets. Data set will be stored on password-protected servers of university Ulm with restricted access. External researches may get access to the final trial dataset on request depending on to be specified data security and data exchange regulation agreements. To ensure confidentiality, data dispersed to any investigator or researcher will be blinded of any identifying participant information.

Abbreviations

ACT	Acceptance and commitment therapy
AQoL-8D	Inventory for the Assessment of Quality of Life
BFI-10	Short version of the Big Five Inventory
CES	Centrality of Event Scale
CEQ	Credibility/Expectancy Questionnaire
DRKS	Deutsches Register Klinischer Studien
ERQ	Emotion Regulation Questionnaire
FAH-II	Acceptance and Action Questionnaire-II
FS-D	Flourishing Scale
IMI	Internet-based intervention
IG	Intervention group
INEP	Inventory for the assessment of negative effects of psychotherapy
RCT	Randomised controlled trial
TAI-SF	Inventory of Technology Alliance – Online Therapy
TAS-20	Toronto Alexithymia Scale
WHO-5	Well-being-Scale
WL	Waiting List Control Group
ZUF-8	Client Satisfaction Questionnaire

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Figure Legends

Figure 1. Content and chronological structure of the study

Figure 2. Flowchart of the planned study procedure.

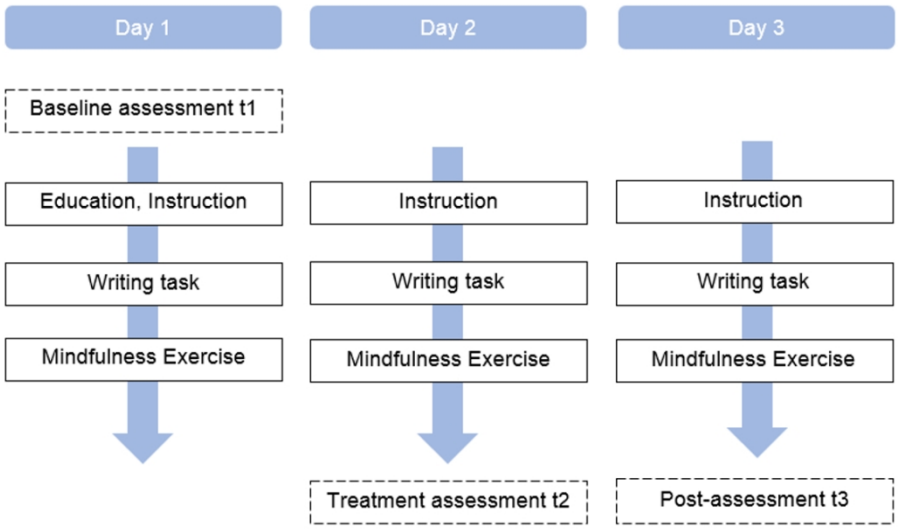

Figure 1. Content and chronological structure of the study

213x132mm (150 x 150 DPI)

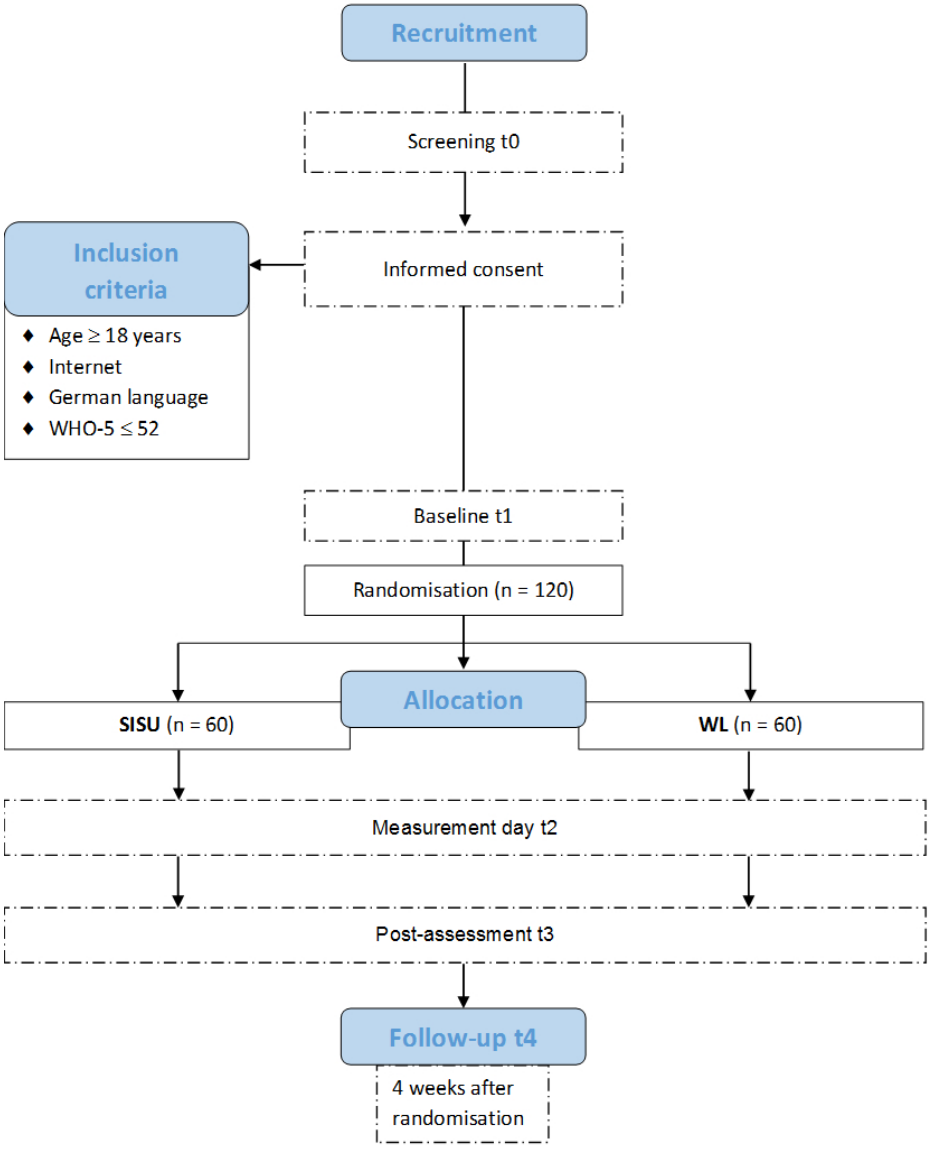

Figure 2. Flowchart of the planned study procedure.

175x226mm (120 x 120 DPI)

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Teilnehmendeninformation

» SISU – Eine randomisiert-kontrollierte Studie zur Evaluation eines Chatbots zur Darbietung einer Schreibintervention zur Steigerung des psychischen Wohlbefindens.«

Sehr geehrte Teilnehmerin, sehr geehrter Teilnehmer,

Wir möchten Sie einladen, an der folgenden Studie teilzunehmen. Die Universität Ulm führt ein Forschungsprojekt durch, in dessen Rahmen ein an der Universität Ulm entwickelter Chatbot überprüft werden soll. Wir möchten Sie einladen, einen innovativen Chatbot zur Steigerung psychischen Wohlbefindens zu testen und an vier kurzen Befragungen teilzunehmen.

WORUM GEHT ES IN DER STUDIE UND WELCHES ZIEL WIRD MIT DER DURCHFÜHRUNG DER STUDIE VERFOLGT?

Ein Chatbot ist ein Computer-Programm, das eine Konversation über ein Chat-Interface (Chat: Onlinekommunikation mit Hilfe eines Chats, Interface: Schnittstelle, an der der Austausch von Daten oder Steuersignalen erfolgt) mit einem Menschen hält. Der Chatbot leitet Sie dazu an, an drei aufeinanderfolgenden Tagen über ein emotional positives Lebensereignis zu schreiben. Das Schreiben über positive, autobiographische Lebensereignisse ist eine Form therapeutischen Schreibens und zielt darauf ab, emotionales Wohlbefinden zu steigern. Das Schreiben über emotionale Lebensereignisse wurde in zahlreichen Studien wissenschaftlich überprüft. Ziel der Studie ist die Untersuchung der Wirksamkeit und Akzeptanz des Chatbots. Durch Ihre Teilnahme leisten Sie einen entscheidenden Beitrag zur Weiterentwicklung eines Chatbots.

VORAUSSETZUNGEN FÜR DIE TEILNAHME:

- Sie sind mindestens 18 Jahre alt.
- Sie sind motiviert, einen Chatbot zum Schreiben über positive Lebensereignisse auszuprobieren und an drei aufeinanderfolgenden Tagen über ein autobiographisches, positives Lebensereignis zu schreiben.
- Sie sind bereit, an 4 Befragungen teilzunehmen.
- Sie verfügen über ein Smartphone und sind bereit, eine Ende-zu-Ende verschlüsselte Instant-Messaging Anwendung zu installieren.

STUDIENABLAUF:

Die erste Befragung enthält Angaben zu Ihrer Person (Geschlecht, Alter, etc.). Die drei nachfolgenden Befragungen bestehen aus Fragen zur Akzeptanz des Chatbots und zum Verbesserungspotenzial sowie aus Fragen zu Ihrem emotionalen und psychischen Wohlbefinden. Eine Befragung dauert ca. 10 Minuten.

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Wenn Sie sich bereit erklären, an der Studie teilzunehmen, senden Sie bitte die unterschriebene Einverständniserklärung zeitnah unterschrieben an uns zurück (z.B. postalisch oder eingescannt per Email an chatbot-studie@uni-ulm.de). Weitere Schritte:

Tag 1

Schritt 1: Nachdem wir die Einverständniserklärung erhalten haben, können Sie sich die App „WIRE“ installieren. Zusätzlich erhalten Sie den Link zur ersten Befragung.

Schritt 2: Sobald Sie die Online-Befragung durchlaufen haben, können Sie über die installierte App zum Chatbot „SISU“ aufnehmen. Die Interaktion mit dem Chatbot SISU dauert ca. 10-20 Minuten. SISU leitet Sie dazu an, über ein selbstgewähltes, positives Lebensereignis zu berichten. Im Anschluss daran, erhalten Sie von SISU eine Achtsamkeitsübung als Audio-Datei.

Tag 2 und Tag 3

Schritt 3: Sie nehmen Kontakt zum Chatbot auf. Die Interaktion mit dem Chatbot SISU dauert ca. 10-20 Minuten. SISU leitet Sie dazu an, über ein selbstgewähltes, positives Lebensereignis zu berichten. Im Anschluss daran, erhalten Sie von SISU eine Achtsamkeitsübung als Audio-Datei. Danach erfolgt eine weitere, kurze Befragung zu Ihrem Wohlbefinden.

Follow-up

Schritt 4: Etwa 4 Wochen später bitten wir Sie per E-Mail, die letzte Befragung auszufüllen.

Bei Teilnahme an der dritten und vierten Befragung haben Sie jeweils die Chance einen von zehn Amazon-Gutscheinen im Wert von 10 Euro zu gewinnen.

FREIWILLIGKEIT:
An diesem Forschungsprojekt nehmen Sie freiwillig teil. Ihr Einverständnis können Sie jederzeit und ohne Angabe von Gründen widerrufen, dann werden alle bis dahin studienbedingt erhobenen Daten gelöscht. Dieser eventuelle Widerruf hat keinerlei Auswirkungen für Sie.

ERREICHBARKEIT DES STUDIENTHERAPEUTEN:
Sollten während des Verlaufes des Forschungsprojektes Fragen auftauchen, so können Sie diese jederzeit an das Studienteam richten (E-Mail an: chatbot-studie@uni-ulm.de). Als Ansprechpartner können Sie jederzeit den Studienleiter Prof. Dr. Harald Baumeister (0731-50-32800) oder die Studienmitarbeiterin Eileen Bendig (M.Sc.) (0731-50-32807) erreichen. In Notfällen gilt folgende Nummer: 116 117.

VERSICHERUNG:
Während der Teilnahme an dem Forschungsprojekt genießen Sie Versicherungsschutz. Die an der Studie mitwirkenden Mitarbeiter sind über die Universität Ulm beim Land Baden-Württemberg haftpflichtversichert für den Fall, dass Sie durch deren Verschulden einen Schaden erleiden. Einen Schaden, der Ihrer Meinung nach auf dieses Forschungsprojekt zurückzuführen ist, melden Sie bitte unverzüglich dem Studienleiter.

SCHWEIGEPFLICHT/DATENSCHUTZ:
Ihre im Rahmen der Studie erhobenen Daten werden vertraulich behandelt. Alle Personen, welche Sie im Rahmen dieses Projektes betreuen, unterliegen der Schweigepflicht und sind auf das Datengeheimnis verpflichtet. Die Datenerhebung erfolgt pseudonymisiert. Die studienbezogenen Untersuchungsergebnisse sollen in anonymisierter Form in wissenschaftlichen Veröffentlichungen verwendet werden.

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Soweit es zur Kontrolle der korrekten Datenerhebung erforderlich ist, dürfen autorisierte Personen (z.B.: des Auftraggebers, der Universität) Einsicht in die studienrelevanten Teile der Krankenakte nehmen. Sofern zur

Einsichtnahme autorisierte Personen nicht der obengenannten ärztlichen Schweigepflicht unterliegen, stellen personenbezogene Daten, von denen sie bei der Kontrolle Kenntnis erlangen, Betriebsgeheimnisse dar, die geheim zu halten sind. Es existiert eine Referenzliste, die Ihren Namen, Adresse, Ihre Email-Adresse, Telefondaten und Ihren Zugangscode verbindet, was für die Zusammenführung der Daten erforderlich ist. Die Referenzliste ist nur den Projektmitarbeitern zugänglich und wird nach Abschluss der Datenerhebung, also am Ende der Rekrutierung (=letzte/r Teilnehmer/in in die Studie eingeschlossen), vernichtet. Das Ende der Rekrutierung und somit der Einschluss des letzten Teilnehmers in die Studie, erfolgt erst nach der Zusendung der korrekt ausgefüllten Einwilligungserklärung, welche Ihnen nach diesem Screening per E-Mail zugesendet wird, sowie der Durchführung der ersten Online-Befragung im Anschluss an dieses Screening. Nach Vernichtung der Referenzliste liegen die Daten nur noch in vollständig anonymisierter Form vor. Ein Rückschluss auf einzelne Teilnehmer/innen ist dann nicht mehr möglich.

Die in diesem Projekt für die Datenverarbeitung verantwortliche Person ist: Prof. Dr. Harald Baumeister, Leiter der Abteilung Klinische Psychologie und Psychotherapie, Universität Ulm, Albert-Einstein-Allee 47, 89091 Ulm, 0049 731-50-32800, E-Mail: Harald.Baumeister@uni-ulm.de. Bei Fragen zur Nutzung oder Verarbeitung Ihrer Daten wenden Sie sich bitte an den/die:

Datenschutzbeauftragte/n des lokalen Studienzentrums Universität Ulm:
Universität Ulm, Helmholtzstr. 16, 89081 Ulm, Telefonnummer.: 0731 50 - 25114,
E-Mail: datenschutz@uni-ulm.de

Falls Sie Bedenken oder Beschwerden hinsichtlich der Verarbeitung Ihrer Daten haben, wenden Sie sich bitte an die Datenschutz-Aufsichtsbehörde Ihres Studienzentrums: Die entsprechenden Kontaktdaten finden Sie auf der Internetseite des Landesbeauftragten für Datenschutz und Informationsfreiheit Baden-Württemberg:
https://www.baden-wuerttemberg.datenschutz.de/dsb-online-melden/

Universität Ulm
Institut für Psychologie und Pädagogik
Abteilung für Klinische Psychologie und Psychotherapie
Mit uns im Gleichgewicht
z. Hd. Lina Braun
Albert-Einstein-Allee 47
89081 Ulm

Prof. Dr. Harald Baumeister

Eileen Bendig

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EINWILLIGUNGSERKLÄRUNG

» SISU – Eine randomisiert-kontrollierte Studie zur Evaluation eines Chatbots zur Darbietung einer Schreibintervention zur Steigerung des psychischen Wohlbefindens.«

Inhalt, Vorgehensweise, Risiken und Ziel des obengenannten Forschungsprojektes sowie die Befugnis zur Einsichtnahme in die erhobenen Daten hat mir …….ausreichend erklärt.

Ich hatte zusätzliche Fragen:
……

……

Ich hatte Gelegenheit Fragen zu stellen und habe hierauf Antwort erhalten.

Ich hatte ausreichend Zeit, mich für oder gegen die Teilnahme am Projekt zu entscheiden.

Eine Kopie der Patienteninformation und Einwilligungserklärung habe ich erhalten.

Ich willige in die Teilnahme am Forschungsprojekt ein.

.....
(Name Teilnehmer/in)

....
Ort, Datum (Unterschrift Teilnehmer/in)

INFORMATION UND EINWILLIGUNGSERKLÄRUNG ZUM DATENSCHUTZ

Bei wissenschaftlichen Studien werden persönliche Daten und medizinische Befunde über Sie erhoben. Die Speicherung, Auswertung und Weitergabe dieser studienbezogenen Daten erfolgt nach gesetzlichen Bestimmungen und setzt vor Teilnahme an der Studie folgende freiwillige Einwilligung voraus:

1. Ich erkläre mich damit einverstanden, dass im Rahmen dieser Studie erhobene Daten/ Krankheitsdaten auf Fragebögen und elektronischen Datenträgern aufgezeichnet und ohne Namensnennung verarbeitet werden
2) Außerdem erkläre ich mich damit einverstanden, dass eine autorisierte und zur Verschwiegenheit verpflichtete Person (z.B.: des Auftraggebers, der Universität) in meine erhobenen personenbezogenen Daten Einsicht nimmt, soweit dies für die Überprüfung des Projektes notwendig ist. Für diese Maßnahme entbinde ich den Arzt von der ärztlichen Schweigepflicht.
3) Ich habe verstanden, dass ich das Recht habe, Auskunft (einschließlich unentgeltlicher Überlassung einer Kopie) über die mich betreffenden personenbezogenen Daten zu erhalten sowie deren Berichtigung oder Löschung zu verlangen.

Ich willige in die die beschriebene Verwendung meiner Daten ein.

.....
(Name Teilnehmer/in)

....
Ort, Datum (Unterschrift Teilnehmer/in)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	0
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	19

Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	0,19
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	n/a
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	19
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	10
Objectives	#7	Specific objectives or hypotheses	5,6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	7
Methods: Participants,			

interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8f
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	8f
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7f
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7f, fig.2
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including	15

		clinical and statistical assumptions supporting any sample size calculations	
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate	11ff, 19

		measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	8f, 19
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	20
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these	16

		interim results and make the final decision to terminate the trial	
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	2, 19
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	1
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7, 17
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
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Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	19
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	19
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

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Based on the SPIRIT guidelines.

Instructions to authors

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Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
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Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13,17

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	13,17
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a