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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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28 **ABSTRACT**

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

53 **Strengths and limitations of this study:**

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

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

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

66 INTRODUCTION

67 The global direct and indirect economic costs of mental disorders are estimated at 2.5 trillion
68 US \$ [1]. Thus, untreated mental disorders are a public health concern worldwide. However,
69 the majority of individuals living with mental disorders do not receive any health care supply
70 [2–4]. In Europe, only about 25% of people with mental disorders receive professional
71 treatment [5].

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

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

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

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

1
2
3 102 disadvantages of conventional computer program-based IMIs (e.g.,[37]. Amongst others, they
4 103 could show human-like, immediate responses with regards to user input [38].

6
7 104 A software agent or “chatbot” is a computer program that can hold a fully automated text-based
8 105 conversation in real-time with people via a chat-interface (e.g., smartphone application) by
9 106 using a natural language style [38]. The growing interest and body of research about software
10 107 agents [39,40] is realised in various populations and contexts, such as problem solving and
11 108 stress [41–43]. In the context of clinical psychology and psychotherapy, research on software
12 109 agents is sparse [44] but could create opportunities for the field regarding the provision of
13 110 mental health services. Software agents could be used to convey therapeutic contents and
14 111 brief interventions [45,46]. Establishing contact to a software agent might not be as stigmatising
15 112 as using formal mental health services like starting a face-to-face therapy or asking a general
16 113 practitioner for possibilities of mental health care [47]. Furthermore, they are flexible regarding
17 114 location and time [48], can be used anonymously [49,50] and provide personalization through
18 115 implicit customization [51]. Therefore, software agents could help to overcome barriers and
19 116 provide psychological and health behaviour change interventions on a large scale in the future.

20
21 117 Current mental health software agents are primarily based on cognitive behavioural therapy
22 118 [44]. However, other popular approaches with proven effectiveness in face-to-face settings
23 119 could also readily be realized in a digital form, such as writing interventions [52] and
24 120 acceptance and commitment-based approaches [53].

25
26 121 Writing with the aim of improving health has a long history [54]. In the current literature, the
27 122 labelling of this kind of intervention varies: Terminology includes expressive writing [55],
28 123 benefit-finding writing [52], or therapeutic writing (e.g., [56]). Regardless of terminology, the
29 124 writing intervention to be investigated in this study will refer to the process of freely and
30 125 emotionally writing about a positive personal life event without paying attention to spelling or
31 126 grammar. The call to write about personal life events, to tell a story, seems to go straight at the
32 127 centre of subjective experiences [57], which in turn is the main medium in traditional face-to-
33 128 face therapy. It has been shown that writing interventions can be highly time- and cost-efficient
34 129 [58]. A recent meta-analysis shows that writing interventions can help to improve general
35 130 psychological health (SMD=-0.46, 95% CI -.86, -0.06) [59]. Finally, a meta-analysis from Bolier
36 131 and colleagues[60] found an effect of Cohen’s $d = 0.34$ (95% CI 0.22, 0.45) for positive
37 132 interventions to uplift cognitive and/or affective appraisal of one’s life as a whole and $d=0.20$
38 133 (95% CI 0.09, 0.30) optimal functioning including mastery, hope and purpose in life.

39
40 134 Acceptance and Commitment Therapy (ACT) [61] aims at acceptance, mindfulness and value-
41 135 based living and has been found to be effective in the prevention of stress and the increase of
42 136 well-being [27,62]. The efficacy of ACT-based interventions in general and ACT-based IMIs in
43 137 particular has been indicated in a number of studies and systematic reviews. Within a

1
2
3 138 randomised-controlled trial, Fledderus and colleagues (2012) investigated an ACT-based IMI
4 139 for people living with depression. The authors found significant reductions in depression,
5 140 anxiety, fatigue, experiential avoidance and improvements in positive mental health, compared
6 141 to a waitlist control condition (effect sizes Cohen's $d = 0.51$ to 1.00) [29]. In their meta-analysis,
7 142 Brown and colleagues[63] examined 10 randomised controlled trials investigating the
8 143 effectiveness of ACT in the treatment of depressive or anxiety symptoms and well-being in
9 144 adult populations. ACT interventions were compared to passive control groups (N=3), active
10 145 control groups (N=4) or both (N=3). The authors found small effect sizes regarding the
11 146 improvement of depression ($g = 0.24$, 95% CI: 0.04 - 0.45) whilst the heterogeneity of
12 147 conditions and outcome measures on anxiety and well-being was too high to draw firm
13 148 conclusions. Spijkerman and colleagues [28] examined 15 randomised controlled trials in
14 149 adults with various mental problems and healthy populations. Mindfulness interventions, of
15 150 which the authors include ACT, were compared to passive control groups (N=10), active
16 151 control groups (N=5) or both (N=2). The authors found small to medium effect sizes concerning
17 152 the improvement of depression ($g = 0.29$, 95% CI: 0.13 - 0.46), anxiety ($g = 0.22$, 95% CI: 0.05
18 153 - 0.39) and well-being ($g = 0.23$, 95% CI: 0.09 - 0.38) [28].

19 154 We developed a software agent called SISU (**S**oftware agent providing an **I**ntervention for **S**elf-
20 155 help to **U**plift psychological well-being and finnish word for inner strength) with the aim to
21 156 provide an easily deployable software agent that improve peoples' well-being. Therefore, SISU
22 157 combines therapeutic writing and acceptance- and commitment-based principles. Results of a
23 158 feasibility trial on SISU [64] showed that SISU is feasible in terms of user acceptance and the
24 159 potential of the software agent to deliver a brief writing intervention. Thus SISU is feasible to
25 160 be implemented within a confirmatory clinical trial. Hence, the present study is designed to
26 161 investigate the clinical effectiveness and acceptance of the Software agent SISU thereby
27 162 focussing on the following specific research questions:

- 28 163 1. Is SISU effective in uplifting psychological well-being compared to the WL at T3 (primary
29 164 outcome)?
- 30 165 2. Is SISU effective regarding the secondary outcomes flourishing, quality of life, and
31 166 psychological flexibility compared to the WL at T3?
- 32 167 3. Which factors are associated with, moderate or mediate the effects of SISU?
- 33 168 4. Is the intervention associated with side effects?
- 34 169 5. What is the level of acceptance (satisfaction, adherence) with the intervention?
- 35 170 6. Does SISU have the potential to act as a therapeutic agent?

171 **METHODS**

172 **Study Design**

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

179 The present study is conducted and will be reported in accordance with the CONSORT 2010
180 guidelines for RCTs [65] and the guidelines for executing and reporting IMI research [66]. The
181 study protocol follows recommendations of the SPIRIT 2013 Checklist for clinical trial protocols
182 [67].

183 **Recruitment**

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

195 **Eligibility criteria**

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

199 **Study Procedures**

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

1
2
3 205 baseline questionnaire (t1) at unipark.de via email. Afterwards, participants will learn about
4 206 their group membership. The IG will get in contact with SISU and the intervention using the
5 207 end-to-end encrypted online messaging app “Wire” after finishing baseline (t1). SISU guides
6 208 participants through a writing intervention on three consecutive days using a standardised
7 209 conversation script. Each writing intervention is automatically followed by an assessment.
8 210 Subjects who are part of the WL will receive access to SISU four weeks after randomisation.
9 211 If participants complete questionnaires for t3 and t4 they will each time get the chance to win
10 212 a 10€ gift card for Amazon as a monetary incentive to promote retention and follow-up
11 213 completion.

17 18 214 **Randomisation and blinding**

19
20 215 Participants will be randomised to either IG or WL. An academic assistant (JM) from the
21 216 Department of Clinical Psychology and Psychotherapy at the University Ulm, not otherwise
22 217 involved in the trial and blinded towards all further procedures, will perform the allocation. A
23 218 permuted block randomisation with 4, 6, 8 and 12-block-size and an allocation ratio of 1:1 will
24 219 be used. The randomisation list will be created by a well-accepted website
25 220 (<https://www.sealedenvelope.com>). Whereas blinding of participants is not possible, data
26 221 collectors and data analysts are blinded regarding group membership.

31 32 222 **Intervention**

33
34 223 The intervention consists of the interaction with a software agent (SISU) that provides a brief
35 224 intervention. The interaction will be implemented using the online messaging service “Wire”.
36 225 The writing instruction provided by SISU is based on the paradigm of positive expressive or
37 226 narrative writing (notions are used synonymously) as well as acceptance and commitment
38 227 therapy [ACT; 69]. The software agent was developed at Ulm University. The version of SISU
39 228 used for this study was improved through participant feedback collected in the feasibility trial
40 229 [64]. Revisions included the enrichment of the instruction for writing about positive life events
41 230 with elements of ACT (more mindfulness exercises, authenticity of the dialog through reduction
42 231 of repetitions, interactions on reported life events) and elements for the reconstruction of
43 232 narrative identity. In its core, the software agent application remains the unmodified version of
44 233 the one used in the feasibility trial.

45
46 234 Using Wire Services SDK enables programmatic end-to-end encrypted communication with
47 235 other Wire users. Thanks to this encryption, messages sent by SISU or participants are not
48 236 accessible by third parties, including the service provider. We further protect participation data
49 237 by hosting SISU on premises and by encrypting the data at rest, thus limiting the access to our
50 238 research group. The communication logic is implemented as a finite-state machine. Our SISU
51 239 implementation parses incoming messages based on a fixed set of rules and responds with

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

244 SISU guides participants through the intervention on three consecutive days, mimicking a
 245 human conversational style. Participants are guided to write each day at the same time for 10-
 246 20 minutes about a self-chosen autobiographical, positive life event. The intervention structure
 247 is basically the same over the three days. However, on day 1 there is psychoeducation in the
 248 beginning additionally. The instructions for the writing tasks are followed by the narratives of
 249 the participants. Participants are instructed to write about a meaningful, outstanding positive
 250 life event on day 1 and about an outstanding positive event from adulthood on day 2. On day
 251 3 participants are guided to write about their best possible future. The paradigm of therapeutic
 252 writing is supplemented with ACT-based mindfulness exercises and metaphors. After the
 253 writing task, SISU encourages participants to experience the positive emotions due to the
 254 reported event in the present moment. Mindfulness exercises are provided by an audio file
 255 right after the writing intervention, whilst ACT-metaphors are integrated into the conversational
 256 content. Participants are encouraged to practice on a daily basis. To increase adherence, SISU
 257 reminds participants at 24 hour intervals. More details on intervention contents can be derived
 258 from Table 1. For an illustration of content and chronological structure see Figure 1.

259 Table 1

260 *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

261 *Note.* ACT = Acceptance and Commitment Therapy

262 --please insert figure 1 around here--

1
2
3 263 The (ultra-)brief intervention rational of 3 days was chosen because we wanted to provide
4 264 participants with a brief possibility to do something for their mental well-being, despite their
5 265 busy everyday lives. Indeed, evidence suggests that brief writing interventions of e. g. only 1
6 266 week can increase emotional well-being even 6 months after the intervention [70], particularly
7 267 in case of interventions focussing on improving mental health rather than treating mental
8 268 disorders.

13 269 **Wait list control group**

14 270 Participants of the WL get access to the writing intervention provided by SISU four weeks after
15 271 randomisation. The intervention has the same content for both groups. Participants with a low
16 272 WHO-5 score (< 28) in the screening receive an automatised email with further information
17 273 about offers of the health care system.

22 274 **Administrative and technical support**

23 275 In case participants forget their individual ID or have other technical issues, they can make use
24 276 of the study team via email for technical support at every point during the training.

27 277 **Outcome Assessment**

28 278 Screening for eligibility takes place at t0. Data for relevant outcomes will be collected prior to
29 279 the intervention (t1), one day after randomisation during the intervention (t2), two days after
30 280 randomisation (t3; intervention completed) and four weeks after randomisation (t4; follow-up).
31 281 It is not necessary that participants have already finished the intervention to participate in the
32 282 t1-survey. Demographic data and personality traits are measured once (t1). A flow chart of the
33 283 study can be seen in Figure 2. The outcomes, their measurement instrument and points of
34 284 assessment are shown in Table 2.

40 285 --please insert figure 2 around here--

286 Table 2

287 *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	-

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

292

1
2
3 293 Screening, t0
4

5 294 The short 5-item Well-being-Scale (WHO-5) is administered to assess the subjective well-
6
7 295 being of participants in the last two weeks [71]. Subjects can answer on a 6-point-Likert scale
8
9 296 (5= "All of the time", 4 = "Most of the time", 3 = "More than half the time", 2 = "Less than half
10
11 297 the time", 1 = "Some of the time", 0 = "At no time"). The sum of raw scores (range: 0-25) is
12
13 298 multiplied with 4 and produces a total score (range: 0-100) with 0 representing the worst
14
15 299 imaginable well-being to 100 representing the best imaginable well-being [71]. Scores \leq 52
16
17 300 indicate a low, scores \leq 28 indicate a very low psychological well-being. Topp and
18
19 301 colleagues[71] mention a comparable cut-off score of \leq 50. The WHO-5 shows a sensitivity of
20
21 302 0.93 and a specificity of 0.83 in the detection of depression [71]. Additionally, the screening
22
23 303 includes age, sex, contact information and the sufficient knowledge of German language.

24 304 Demographic data

25 305 The following information will be collected from each participant at T1: sex, age, education,
26
27 306 nationality, German speaking skills, relationship status, profession and highest educational
28
29 307 attainment.

30 308 Primary outcome

31 309 *Psychological well-being*

32 310 Primary outcome is psychological well-being at t3 measured by the Well-being-Scale [71]
33
34 311 already described in the section for screening.

35 312 Secondary outcomes and covariates

36 313 *Emotional well-being.*

37 314 The German version of the Flourishing Scale [FS-D; 72] is a measure of psychosocial well-
38
39 315 being and personal growth and development (i.e., flourishing). Each of the 8 items is rated on
40
41 316 a 7-point-Likert scale ranging from 1 = "strongly disagree" to 7 = "strongly agree". A sum score
42
43 317 is computed with higher scores indicating higher flourishing. With a Cronbach's α of 0.87 the
44
45 318 scale shows good internal consistency [72].

46 319 *Psychological flexibility*

47 320 The German version of the Acceptance and Action Questionnaire-II [73] is a general measure
48
49 321 for psychological inflexibility and consists of 7 items. On a 7-point-Likert scale that ranges from
50
51 322 0 = "never true" to 6 = "always true", the questionnaire assesses a person's willingness to
52
53 323 experience unwanted thoughts and feeling and a person's ability to act despite the presence
54
55 324 of undesirable thoughts and feelings. In this study items were reverse coded to assess
56
57 325 psychological flexibility. Sum scores (range: 0-42) are computed with higher scores indicating
58
59
60

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

328 *Quality of life*

329 With the help of the inventory Assessment of Quality of Life (AQoL-8D) participants quality of
330 life is recorded [74]. Each of 35 items loads on one of eight dimensions of quality of life and is
331 rated on 4- to 6-point-Likert scales. For analysis there is an algorithm which can be used for
332 quality of life in general as well as for particular sub dimensions. In total, scores between 0 and
333 1 are possible. Standard values are available. Reliability of AQoL-8D is very good with
334 Cronbach's α of 0.96 [74].

335 *Side-effects*

336 Subjective adverse events of the intervention are recorded with the 15-item inventory for the
337 assessment of negative effects of psychotherapy [75]. Items are rated on a 4-point-Likert scale
338 (0 = "no agreement" to 3 = "total agreement") or a bipolar 7-point scale. Adverse effects in
339 social life, intrapersonal factors or work-related situations are taken in consideration. The
340 original inventory with 32 items has an internal consistency of $\alpha = 0.95$ [76].

341 *Satisfaction with the intervention*

342 To assess the global satisfaction with the intervention a revised version of the German version
343 of the Client Satisfaction Questionnaire [ZUF-8; 77] was used. Participants rate their
344 satisfaction on a 4-point-Likert scale for each of the 8 items. A sum score is computed. Higher
345 scores indicate higher satisfaction. Internal consistency of the ZUF-8 is very good with $\alpha = 0.90$
346 [78]. A study on reliability and validity of assessing user satisfaction with internet-based
347 interventions indicates good overall psychometric quality of the measure [79].

348 *Post-Writing Questionnaire*

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

354 *Open questions*

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

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3 358 *Questions for the future of software agents*

4 359 The final survey (t3) will assess the behavioural intention to use a software agent in the
5 360 future or recommend one to friends as well as the future performance expectancy of software
6 361 agents providing psychological interventions to uplift psychological well-being in three open
7 362 questions. Participant responses will be analysed on a qualitative basis.

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11 363 Moderators/Mediators

12 364 *Centrality of events*

13 365 The Centrality of Event Scale [CES; 82] assesses the centrality of an event to a person,
14 366 differentiating three independent characteristics. Whether the event is seen as (1) a reference
15 367 point for everyday inferences, (2) a turning point in the life story and (3) as an element of the
16 368 personal identity. Participants rate the 7 items of the short-term version on a 5-point-Likert
17 369 scale from 1 = "totally disagree" to 5 = "totally agree". With a Cronbach's α of 0.88 the scale
18 370 shows high internal consistency [82].

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21 371 *Personality*

22 372 To assess the Big Five personality traits of participants the short version of the Big Five
23 373 Inventory [BFI-10; 83] is used. Each of the five personality dimensions is measured with two
24 374 items depicting either the positive or the negative pole of the spectrum. Participants rate the
25 375 items on a 5-point-Likert scale from 1 = "fully disagree" to 5 = "fully agree". The questionnaire
26 376 shows average retest-reliabilities ranging from 0.56 to 0.60 [83].

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29 377 *Alexithymia*

30 378 The German version of the Toronto Alexithymia Scale [TAS-20; 84] assesses alexithymia of
31 379 participants. Each of the 20 items is rated on a 5-point-Likert scale ranging from 1 = "strongly
32 380 disagree" to 5 = "strongly agree". The German version assesses 3 factors [85]: "difficulties in
33 381 identifying and describing feelings", "external oriented thinking" and "importance of emotional
34 382 introspection". For each dimension sum scores are computed with higher scores each
35 383 indicating higher manifestations of alexithymia. Internal consistency of the scale is good with
36 384 a $\alpha = 0.80$ [85].

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39 385 *Emotion regulation*

40 386 The Emotion Regulation Questionnaire [ERQ; 86] is a 10-item questionnaire measuring
41 387 positive and negative feelings as well as their regulation. Items refer to two different emotion
42 388 regulation strategies: Reappraisal and suppression. Participants rate the items on a scale from
43 389 1 = "strongly disagree" to 7 = "strongly agree". Means show the preference for each strategy
44 390 indicating higher preference at higher mean scores. Internal consistencies are acceptable to
45 391 good and differ from $\alpha = 0.75$ to $\alpha = 0.82$ [86].

392 *Treatment expectancy*

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

398 *Technology alliance*

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

405 **Data privacy and ethics**

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

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

422 **Sample Size**

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

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3 426 based mindfulness interventions, Spijkerman and colleagues [28] found a somewhat smaller
4 427 effect of $g=0.23$.

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7 428 Based on these previous findings, a small effect size of $d = 0.30$ is expected. Power analysis
8 429 for an ANOVA with repeated measures with g-power (<http://gpower.hhu.de/>) recommends a
9 430 sample size of at least 60 participants per group ($N=120$) on the assumption of two-tailed
11 431 testing, an alpha error $\alpha = 0.05$ and power $1-\beta = 0.90$.

14 432 **Statistical Analysis**

15 433 Patterns of missing data will be investigated, and analyses will be adjusted accordingly (e.g.,
16 434 MI or FIML). All analyses will be conducted on a two-sided level of significance ($\alpha=.05$).
18 435 Participant characteristics will be described descriptively.

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21 436 All statistical analyses will be performed based on the intention-to-treat (ITT) principle.
22 437 Additional per protocol analyses will be conducted in order to examine the effects of SISU in
23 438 case of patients adhering to the intervention protocol. Participants who completed at least 66%
24 439 of the intervention are defined as intervention completer (=per protocol).

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28 440 The primary outcome will be analysed using linear regression models at T3 as dependent
29 441 variable and the baseline value as covariate, adjusting for sex and age. To analyse between-
30 442 group effect sizes, standardised mean differences with 95% confidence intervals will be
31 443 calculated for post-treatment (t3) and follow-up (t4). Secondary outcomes will be analysed
32 444 accordingly.

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36 445 Exploratory mediation and moderator analyses involving the primary and secondary outcomes
37 446 as well as demographic data will be conducted. Moderator and subgroup analyses are aimed
38 447 for in case of a sufficiently large sample size.

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43 449 For the planned exploratory moderator analyses, regression models will be employed. Initially,
44 450 each potential moderator described under "Covariates" will be analysed in a separate
45 451 regression model. The primary outcome psychological well-being at t3 will be the dependent
46 452 variable. Predictors will comprise group, the moderator variable and the interaction of group
47 453 and moderator. In a next step, a comprising model of all identified moderators will be tested.
48 454 Mediation analyses will be conducted according to the principles of time-lagged mediation [90].
49 455 Psychological well-being at t3 will be the outcome variable. Group will be chosen as
50 456 independent variable, whereas the variables defined in the section "Potentials mediators" will
51 457 constitute the respective mediating variables. No interim analyses will be applied to the data.

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459 Discussion

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

465 The proposed study can be characterized by several strengths. First, our software agent SISU
466 was successfully tested within a feasibility trial of Bendig and colleagues in preparation,[64]
467 and provides elements of established approaches [69,88]. Therefore, we consider SISU to
468 provide an eligible intervention and the potential to uplift psychological well-being in
469 participants. To our knowledge, there are no known risks or negative effects for internet-based
470 intervention in the context of self-help interventions to uplift psychological well-being. Still, we
471 will systematically record via questionnaire (INEP) if and which negative effects of our IMI might
472 appear. This will contribute to the still understudied area of research on risks and side effect
473 [91] and therefore help make future IMIs safer.

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

483 Another strength concerns our recruitment strategy. We will be able to reach students from
484 many different universities in Germany, Austria and Switzerland. The StudiCare website offers
485 [68]recruitment possibilities at more than 15 cooperating colleges by sending out circular
486 emails to all their students on a regular basis, informing them about all of their StudiCare online
487 trainings (usually in the context of their student counselling or health management).
488 Furthermore, recruitment takes place on various social media platforms to ensure the
489 enrollment of a wide-ranged population of participants.

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

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3 495 intervention with SISU (intervention dropout) is comparably low, which could be traced back to
4 496 the responsiveness/guidance by SISU. Those have been shown to improve intervention
5 497 adherence [94]. For the present trial we maintained these successfully tested techniques.

8 498 Another possible limitation is the use a waitlist control group. This can be associated with
9 499 overestimation of effects compared to psychological placebo or no intervention [95]. If *SISU*
10 500 shows its effectiveness compared to a waitlist control group, a next step should be to compare
11 501 it with an active control group like e. g. participants receiving a pamphlet with instructions for
12 502 doing mindfulness exercises at home.

17 503 Furthermore, only participants with internet-access and email-address can be included in the
18 504 intervention. Whereas this is probably not relevant for younger people, it might still be a
19 505 potential reason for selection and limited generalizability, especially with regard to elder
20 506 generations.

24 507 **Conclusion**

26 508 Internet-based interventions aimed at the improvement of mental well-being have the potential
27 509 to improve the general mental health care situation substantially. The proposed brief writing
28 510 intervention that SISU enriches with mindfulness-based exercises and provides through a
29 511 software agent could be a widely practicable, low-threshold self-help way to support users in
30 512 increasing their psychological well-being with relatively little effort, when- and wherever they
31 513 are in need.

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39 516 Institute of Psychology and Education, Ulm University, Albert-Einstein-Allee 47, 89069 Ulm,
40 517 Germany.

43 518 **Author contributions**

45 519 EB had the idea of SISU. SISU was developed by the Department of Clinical Psychology and
46 520 Psychotherapy and the Institute of Distributed Systems at Ulm University (lead developer
47 521 DM, BE and EB). EB and HB designed and planned the study. EB and HB supervised the
48 522 study. EB and LW operatively perform the study. EB drafted the manuscript, all other authors
49 523 critically revised the work for important intellectual content. All authors approved the final
50 524 version to be published and agree to be accountable for all aspects of the work.

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58 527 SISU and the surveys as well as for helping with study recruitment. We kindly thank Jana Moos
59 528 for performing the allocation procedure.

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3 **529 Declaration of interest**

4 530 HB reports to have received consultancy fees and fees for lectures/workshops from chambers
5 531 of psychotherapists and training institutes for psychotherapists in the e-mental-health context.
6 532 AK has received fees for lectures/workshops from chambers of psychotherapists and health
7 533 insurance companies. DDE reports to have received consultancy fees/served in the scientific
8 534 advisory board from several companies such as Minddistrict, Lantern, Schoen Kliniken and
9 535 German health insurance companies. He is stakeholder of the Institute for health training online
10 536 (GET.ON), which aims to implement scientific findings related to digital health interventions
11 537 into routine care.

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18 538 All other authors declare not to have competing interests.

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20 **539 Access to data and availability**

21 540 All principal investigators will be given full access to the data sets. Data set will be stored on
22 541 password-protected servers of university Ulm with restricted access. External researches may
23 542 get access to the final trial dataset on request depending on to be specified data security and
24 543 data exchange regulation agreements. To ensure confidentiality, data dispersed to any
25 544 investigator or researcher will be blinded of any identifying participant information.

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31 **545 Patient and public involvement**

32 546 Patient and public involvement (PPI) representatives provide input to the present study in
33 547 several stages. Results of the feasibility trial on SISU (DRKS-ID: DRKS00014933) were used
34 548 to further develop and optimise study design and procedures. PPI representatives were
35 549 included in the intervention development to improve content, usability and design of SISU.
36 550 However, acceptance of SISU from the participants' perspective is a crucial outcome of the
37 551 study and both quantitative and qualitative methods are applied to capture acceptance and
38 552 side-effects. The dissemination plan of the study results includes presentations on international
39 553 conferences and publications in peer-reviewed journals.

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3 **554 Abbreviations**

4 555 ACT Acceptance and commitment therapy
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6 556 AQL-8D Inventory for the Assessment of Quality of Life
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8 557 BFI-10 Short version of the Big Five Inventory
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10 558 CES Centrality of Event Scale
11
12 559 CEQ Credibility/Expectancy Questionnaire
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14 560 DRKS Deutsches Register Klinischer Studien
15
16 561 ERQ Emotion Regulation Questionnaire
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18 562 FAH-II Acceptance and Action Questionnaire-II
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20 563 FS-D Flourishing Scale
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22 564 IMI Internet-based intervention
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24 565 IG Intervention group
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26 566 INEP Inventory for the assessment of negative effects of psychotherapy
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28 567 RCT Randomised controlled trial
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30 568 TAI-SF Inventory of Technology Alliance – Online Therapy
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32 569 TAS-20 Toronto Alexithymia Scale
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34 570 WHO-5 Well-being-Scale
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36 571 WL Waiting List Control Group
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38 572 ZUF-8 Client Satisfaction Questionnaire
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Figures

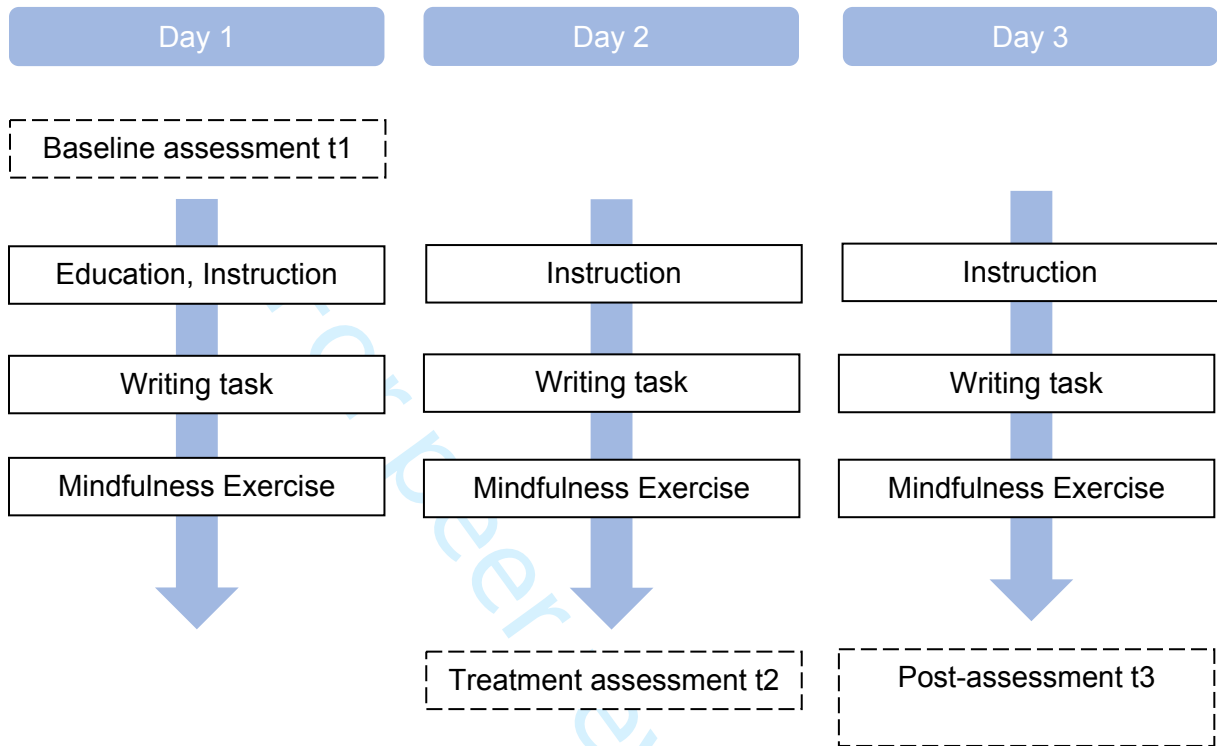


Figure 1. Content and chronological structure of the study

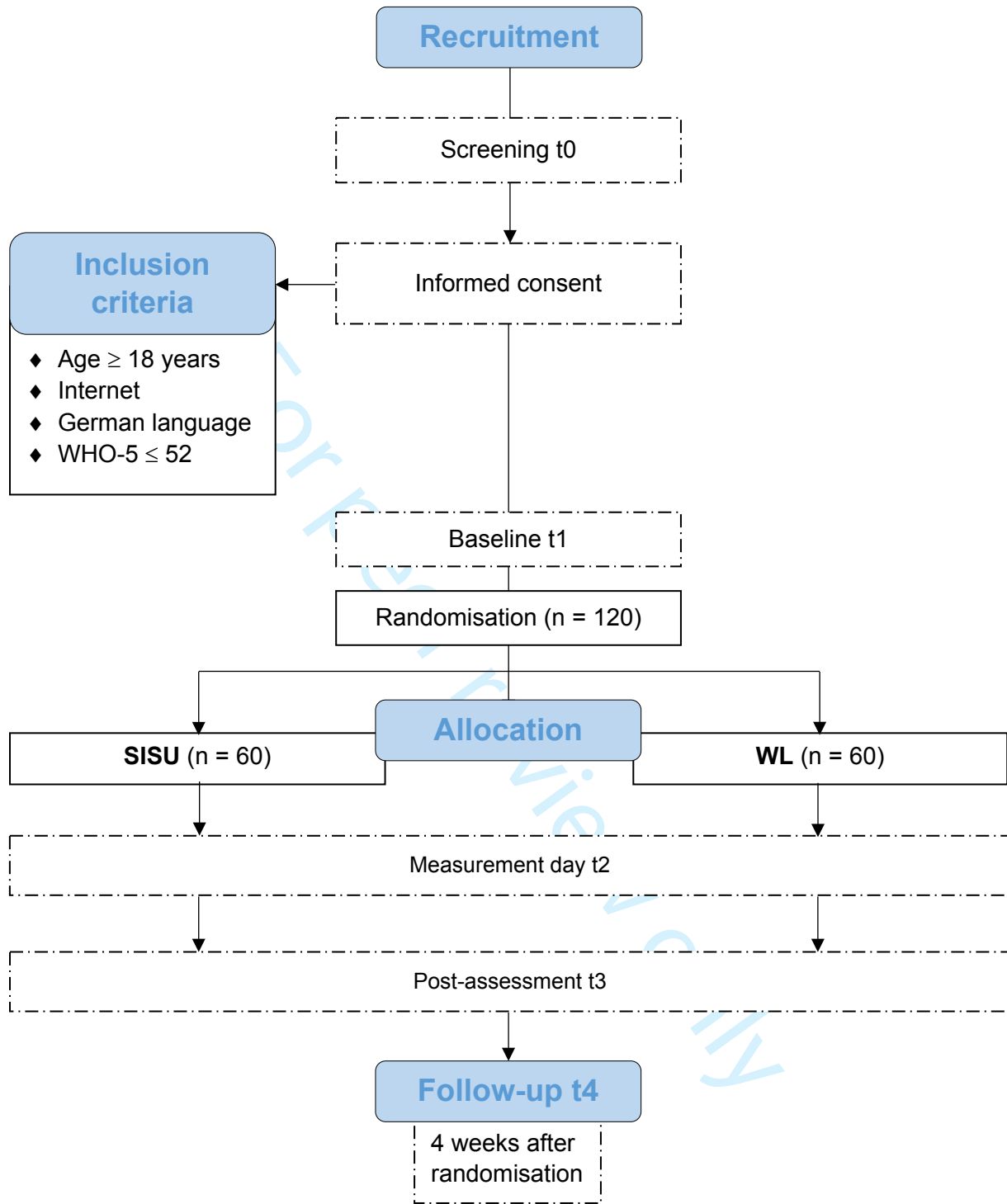


Figure 2. Flowchart of the planned study procedure.

For peer review only

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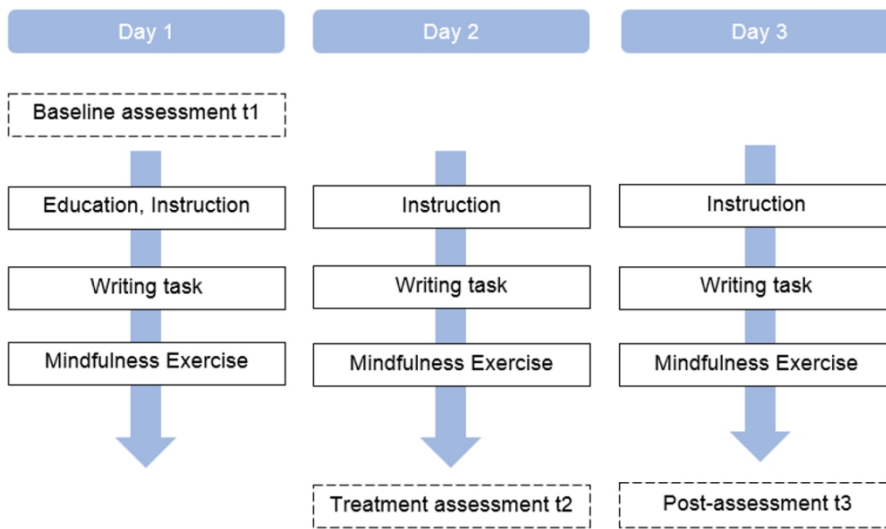


Figure 1. Content and chronological structure of the study

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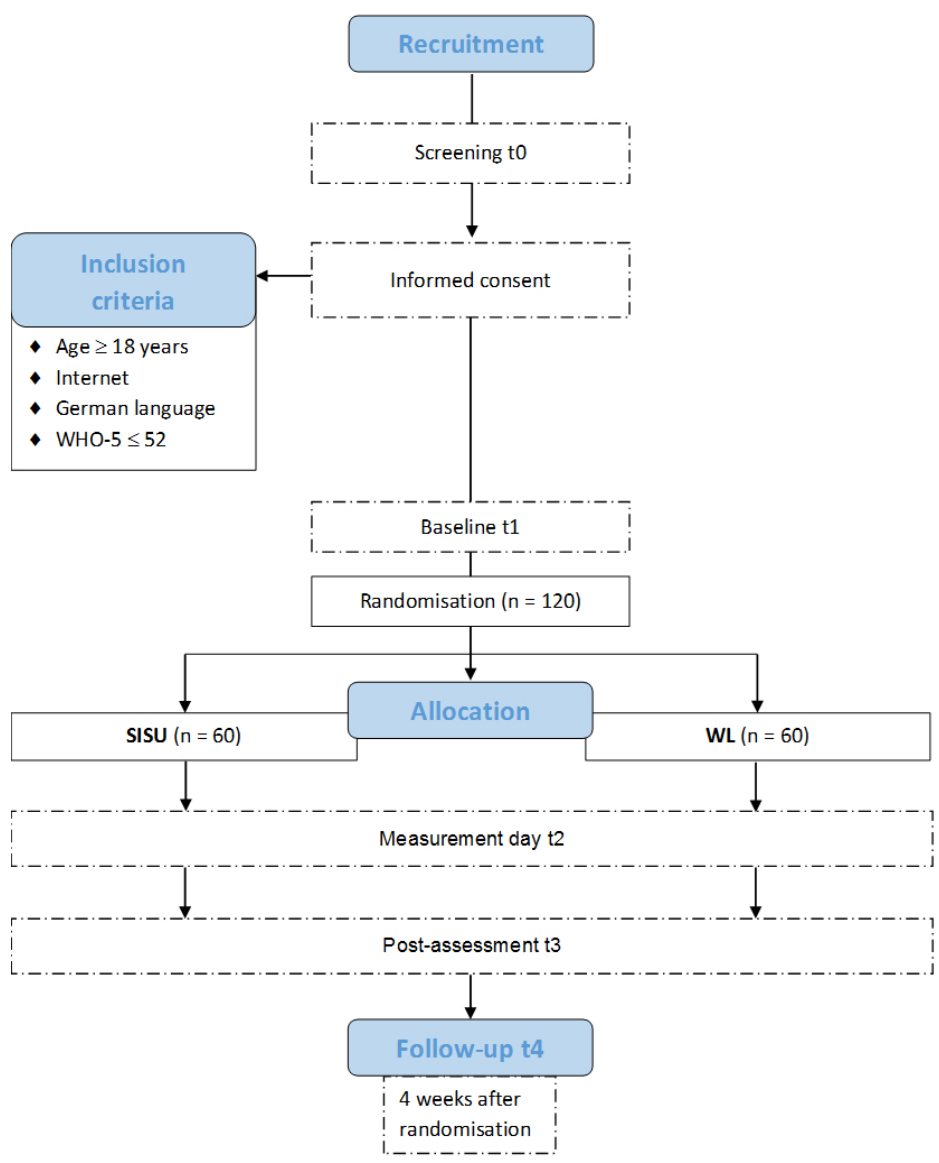


Figure 2. Flowchart of the planned study procedure.

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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 SPIRIT reporting 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

			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

1	Roles and	#5b	Name and contact information for the trial sponsor	n/a
2	responsibilities: sponsor			
3	contact information			
4				
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6	Roles and	#5c	Role of study sponsor and funders, if any, in study design; collection, management,	n/a
7	responsibilities: sponsor		analysis, and interpretation of data; writing of the report; and the decision to submit the	
8	and funder		report for publication, including whether they will have ultimate authority over any of	
9			these activities	
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13	Roles and	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee,	16
14	responsibilities:		endpoint adjudication committee, data management team, and other individuals or	
15	committees		groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
16				
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18				
19	Introduction			
20				
21	Background and	#6a	Description of research question and justification for undertaking the trial, including	2-4
22	rationale		summary of relevant studies (published and unpublished) examining benefits and harms	
23			for each intervention	
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25				
26	Background and	#6b	Explanation for choice of comparators	8
27	rationale: choice of			
28	comparators			
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32	Objectives	#7	Specific objectives or hypotheses	4
33				
34	Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial,	5
35			single group), allocation ratio, and framework (eg, superiority, equivalence, non-	
36			inferiority, exploratory)	
37				
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40	Methods: Participants,			
41	interventions, and			
42	outcomes			
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44				
45	Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of	5
46			countries where data will be collected. Reference to where list of study sites can be	
47			obtained	
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51	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for	5
52			study centres and individuals who will perform the interventions (eg, surgeons,	
53			psychotherapists)	
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56	Interventions:	#11a	Interventions for each group with sufficient detail to allow replication, including how	6f
57	description		and when they will be administered	
58				
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1	Interventions:	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial	6f
2	modifications		participant (eg, drug dose change in response to harms, participant request, or improving	
3			/ worsening disease)	
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6	Interventions: adherence	#11c	Strategies to improve adherence to intervention protocols, and any procedures for	7
7			monitoring adherence (eg, drug tablet return; laboratory tests)	
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10	Interventions:	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the	n/a
11	concomitant care		trial	
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14	Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable	9
15			(eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time	
16			to event), method of aggregation (eg, median, proportion), and time point for each	
17			outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is	
18			strongly recommended	
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22	Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts),	5f, fig.2
23			assessments, and visits for participants. A schematic diagram is highly recommended	
24			(see Figure)	
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28	Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was	13
29			determined, including clinical and statistical assumptions supporting any sample size	
30			calculations	
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33	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5
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36	Methods: Assignment			
37	of interventions (for			
38	controlled trials)			
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41	Allocation: sequence	#16a	Method of generating the allocation sequence (eg, computer-generated random	6
42	generation		numbers), and list of any factors for stratification. To reduce predictability of a random	
43			sequence, details of any planned restriction (eg, blocking) should be provided in a	
44			separate document that is unavailable to those who enrol participants or assign	
45			interventions	
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49	Allocation concealment	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially	6
50	mechanism		numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until	
51			interventions are assigned	
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55	Allocation:	#16c	Who will generate the allocation sequence, who will enrol participants, and who will	6
56	implementation		assign participants to interventions	
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1	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
2				
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4	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for	n/a
5	emergency unblinding		revealing a participant's allocated intervention during the trial	
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8	Methods: Data			
9	collection,			
10	management, and			
11	analysis			
12				
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15	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
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24	Data collection plan:	#18b	Plans to promote participant retention and complete follow-up, including list of any	6,7
25	retention		outcome data to be collected for participants who discontinue or deviate from intervention protocols	
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30	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
31				
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35	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
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39	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
40	analyses			
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43	Statistics: analysis	#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
44	population and missing			
45	data			
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48	Methods: Monitoring			
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51	Data monitoring: formal	#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
52	committee			
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1	Data monitoring: interim	#21b	Description of any interim analyses and stopping guidelines, including who will have	14
2	analysis		access to these interim results and make the final decision to terminate the trial	
3				
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5	Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously	11
6			reported adverse events and other unintended effects of trial interventions or trial	
7			conduct	
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10	Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will	n/a
11			be independent from investigators and the sponsor	
12				
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14	Ethics and			
15	dissemination			
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18	Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB)	5,13
19			approval	
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21				
22	Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility	1
23			criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial	
24			participants, trial registries, journals, regulators)	
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27	Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or	5, 15
28			authorised surrogates, and how (see Item 32)	
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31	Consent or assent:	#26b	Additional consent provisions for collection and use of participant data and biological	n/a
32	ancillary studies		specimens in ancillary studies, if applicable	
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35	Confidentiality	#27	How personal information about potential and enrolled participants will be collected,	13
36			shared, and maintained in order to protect confidentiality before, during, and after the	
37			trial	
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41	Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial	17
42			and each study site	
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45	Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual	13,17
46			agreements that limit such access for investigators	
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48	Ancillary and post trial	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who	n/a
49	care		suffer harm from trial participation	
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52	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate trial results to participants,	13,17
53	trial results		healthcare professionals, the public, and other relevant groups (eg, via publication,	
54			reporting in results databases, or other data sharing arrangements), including any	
55			publication restrictions	
56				
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1	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
2	authorship			
3				
4	Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and	13,17
5	reproducible research		statistical code	
6				
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8 Appendices

10	Informed consent	#32	Model consent form and other related documentation given to participants and	n/a
11	materials		authorised surrogates	
12				
13	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for	n/a
14			genetic or molecular analysis in the current trial and for future use in ancillary studies, if	
15			applicable	
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 21 completed on 10. June 2020 using <https://www.goodreports.org/>, a tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
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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 trial, 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].

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

10
11 A software agent or “chatbot” is a computer program that can hold a fully automated text-based
12 conversation in real-time with people via a chat-interface (e.g., smartphone application) by
13 using a natural language style [38]. The growing interest and body of research about software
14 agents [39,40] is realised in various populations and contexts, such as problem solving and
15 stress [41–43]. In the context of clinical psychology and psychotherapy, research on software
16 agents is sparse [44] but could create opportunities for the field regarding the provision of
17 mental health services. Software agents could be used to convey therapeutic contents and
18 brief interventions [45,46]. Establishing contact to a software agent might not be as stigmatising
19 as using formal mental health services like starting a face-to-face therapy or asking a general
20 practitioner for possibilities of mental health care [47]. Furthermore, they are flexible regarding
21 location and time [48], can be used anonymously [49,50] and provide personalization through
22 implicit customization [51]. Therefore, software agents could help to overcome barriers and
23 provide psychological and health behaviour change interventions on a large scale in the future.

24
25 Current mental health software agents are primarily based on cognitive behavioural therapy
26 [44]. However, other popular approaches with proven effectiveness in face-to-face settings
27 could also readily be realized in a digital form, such as writing interventions [52] and
28 acceptance and commitment-based approaches [53].

29
30 Writing with the aim of improving health has a long history [54]. In the current literature, the
31 labelling of this kind of intervention varies: Terminology includes expressive writing [55,56],
32 benefit-finding or positive writing [57,58] and therapeutic writing (e.g., [59]). Regardless of
33 terminology, the writing intervention to be investigated in this study will refer to the process of
34 freely and emotionally writing about a positive personal life event without paying attention to
35 spelling or grammar. The call to write about personal life events, to tell a story, seems to go
36 straight at the centre of subjective experiences [60], which in turn is the main medium in
37 traditional face-to-face therapy. In that, the term therapeutic writing will be used in this context
38 to acknowledge that the intervention refers to some kind of therapeutic work [61]. It has been
39 shown that writing interventions can be highly time- and cost-efficient [62]. A recent meta-
40 analysis shows that writing interventions can help to improve general psychological health
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2 (SMD=-0.46, 95% CI -.86, -0.06) [63]. Finally, a meta-analysis from Bolier and colleagues [64]
3 found an effect of Cohen's $d = 0.34$ (95% CI 0.22, 0.45) for positive interventions to uplift
4 cognitive and/or affective appraisal of one's life as a whole and $d=0.20$ (95% CI 0.09, 0.30)
5 optimal functioning including mastery, hope and purpose in life.
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9 Acceptance and Commitment Therapy (ACT) [65] aims at acceptance, mindfulness and value-
10 based living and has been found to be effective in the prevention of stress and the increase of
11 well-being [27,66]. The efficacy of ACT-based interventions in general and ACT-based IMIs in
12 particular has been indicated in a number of studies and systematic reviews. Within a
13 randomised-controlled trial, Fledderus and colleagues (2012) investigated an ACT-based IMI
14 for people living with depression. The authors found significant reductions in depression,
15 anxiety, fatigue, experiential avoidance and improvements in positive mental health, compared
16 to a waitlist control condition (effect sizes Cohen's $d = 0.51$ to 1.00) [29]. In their meta-analysis,
17 Brown and colleagues [67] examined 10 randomised controlled trials investigating the
18 effectiveness of ACT in the treatment of depressive or anxiety symptoms and well-being in
19 adult populations. ACT interventions were compared to passive control groups (N=3), active
20 control groups (N=4) or both (N=3). The authors found small effect sizes regarding the
21 improvement of depression ($g = 0.24$, 95% CI: 0.04 - 0.45) whilst the heterogeneity of
22 conditions and outcome measures on anxiety and well-being was too high to draw firm
23 conclusions. Spijkerman and colleagues [28] examined 15 randomised controlled trials in
24 adults with various mental problems and healthy populations. Mindfulness interventions, of
25 which the authors include ACT, were compared to passive control groups (N=10), active
26 control groups (N=5) or both (N=2). The authors found small to medium effect sizes concerning
27 the improvement of depression ($g = 0.29$, 95% CI: 0.13 - 0.46), anxiety ($g = 0.22$, 95% CI: 0.05
28 - 0.39) and well-being ($g = 0.23$, 95% CI: 0.09 - 0.38) [28].
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41 We developed a software agent gender neutrally called SISU (**S**oftware agent providing an
42 **I**ntervention for **S**elf-help to **U**plift psychological well-being and Finnish word ['sisu] for inner
43 strength) with the aim to provide an easily deployable software agent that improve peoples'
44 well-being. Therefore, SISU combines therapeutic writing and acceptance- and commitment-
45 based principles. Results of a feasibility trial on SISU [68] showed that SISU is feasible in terms
46 of user acceptance and the potential of the software agent to deliver a brief writing intervention.
47 Thus SISU is feasible to be implemented within a confirmatory clinical trial. Hence, the present
48 study is designed to investigate the clinical effectiveness and acceptance of the Software agent
49 SISU thereby focusing on the following specific research aims:
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56 1. To estimate the effects of SISU on psychological well-being compared to the WL at T3
57 (primary outcome).
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- 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?

For peer review only

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

1
2 or WL condition. Following, they will receive their individual ID and get an invitation for the
3 baseline questionnaire (t1) at unipark.de via email. Afterwards, participants will learn about
4 their group membership. The IG will get in contact with SISU and the intervention using the
5 end-to-end encrypted online messaging app “Wire” after finishing baseline (t1). SISU guides
6 participants through a writing intervention on three consecutive days using a standardised
7 conversation script. Each writing intervention is automatically followed by an assessment.
8 Participants who are part of the WL will receive access to SISU four weeks after randomisation.
9
10 If participants complete questionnaires for t3 and t4 they will each time get the chance to win
11 a 10€ gift card for Amazon as a monetary incentive to promote retention and follow-up
12 completion. All participants with a low WHO-5 score (< 28) in the screening receive an
13 automatised email with further information about offers of the health care system.
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20 **Randomisation and blinding**

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

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36 The software agent (SISU) provides a brief three-day intervention. The writing instruction
37 provided by SISU is based on the paradigm of therapeutic writing as well as acceptance and
38 commitment therapy [ACT; 73]. The version of SISU used for this study was improved through
39 participant feedback collected in the feasibility trial [68]. Revisions included the enrichment of
40 the instruction for writing about positive life events with elements of ACT (more mindfulness
41 exercises, authenticity of the dialog through reduction of repetitions, interactions on reported
42 life events) and elements for the reconstruction of narrative identity.
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48 SISU mimicks a human conversational style. Participants are guided to write each day at the
49 same time for 10-20 minutes about a self-chosen autobiographical, positive life event. On day
50 1 there is psychoeducation in the beginning. Then, instructions for the writing tasks are
51 followed by the narratives of the participants. Participants are instructed to write about a
52 meaningful, outstanding positive life event on day 1 and about an outstanding positive event
53 from adulthood on day 2. On day 3 participants are guided to write about their best possible
54 future. After the writing task, SISU encourages participants to experience the positive emotions
55 due to the reported event in the present moment. Mindfulness exercises are provided by an
56 audio file right after the writing intervention, whilst ACT-metaphors are integrated into the
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2 conversational content. Participants are encouraged to practice on a daily basis. To increase
3 adherence, SISU reminds participants at 24 hour intervals. More details on intervention
4 contents can be derived from Table 1. For an illustration of content and chronological structure
5 see Figure 1.
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9 Using the online messaging Wire Services SDK enables programmatic end-to-end encrypted
10 communication. Thanks to this encryption, messages sent by SISU or participants are not
11 accessible by third parties, including the service provider. We further protect participation data
12 by hosting SISU on premises and by encrypting the data at rest, thus limiting the access to our
13 research group. The communication logic is implemented as a finite-state machine. Our SISU
14 implementation parses incoming messages based on a fixed set of rules and responds with
15 an appropriate answer. In addition, SISU can react to external triggers. That is, external
16 triggers can lead to a status change of SISU. For example, the termination of a survey at
17 Unipark can cause a status change of SISU from “user is active” to “user finished the
18 interaction for the day”. External triggers can be (a) conversation timeouts (i.e., the participant
19 has not responded in a set time frame), (b) Unipark events (i.e., participant has completed an
20 external survey), and (c) scheduled events (e.g., daily participation reminder at pre-defined
21 time frames).
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32 Table 1

33 *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

51 *Note.* ACT = Acceptance and Commitment Therapy

52 --please insert figure 1 around here--

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56 The (ultra-)brief intervention rational of 3 days was chosen because we wanted to provide
57 participants with a brief possibility to do something for their mental well-being, despite their
58 busy everyday lives. Indeed, evidence suggests that brief writing interventions of e. g. only 1
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2 week can increase emotional well-being even 6 months after the intervention [74], particularly
3 in case of interventions focusing on improving mental health rather than treating mental
4 disorders.
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6 7 **Wait list control group**

8
9 Participants of the WL get access to the writing intervention provided by SISU four weeks after
10 randomisation. The intervention has the same content for both groups.
11

12 13 **Administrative and technical support**

14 In case participants forget their individual ID or have other technical issues, they can make use
15 of the study team via email for technical support at every point during the training.
16
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18 19 **Outcome Assessment**

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

1
2 higher psychological flexibility. The questionnaire shows good to excellent psychometric
3 properties in a German sample [77].
4

5 6 *Quality of life*

7 With the help of the inventory Assessment of Quality of Life (AQoL-8D) participants quality of
8 life is recorded [78]. Each of 35 items loads on one of eight dimensions of quality of life and is
9 rated on 4- to 6-point-Likert scales. For analysis there is an algorithm which can be used for
10 quality of life in general as well as for particular sub dimensions. In total, scores between 0 and
11 1 are possible. Standard values are available. Reliability of AQoL-8D is very good with
12 Cronbach's α of 0.96 [78].
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15 16 17 *Side-effects*

18 Subjective adverse events of the intervention are recorded with the 15-item inventory for the
19 assessment of negative effects of psychotherapy [79]. Items are rated on a 4-point-Likert scale
20 (0 = "no agreement" to 3 = "total agreement") or a bipolar 7-point scale. Adverse effects in
21 social life, intrapersonal factors or work-related situations are taken in consideration. The
22 original inventory with 32 items has an internal consistency of $\alpha = 0.95$ [80].
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27 28 *Satisfaction with the intervention*

29 To assess the global satisfaction with the intervention a revised version of the German version
30 of the Client Satisfaction Questionnaire [ZUF-8; 81] was used. Participants rate their
31 satisfaction on a 4-point-Likert scale for each of the 8 items. A sum score is computed. Higher
32 scores indicate higher satisfaction. Internal consistency of the ZUF-8 is very good with $\alpha = 0.90$
33 [82]. A study on reliability and validity of assessing user satisfaction with internet-based
34 interventions indicates good overall psychometric quality of the measure [83].
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39 40 *Post-Writing Questionnaire*

41 To assess therapeutic writing after every writing session the participants answer four questions
42 about their feelings and thoughts during and after the writing experience. Answers are rated
43 on a 5-point-Likert scale (1 = "not at all", 3 = "few", 5 = "very much/extremely"). The
44 questionnaire was adapted from the English version of Pennebaker and Beall [56].
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48 49 *Open questions*

50 For the final survey (t3) four open questions inspired by the open questions from Fitzpatrick,
51 Darcy and Vierhile [84] about the interaction with SISU are provided. The answers are
52 individually evaluated and thematically summarised.
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55 56 *Questions for the future of software agents*

57 The final survey (t3) will assess the behavioural intention to use a software agent in the
58 future or recommend one to friends as well as the future performance expectancy of software
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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 $\alpha = 0.80$ [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 $\alpha = 0.75$ to $\alpha = 0.82$ [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.

1
2 Cronbach's α for credibility differs from 0.79 to 0.90, for expectancy from 0.81 to 0.86 and for
3 the total scale from 0.84 to 0.85 indicating acceptable to high internal consistency [90].
4

5 *Technology alliance*

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

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19 Data will be pseudonymised and analysed in the Department of Clinical Psychology and
20 Psychotherapy of the Ulm University via individual ID and an internal participant ID for every
21 participant to encode the individual datasets. Messages exchanged between participants and
22 SISU are encrypted in-transit by the end-to-end encryption of the “Wire” application. Thus, only
23 the study team will have access to the collected data. Participants will have the opportunity to
24 have all of their collected data deleted. External researchers may get access to the final trial
25 dataset (from HB) on request depending on to be specified data security and data exchange
26 regulation agreements. To ensure confidentiality, data dispersed to any investigator or
27 researcher will be blinded of any identifying participant information. Anonymised results will be
28 published in peer-reviewed journals and presented on international conferences.
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36 The participation in this study should not be associated with any specific risks. However,
37 temporary changes in mood could arise directly after the writing task [91]. Furthermore,
38 therapeutic writing can lead to emotional-cognitive (change) processes [61] with which the
39 participants could have difficulties in dealing with. Therefore, participants will have the
40 opportunity to contact the study team at every point during the trial. Additionally to the
41 interventions, participants with a very low WHO-5 score (< 28) in the screening will be sent an
42 automatised email with further information about offers of the health care system.
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47 **Sample Size**

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49 A meta-analysis by Bolier and colleagues [64] found an effect size of $d=0.34$ for positive
50 psychological interventions aiming at uplifting well-being. Riddle and colleagues [92] reported
51 an effect size of $d=0.46$ for writing interventions to enhance well-being. However, for internet-
52 based mindfulness interventions, Spijkerman and colleagues [28] found a somewhat smaller
53 effect of $g=0.23$.
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58 Based on these previous findings, a small effect size of $d = 0.30$ is expected. Power analysis
59 for an ANOVA with repeated measures with g-power (<http://gpower.hhu.de/>) recommends a
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2 sample size of at least 60 participants per group (N=120) on the assumption of two-tailed
3 testing, an alpha error $\alpha = 0.05$ and power $1-\beta = 0.90$.
4

5 6 **Statistical Analysis**

7 Patterns of missing data will be investigated, and analyses will be adjusted accordingly
8 (multiple imputation). Regarding the imputation method and predictor selection we will follow
9 the recommendations of van Buuren and colleagues [93]. It will be assumed that missing
10 values are missing at random. Analyses will be conducted on a two-sided level of significance
11 ($\alpha=0.05$). Participant characteristics will be described descriptively.
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16 All statistical analyses will be performed based on the intention-to-treat (ITT) principle.
17 Additional per protocol analyses will be conducted in order to examine associations in case of
18 patients adhering to the intervention protocol. Participants who completed at least 66% of the
19 intervention are defined as intervention completer (=per protocol).
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23 The primary outcome will be analysed using linear regression models at T3 as dependent
24 variable and the baseline value as covariate, adjusting for sex and age. The necessity of
25 multilevel models will be explored by interclass correlations. On substantial ICC ($>.05$) the use
26 of multilevel models will be considered or other adjustments of standard errors will be used.
27 To analyse between-group effect sizes, standardised mean differences with 95% confidence
28 intervals will be calculated for post-treatment (t3) and follow-up (t4). Secondary outcomes will
29 be analysed accordingly.
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34 Exploratory mediation and moderator analyses involving the primary and secondary outcomes
35 as well as demographic data will be conducted. Moderator and subgroup analyses are aimed
36 for in case of a sufficiently large sample size.
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41 For the planned exploratory moderator analyses, regression models will be employed. Initially,
42 each potential moderator described under "Covariates" will be analysed in a separate
43 regression model. The primary outcome psychological well-being at t3 will be the dependent
44 variable. Predictors will comprise group, the moderator variable and the interaction of group
45 and moderator. In a next step, a comprising model of all identified moderators will be tested.
46 Mediation analyses will be conducted according to the principles of time-lagged mediation [94].
47 Psychological well-being at t3 will be the outcome variable. Group will be chosen as
48 independent variable, whereas the variables defined in the section "Potentials mediators" will
49 constitute the respective mediating variables. No interim analyses will be applied to the data.
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56 **Patient and public involvement**

57 Patient and public involvement (PPI) representatives provide input to the present study in
58 several stages. Results of the feasibility trial on SISU (DRKS-ID: DRKS00014933) were used
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1
2 to further develop and optimise study design and procedures. PPI representatives were
3 included in the intervention development to improve content, usability and design of SISU.
4 However, acceptance of SISU from the participants' perspective is a crucial outcome of the
5 study and both quantitative and qualitative methods are applied to capture acceptance and
6 side-effects. The dissemination plan of the study results includes presentations on international
7 conferences and publications in peer-reviewed journals.
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For peer review only

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

1
2 will be excluded. Thus, it is not possible to say whether SISU is useful in people with already
3 high psychological well-being. Furthermore, new technologies like chatbots could be especially
4 attractive to the youth, which were excluded as a population. Thus it remains unclear if SISU
5 could be useful in younger people living with low psychological well-being. Self-selection bias
6 could lead to a population which has an internet affinity. Only participants with internet-access
7 and email-address can be included in the intervention. Whereas this is probably not relevant
8 for younger people, it might still be a potential reason for selection and limited generalizability,
9 especially with regard to elder people. To rule out a potential gender bias due to a male or
10 female software agent, SISU was conceptualised gender neutral so that members of all sexes
11 feel equally addressed.
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13
14 Usually, moderate to high dropout rates are a problem within online interventions, which needs
15 to be addressed in the planning of a study [98]. In our feasibility trial 39% of the participants
16 dropped out during study progress (assessment dropout), which could be (partly) explained by
17 organisational effort providing informed consent and unfulfilled expectations concerning the
18 intervention or the interaction with SISU. Nonetheless, the dropout rate of 14% during the
19 intervention with SISU (intervention dropout) is comparably low, which could be traced back to
20 the responsiveness/guidance by SISU. Those have been shown to improve intervention
21 adherence [99]. For the present trial we maintained these successfully tested techniques.
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23
24 Another possible limitation is the use a waitlist control group. This can be associated with
25 overestimation of effects compared to psychological placebo or no intervention [100]. If SISU
26 shows its effectiveness compared to a waitlist control group, a next step should be to compare
27 it with an active control group like e. g. participants receiving a pamphlet with instructions for
28 doing mindfulness exercises at home. Furthermore, a potential methodological confound
29 concerns blinding. Participants are not blinded towards the primary outcome and could
30 possibly answer in a socially desirable way. However, as participants are unlikely to know the
31 study team personally, test manager effects might be low. Another methodological problem
32 could arise from assessment reactivity. Frequent assessments can trigger self-reflection which
33 can lead to an incremental effect regardless of the intervention [101]. However, this is a general
34 problem which can be particularly noticeable in control groups and in groups which receive
35 low-threshold intervention offers.
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38 Last but not least, the planned analyses are based on classic inferential statistics to test the
39 significance of group differences. A sample size calculation (g*power) was performed to plan
40 the sample size accordingly. However, recent evidence emphasises, that it might be fruitful not
41 to test for differences from zero. Instead, Bayesian methods could be used. They allow
42 discovering uncertainties of the effects of treatments instead of solemnly focusing on
43 dichotomising evidence into significant and not significant [102]. If this trial points towards the
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2 usefulness / effectiveness of SISU, future trials could substantiate results using Bayesian
3 methods.
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8 **Ethics and Dissemination:** This trial has been approved by the ethics committee of the
9 University of Ulm (No. 448/18, 18.02.2019) and registered in the German Clinical Trials
10 Register (DRKS-ID: DRKS00014933) on 25 April 2019. Written informed consent for
11 participation in the study will be obtained from all participants prior to their involvement.
12 Participants will receive written information on study conditions, data security, publication of
13 anonymised results, voluntariness of participation and the right to leave the study at all times.
14 They will also be informed that in case of study withdrawal, they will be able to decide whether
15 they want their data to be included in the analysis or to be deleted. Additionally, participants
16 will be asked for permission for the research team to share relevant data with people from
17 regulatory authorities, where necessary. This trial will only involve the collection and storage
18 of self-report data, not of biological specimens. Data collection will be pseudonymised and
19 data will only be accessed by authorized study personnel obliged to secrecy. After data
20 collection is completed, personalised information will be deleted and all data will be completely
21 anonymised. All participant information will be stored securely in locked file cabinets and/or
22 password-protected in a secured cloud storage with restricted access. All reports, data
23 collection, and administrated forms will be identified by a coded ID number only to maintain
24 participant confidentiality. All records that contain names or other personal identifiers, such as
25 informed consent forms will be stored separately from study records identified by ID number.
26 Listings that link participant ID numbers to other identifying information will be stored in
27 separate password-protected files with limited access. According to German law, data will only
28 be shared with parties outside the project team in anonymised form. Trial results will be
29 submitted for publication in a peer-reviewed journal and presented at conferences.
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49
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51 **Author contributions**

52 EB had the idea of SISU. SISU was developed by the Department of Clinical Psychology and
53 Psychotherapy and the Institute of Distributed Systems at Ulm University (lead developer
54 DM, BE and EB). EB and HB designed and planned the study. EB and HB supervised the
55 study. EB and LW operatively perform the study. EB drafted the manuscript, all other authors
56 critically revised the work for important intellectual content. All authors (HB, BE, DE, A-MK,
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1
2 NB, LW) approved the final version to be published and agree to be accountable for all
3 aspects of the work.
4

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8 SISU and the surveys as well as for helping with study recruitment. We kindly thank Jana Moos
9 for performing the allocation procedure.
10
11

12 13 **Declaration of interest**

14 HB reports to have received consultancy fees and fees for lectures/workshops from chambers
15 of psychotherapists and training institutes for psychotherapists in the e-mental-health context.
16 A-MK has received fees for lectures/workshops from chambers of psychotherapists and health
17 insurance companies. DE reports to have received consultancy fees/served in the scientific
18 advisory board from several companies such as Minddistrict, Lantern, Schoen Kliniken and
19 German health insurance companies. He is stakeholder of the Institute for health training online
20 (GET.ON), which aims to implement scientific findings related to digital health interventions
21 into routine care.
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24 All other authors declare not to have competing interests.
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28 29 **Access to data and availability**

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

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4	ACT	Acceptance and commitment therapy
5	AQoL-8D	Inventory for the Assessment of Quality of Life
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7	BFI-10	Short version of the Big Five Inventory
8		
9	CES	Centrality of Event Scale
10		
11	CEQ	Credibility/Expectancy Questionnaire
12		
13	DRKS	Deutsches Register Klinischer Studien
14	ERQ	Emotion Regulation Questionnaire
15		
16	FAH-II	Acceptance and Action Questionnaire-II
17		
18	FS-D	Flourishing Scale
19		
20	IMI	Internet-based intervention
21		
22	IG	Intervention group
23		
24	INEP	Inventory for the assessment of negative effects of psychotherapy
25		
26	RCT	Randomised controlled trial
27		
28	TAI-SF	Inventory of Technology Alliance – Online Therapy
29		
30	TAS-20	Toronto Alexithymia Scale
31		
32	WHO-5	Well-being-Scale
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34	WL	Waiting List Control Group
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36	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.

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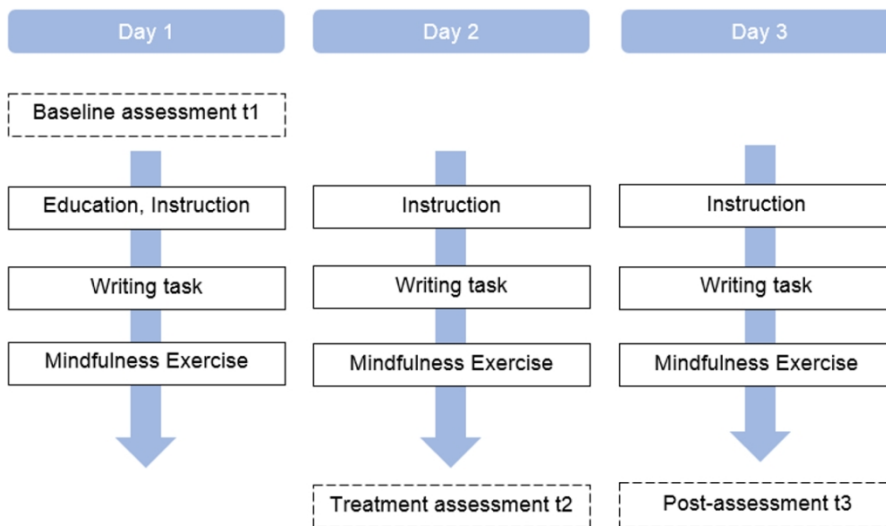


Figure 1. Content and chronological structure of the study

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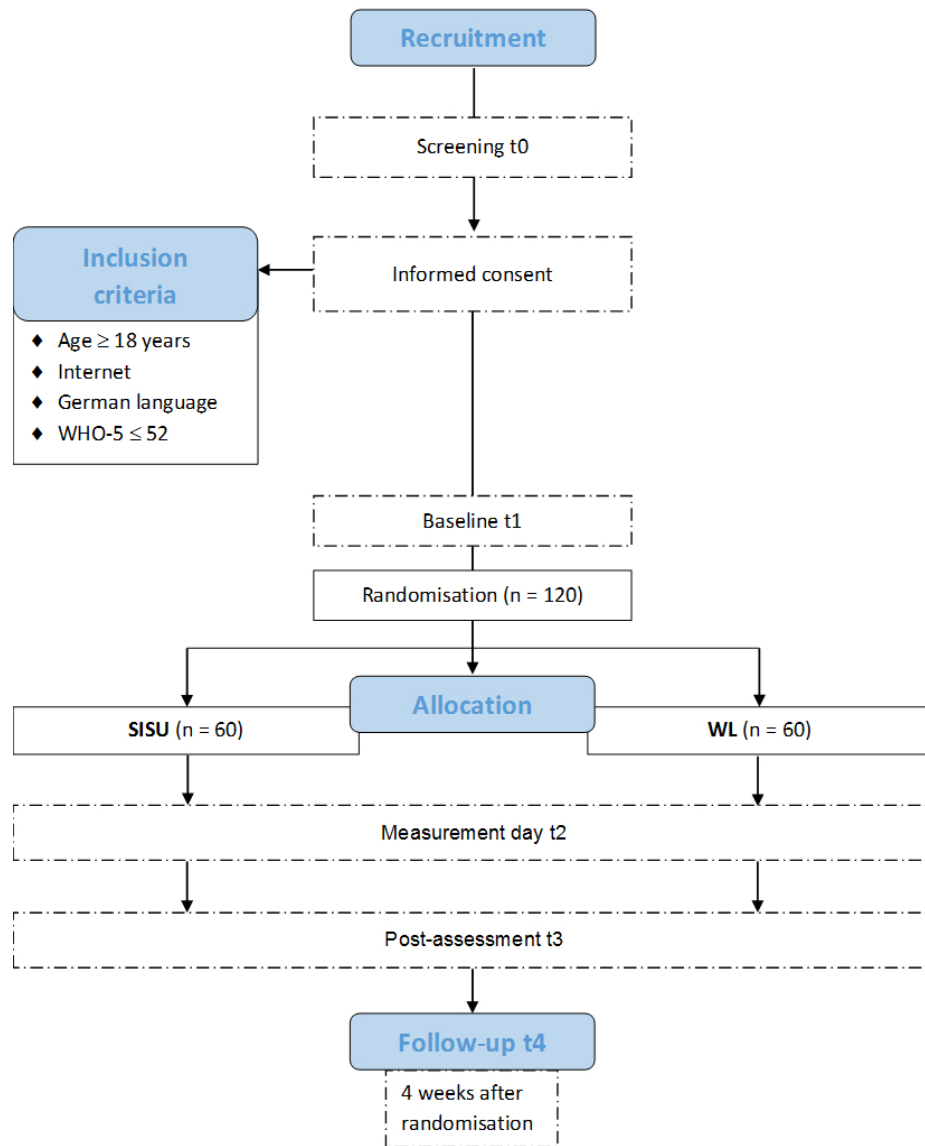


Figure 2. Flowchart of the planned study procedure.

175x226mm (120 x 120 DPI)



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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.



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:

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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:

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Universität Ulm, Helmholtzstr. 16, 89081 Ulm, Telefonnummer.: 0731 50 - 25056,
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.....
Ort, Datum

.....
Name der aufklärenden Mitarbeiters/in



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 mirausreichend 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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.....
 (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 SPIRIT reporting 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

1	Roles and	#5a	Names, affiliations, and roles of protocol contributors	0,19
2	responsibilities:			
3	contributorship			
4				
5				
6	Roles and	#5b	Name and contact information for the trial sponsor	n/a
7	responsibilities:			
8	sponsor contact			
9	information			
10				
11				
12				
13	Roles and	#5c	Role of study sponsor and funders, if any, in study	n/a
14	responsibilities:		design; collection, management, analysis, and	
15	sponsor and funder		interpretation of data; writing of the report; and the	
16			decision to submit the report for publication, including	
17			whether they will have ultimate authority over any of	
18			these activities	
19				
20				
21				
22				
23	Roles and	#5d	Composition, roles, and responsibilities of the	19
24	responsibilities:		coordinating centre, steering committee, endpoint	
25	committees		adjudication committee, data management team, and	
26			other individuals or groups overseeing the trial, if	
27			applicable (see Item 21a for data monitoring committee)	
28				
29				
30				
31	Introduction			
32				
33	Background and	#6a	Description of research question and justification for	3-6
34	rationale		undertaking the trial, including summary of relevant	
35			studies (published and unpublished) examining benefits	
36			and harms for each intervention	
37				
38				
39				
40	Background and	#6b	Explanation for choice of comparators	10
41	rationale: choice of			
42	comparators			
43				
44				
45	Objectives	#7	Specific objectives or hypotheses	5,6
46				
47				
48	Trial design	#8	Description of trial design including type of trial (eg,	7
49			parallel group, crossover, factorial, single group),	
50			allocation ratio, and framework (eg, superiority,	
51			equivalence, non-inferiority, exploratory)	
52				
53				
54				

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: adherence	#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

1 2 3 4 5 6 7 8 9 10 11 12 13 14	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
15 16 17 18 19 20 21 22 23	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
24 25 26 27 28 29	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
30 31 32 33	Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16
34 35 36 37 38 39 40	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
41 42	Methods: Monitoring			
43 44 45 46 47 48 49 50 51 52 53	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
54 55 56 57 58 59 60	Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these	16

1		interim results and make the final decision to terminate	
2		the trial	
3			
4	Harms	#22 Plans for collecting, assessing, reporting, and managing	13
5		solicited and spontaneously reported adverse events	
6		and other unintended effects of trial interventions or trial	
7		conduct	
8			
9			
10			
11	Auditing	#23 Frequency and procedures for auditing trial conduct, if	n/a
12		any, and whether the process will be independent from	
13		investigators and the sponsor	
14			
15			
16	Ethics and		
17	dissemination		
18			
19			
20	Research ethics	#24 Plans for seeking research ethics committee /	2, 19
21	approval	institutional review board (REC / IRB) approval	
22			
23			
24	Protocol amendments	#25 Plans for communicating important protocol	1
25		modifications (eg, changes to eligibility criteria,	
26		outcomes, analyses) to relevant parties (eg,	
27		investigators, REC / IRBs, trial participants, trial	
28		registries, journals, regulators)	
29			
30			
31			
32	Consent or assent	#26a Who will obtain informed consent or assent from	7, 17
33		potential trial participants or authorised surrogates, and	
34		how (see Item 32)	
35			
36			
37	Consent or assent:	#26b Additional consent provisions for collection and use of	n/a
38	ancillary studies	participant data and biological specimens in ancillary	
39		studies, if applicable	
40			
41			
42			
43	Confidentiality	#27 How personal information about potential and enrolled	15
44		participants will be collected, shared, and maintained in	
45		order to protect confidentiality before, during, and after	
46		the trial	
47			
48			
49	Declaration of	#28 Financial and other competing interests for principal	20
50	interests	investigators for the overall trial and each study site	
51			
52			
53	Data access	#29 Statement of who will have access to the final trial	15,20
54		dataset, and disclosure of contractual agreements that	
55		limit such access for investigators	
56			
57			
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60			

1	Ancillary and post trial	#30	Provisions, if any, for ancillary and post-trial care, and for	n/a
2	care		compensation to those who suffer harm from trial	
3			participation	
4				
5				
6	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate trial	19
7	trial results		results to participants, healthcare professionals, the	
8			public, and other relevant groups (eg, via publication,	
9			reporting in results databases, or other data sharing	
10			arrangements), including any publication restrictions	
11				
12				
13				
14	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of	n/a
15	authorship		professional writers	
16				
17				
18	Dissemination policy:	#31c	Plans, if any, for granting public access to the full	19
19	reproducible research		protocol, participant-level dataset, and statistical code	
20				
21				
22	Appendices			
23				
24	Informed consent	#32	Model consent form and other related documentation	n/a
25	materials		given to participants and authorised surrogates	
26				
27				
28	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of	n/a
29			biological specimens for genetic or molecular analysis in	
30			the current trial and for future use in ancillary studies, if	
31			applicable	
32				
33				
34				

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 37 tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

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

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			Page Number
Administrative information			
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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

1	Roles and	#5b	Name and contact information for the trial sponsor	n/a
2	responsibilities: sponsor			
3	contact information			
4				
5				
6	Roles and	#5c	Role of study sponsor and funders, if any, in study design; collection, management,	n/a
7	responsibilities: sponsor		analysis, and interpretation of data; writing of the report; and the decision to submit the	
8	and funder		report for publication, including whether they will have ultimate authority over any of	
9			these activities	
10				
11				
12				
13	Roles and	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee,	16
14	responsibilities:		endpoint adjudication committee, data management team, and other individuals or	
15	committees		groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
16				
17				
18				
19	Introduction			
20				
21	Background and	#6a	Description of research question and justification for undertaking the trial, including	2-4
22	rationale		summary of relevant studies (published and unpublished) examining benefits and harms	
23			for each intervention	
24				
25				
26	Background and	#6b	Explanation for choice of comparators	8
27	rationale: choice of			
28	comparators			
29				
30				
31				
32	Objectives	#7	Specific objectives or hypotheses	4
33				
34	Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial,	5
35			single group), allocation ratio, and framework (eg, superiority, equivalence, non-	
36			inferiority, exploratory)	
37				
38				
39				
40	Methods: Participants,			
41	interventions, and			
42	outcomes			
43				
44				
45	Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of	5
46			countries where data will be collected. Reference to where list of study sites can be	
47			obtained	
48				
49				
50				
51	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for	5
52			study centres and individuals who will perform the interventions (eg, surgeons,	
53			psychotherapists)	
54				
55				
56	Interventions:	#11a	Interventions for each group with sufficient detail to allow replication, including how	6f
57	description		and when they will be administered	
58				
59				
60				

1	Interventions:	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial	6f
2	modifications		participant (eg, drug dose change in response to harms, participant request, or improving	
3			/ worsening disease)	
4				
5				
6	Interventions: adherence	#11c	Strategies to improve adherence to intervention protocols, and any procedures for	7
7			monitoring adherence (eg, drug tablet return; laboratory tests)	
8				
9				
10	Interventions:	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the	n/a
11	concomitant care		trial	
12				
13				
14	Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable	9
15			(eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time	
16			to event), method of aggregation (eg, median, proportion), and time point for each	
17			outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is	
18			strongly recommended	
19				
20				
21				
22	Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts),	5f, fig.2
23			assessments, and visits for participants. A schematic diagram is highly recommended	
24			(see Figure)	
25				
26				
27				
28	Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was	13
29			determined, including clinical and statistical assumptions supporting any sample size	
30			calculations	
31				
32				
33	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5
34				
35				
36	Methods: Assignment			
37	of interventions (for			
38	controlled trials)			
39				
40				
41	Allocation: sequence	#16a	Method of generating the allocation sequence (eg, computer-generated random	6
42	generation		numbers), and list of any factors for stratification. To reduce predictability of a random	
43			sequence, details of any planned restriction (eg, blocking) should be provided in a	
44			separate document that is unavailable to those who enrol participants or assign	
45			interventions	
46				
47				
48				
49	Allocation concealment	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially	6
50	mechanism		numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until	
51			interventions are assigned	
52				
53				
54	Allocation:	#16c	Who will generate the allocation sequence, who will enrol participants, and who will	6
55	implementation		assign participants to interventions	
56				
57				
58				
59				
60				

1	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
2				
3				
4	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for	n/a
5	emergency unblinding		revealing a participant's allocated intervention during the trial	
6				
7				
8	Methods: Data			
9	collection,			
10	management, and			
11	analysis			
12				
13				
14				
15	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
16				
17				
18				
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20				
21				
22				
23				
24	Data collection plan:	#18b	Plans to promote participant retention and complete follow-up, including list of any	6,7
25	retention		outcome data to be collected for participants who discontinue or deviate from intervention protocols	
26				
27				
28				
29				
30	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
31				
32				
33				
34				
35	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
36				
37				
38				
39	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
40	analyses			
41				
42				
43	Statistics: analysis	#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
44	population and missing			
45	data			
46				
47				
48	Methods: Monitoring			
49				
50				
51	Data monitoring: formal	#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
52	committee			
53				
54				
55				
56				
57				
58				
59				
60				

1	Data monitoring: interim	#21b	Description of any interim analyses and stopping guidelines, including who will have	14
2	analysis		access to these interim results and make the final decision to terminate the trial	
3				
4				
5	Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously	11
6			reported adverse events and other unintended effects of trial interventions or trial	
7			conduct	
8				
9				
10	Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will	n/a
11			be independent from investigators and the sponsor	
12				
13				
14	Ethics and			
15	dissemination			
16				
17				
18	Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB)	5,13
19			approval	
20				
21				
22	Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility	1
23			criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial	
24			participants, trial registries, journals, regulators)	
25				
26				
27	Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or	5, 15
28			authorised surrogates, and how (see Item 32)	
29				
30				
31	Consent or assent:	#26b	Additional consent provisions for collection and use of participant data and biological	n/a
32	ancillary studies		specimens in ancillary studies, if applicable	
33				
34				
35	Confidentiality	#27	How personal information about potential and enrolled participants will be collected,	13
36			shared, and maintained in order to protect confidentiality before, during, and after the	
37			trial	
38				
39				
40				
41	Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial	17
42			and each study site	
43				
44				
45	Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual	13,17
46			agreements that limit such access for investigators	
47				
48	Ancillary and post trial	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who	n/a
49	care		suffer harm from trial participation	
50				
51				
52	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate trial results to participants,	13,17
53	trial results		healthcare professionals, the public, and other relevant groups (eg, via publication,	
54			reporting in results databases, or other data sharing arrangements), including any	
55			publication restrictions	
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1	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
2	authorship			
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4	Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and	13,17
5	reproducible research		statistical code	
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8	Appendices			
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10	Informed consent	#32	Model consent form and other related documentation given to participants and	n/a
11	materials		authorised surrogates	
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13	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for	n/a
14			genetic or molecular analysis in the current trial and for future use in ancillary studies, if	
15			applicable	
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 21 completed on 10. June 2020 using <https://www.goodreports.org/>, a tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
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BMJ Open

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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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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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 trial, 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].

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

10
11 A software agent or “chatbot” is a computer program that can hold a fully automated text-based
12 conversation in real-time with people via a chat-interface (e.g., smartphone application) by
13 using a natural language style [38]. The growing interest and body of research about software
14 agents [39,40] is realised in various populations and contexts, such as problem solving and
15 stress [41–43]. In the context of clinical psychology and psychotherapy, research on software
16 agents is sparse [44] but could create opportunities for the field regarding the provision of
17 mental health services. Software agents could be used to convey therapeutic contents and
18 brief interventions [45,46]. Establishing contact to a software agent might not be as stigmatising
19 as using formal mental health services like starting a face-to-face therapy or asking a general
20 practitioner for possibilities of mental health care [47]. Furthermore, they are flexible regarding
21 location and time [48], can be used anonymously [49,50] and provide personalization through
22 implicit customization [51]. Therefore, software agents could help to overcome barriers and
23 provide psychological and health behaviour change interventions on a large scale in the future.

24
25 Current mental health software agents are primarily based on cognitive behavioural therapy
26 [44]. However, other popular approaches with proven effectiveness in face-to-face settings
27 could also readily be realized in a digital form, such as writing interventions [52] and
28 acceptance and commitment-based approaches [53].

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30 Writing with the aim of improving health has a long history [54]. In the current literature, the
31 labelling of this kind of intervention varies: Terminology includes expressive writing [55,56],
32 benefit-finding or positive writing [57,58] and therapeutic writing (e.g., [59]). Regardless of
33 terminology, the writing intervention to be investigated in this study will refer to the process of
34 freely and emotionally writing about a positive personal life event without paying attention to
35 spelling or grammar. The call to write about personal life events, to tell a story, seems to go
36 straight at the centre of subjective experiences [60], which in turn is the main medium in
37 traditional face-to-face therapy. In that, the term therapeutic writing will be used in this context
38 to acknowledge that the intervention refers to some kind of therapeutic work [61]. It has been
39 shown that writing interventions can be highly time- and cost-efficient [62]. A recent meta-
40 analysis shows that writing interventions can help to improve general psychological health
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2 (SMD=-0.46, 95% CI -.86, -0.06) [63]. Finally, a meta-analysis from Bolier and colleagues [64]
3 found an effect of Cohen's $d = 0.34$ (95% CI 0.22, 0.45) for positive interventions to uplift
4 cognitive and/or affective appraisal of one's life as a whole and $d=0.20$ (95% CI 0.09, 0.30)
5 optimal functioning including mastery, hope and purpose in life.
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9 Acceptance and Commitment Therapy (ACT) [65] aims at acceptance, mindfulness and value-
10 based living and has been found to be effective in the prevention of stress and the increase of
11 well-being [27,66]. The efficacy of ACT-based interventions in general and ACT-based IMIs in
12 particular has been indicated in a number of studies and systematic reviews. Within a
13 randomised-controlled trial, Fledderus and colleagues (2012) investigated an ACT-based IMI
14 for people living with depression. The authors found significant reductions in depression,
15 anxiety, fatigue, experiential avoidance and improvements in positive mental health, compared
16 to a waitlist control condition (effect sizes Cohen's $d = 0.51$ to 1.00) [29]. In their meta-analysis,
17 Brown and colleagues [67] examined 10 randomised controlled trials investigating the
18 effectiveness of ACT in the treatment of depressive or anxiety symptoms and well-being in
19 adult populations. ACT interventions were compared to passive control groups (N=3), active
20 control groups (N=4) or both (N=3). The authors found small effect sizes regarding the
21 improvement of depression ($g = 0.24$, 95% CI: 0.04 - 0.45) whilst the heterogeneity of
22 conditions and outcome measures on anxiety and well-being was too high to draw firm
23 conclusions. Spijkerman and colleagues [28] examined 15 randomised controlled trials in
24 adults with various mental problems and healthy populations. Mindfulness interventions, of
25 which the authors include ACT, were compared to passive control groups (N=10), active
26 control groups (N=5) or both (N=2). The authors found small to medium effect sizes concerning
27 the improvement of depression ($g = 0.29$, 95% CI: 0.13 - 0.46), anxiety ($g = 0.22$, 95% CI: 0.05
28 - 0.39) and well-being ($g = 0.23$, 95% CI: 0.09 - 0.38) [28].
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41 We developed a gender neutral software agent called SISU (**S**oftware agent providing an
42 **I**ntervention for **S**elf-help to **U**plift psychological well-being and finnish word ['sisu] for inner
43 strength) with the aim to provide an easily deployable software agent that improve peoples'
44 well-being. Therefore, SISU combines therapeutic writing and acceptance- and commitment-
45 based principles. Results of a feasibility trial on SISU [68] showed that SISU is feasible in terms
46 of user acceptance and the potential of the software agent to deliver a brief writing intervention.
47 Thus SISU is feasible to be implemented within a confirmatory clinical trial. Hence, the present
48 study is designed to investigate the clinical effectiveness and acceptance of the Software agent
49 SISU thereby focusing on the following specific research aims:
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56 1. To estimate the effects of SISU on psychological well-being compared to the WL at T3
57 (primary outcome).
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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.

For peer review only

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

1
2 or WL condition. Following, they will receive their individual ID and get an invitation for the
3 baseline questionnaire (t1) at unipark.de via email. Afterwards, participants will learn about
4 their group membership. The IG will get in contact with SISU and the intervention using the
5 end-to-end encrypted online messaging app “Wire” after finishing baseline (t1). SISU guides
6 participants through a writing intervention on three consecutive days using a standardised
7 conversation script. Each writing intervention is automatically followed by an assessment.
8 Participants who are part of the WL will receive access to SISU four weeks after randomisation.
9 If participants complete questionnaires for t3 and t4 they will each time get the chance to win
10 a 10€ gift card for Amazon as a monetary incentive to promote retention and follow-up
11 completion. All participants with a low WHO-5 score (< 28) in the screening receive an
12 automatised email with further information about offers of the health care system.
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20 **Randomisation and blinding**

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

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36 The software agent (SISU) provides a brief three-day intervention. The writing instruction
37 provided by SISU is based on the paradigm of therapeutic writing as well as acceptance and
38 commitment therapy [ACT; 73]. The version of SISU used for this study was improved through
39 participant feedback collected in the feasibility trial [68]. Revisions included the enrichment of
40 the instruction for writing about positive life events with elements of ACT (more mindfulness
41 exercises, authenticity of the dialog through reduction of repetitions, interactions on reported
42 life events) and elements for the reconstruction of narrative identity.
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48 SISU mimics a human conversational style. Participants are guided to write each day at the
49 same time for 10-20 minutes about a self-chosen autobiographical, positive life event. On day
50 1 there is psychoeducation in the beginning. Then, instructions for the writing tasks are
51 followed by the narratives of the participants. Participants are instructed to write about a
52 meaningful, outstanding positive life event on day 1 and about an outstanding positive event
53 from adulthood on day 2. On day 3 participants are guided to write about their best possible
54 future. After the writing task, SISU encourages participants to experience the positive emotions
55 due to the reported event in the present moment. Mindfulness exercises are provided by an
56 audio file right after the writing intervention, whilst ACT-metaphors are integrated into the
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2 conversational content. Participants are encouraged to practice on a daily basis. To increase
3 adherence, SISU reminds participants at 24 hour intervals. More details on intervention
4 contents can be derived from Table 1. For an illustration of content and chronological structure
5 see Figure 1.
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9 Using the online messaging Wire Services SDK enables programmatic end-to-end encrypted
10 communication. Thanks to this encryption, messages sent by SISU or participants are not
11 accessible by third parties, including the service provider. We further protect participation data
12 by hosting SISU on premises and by encrypting the data at rest, thus limiting the access to our
13 research group. The communication logic is implemented as a finite-state machine. Our SISU
14 implementation parses incoming messages based on a fixed set of rules and responds with
15 an appropriate answer. In addition, SISU can react to external triggers. That is, external
16 triggers can lead to a status change of SISU. For example, the termination of a survey at
17 Unipark can cause a status change of SISU from “user is active” to “user finished the
18 interaction for the day”. External triggers can be (a) conversation timeouts (i.e., the participant
19 has not responded in a set time frame), (b) Unipark events (i.e., participant has completed an
20 external survey), and (c) scheduled events (e.g., daily participation reminder at pre-defined
21 time frames).
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32 Table 1

33 *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

51 *Note.* ACT = Acceptance and Commitment Therapy

52 --please insert figure 1 around here--

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56 The (ultra-)brief intervention rational of 3 days was chosen because we wanted to provide
57 participants with a brief possibility to do something for their mental well-being, despite their
58 busy everyday lives. Indeed, evidence suggests that brief writing interventions of e. g. only 1
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2 week can increase emotional well-being even 6 months after the intervention [74], particularly
3 in case of interventions focusing on improving mental health rather than treating mental
4 disorders.
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6 7 **Wait list control group**

8
9 Participants of the WL get access to the writing intervention provided by SISU four weeks after
10 randomisation. The intervention has the same content for both groups.
11

12 13 **Administrative and technical support**

14 In case participants forget their individual ID or have other technical issues, they can make use
15 of the study team via email for technical support at every point during the training.
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18 19 **Outcome Assessment**

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

1
2 higher psychological flexibility. The questionnaire shows good to excellent psychometric
3 properties in a German sample [77].
4

5 6 *Quality of life*

7 With the help of the inventory Assessment of Quality of Life (AQoL-8D) participants quality of
8 life is recorded [78]. Each of 35 items loads on one of eight dimensions of quality of life and is
9 rated on 4- to 6-point-Likert scales. For analysis there is an algorithm which can be used for
10 quality of life in general as well as for particular sub dimensions. In total, scores between 0 and
11 1 are possible. Standard values are available. Reliability of AQoL-8D is very good with
12 Cronbach's α of 0.96 [78].
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15 16 17 *Side-effects*

18 Subjective adverse events of the intervention are recorded with the 15-item inventory for the
19 assessment of negative effects of psychotherapy [79]. Items are rated on a 4-point-Likert scale
20 (0 = "no agreement" to 3 = "total agreement") or a bipolar 7-point scale. Adverse effects in
21 social life, intrapersonal factors or work-related situations are taken in consideration. The
22 original inventory with 32 items has an internal consistency of $\alpha = 0.95$ [80].
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27 28 *Satisfaction with the intervention*

29 To assess the global satisfaction with the intervention a revised version of the German version
30 of the Client Satisfaction Questionnaire [ZUF-8; 81] was used. Participants rate their
31 satisfaction on a 4-point-Likert scale for each of the 8 items. A sum score is computed. Higher
32 scores indicate higher satisfaction. Internal consistency of the ZUF-8 is very good with $\alpha = 0.90$
33 [82]. A study on reliability and validity of assessing user satisfaction with internet-based
34 interventions indicates good overall psychometric quality of the measure [83].
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39 40 *Post-Writing Questionnaire*

41 To assess therapeutic writing after every writing session the participants answer four questions
42 about their feelings and thoughts during and after the writing experience. Answers are rated
43 on a 5-point-Likert scale (1 = "not at all", 3 = "few", 5 = "very much/extremely"). The
44 questionnaire was adapted from the English version of Pennebaker and Beall [56].
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48 49 *Open questions*

50 For the final survey (t3) four open questions inspired by the open questions from Fitzpatrick,
51 Darcy and Vierhile [84] about the interaction with SISU are provided. The answers are
52 individually evaluated and thematically summarised.
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55 56 *Questions for the future of software agents*

57 The final survey (t3) will assess the behavioural intention to use a software agent in the
58 future or recommend one to friends as well as the future performance expectancy of software
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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 $\alpha = 0.80$ [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 $\alpha = 0.75$ to $\alpha = 0.82$ [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.

1
2 Cronbach's α for credibility differs from 0.79 to 0.90, for expectancy from 0.81 to 0.86 and for
3 the total scale from 0.84 to 0.85 indicating acceptable to high internal consistency [90].
4

5 *Technology alliance*

6
7 The Inventory of Technology Alliance – Online Therapy (TAI-SF) was used to evaluate the
8 technological alliance between the participants and the online intervention, thus the software
9 agent. The TAI-SF is a 12-items questionnaire developed by Labpsitec
10 (<http://www.labpsitec.uji.es/eng/index.php>) that assesses the degree to which the participant
11 perceives the online intervention as helpful. Items are rated on a 7-point-Likert scale from 1 =
12 “never” to 7 = “always”.
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17 **Data privacy and ethics**

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19 Data will be pseudonymised and analysed in the Department of Clinical Psychology and
20 Psychotherapy of the Ulm University via individual ID and an internal participant ID for every
21 participant to encode the individual datasets. Messages exchanged between participants and
22 SISU are encrypted in-transit by the end-to-end encryption of the “Wire” application. Thus, only
23 the study team will have access to the collected data. Participants will have the opportunity to
24 have all of their collected data deleted. External researchers may get access to the final trial
25 dataset (from HB) on request depending on to be specified data security and data exchange
26 regulation agreements. To ensure confidentiality, data dispersed to any investigator or
27 researcher will be blinded of any identifying participant information. Anonymised results will be
28 published in peer-reviewed journals and presented on international conferences.
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36 The participation in this study should not be associated with any specific risks. However,
37 temporary changes in mood could arise directly after the writing task [91]. Furthermore,
38 therapeutic writing can lead to emotional-cognitive (change) processes [61] with which the
39 participants could have difficulties in dealing with. Therefore, participants will have the
40 opportunity to contact the study team at every point during the trial. Additionally to the
41 interventions, participants with a very low WHO-5 score (< 28) in the screening will be sent an
42 automatised email with further information about offers of the health care system.
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47 **Sample Size**

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49 A meta-analysis by Bolier and colleagues [64] found an effect size of $d=0.34$ for positive
50 psychological interventions aiming at uplifting well-being. Riddle and colleagues [92] reported
51 an effect size of $d=0.46$ for writing interventions to enhance well-being. However, for internet-
52 based mindfulness interventions, Spijkerman and colleagues [28] found a somewhat smaller
53 effect of $g=0.23$.
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58 Based on these previous findings, a small effect size of $d = 0.30$ is expected. Power analysis
59 for an ANOVA with repeated measures with g-power (<http://gpower.hhu.de/>) recommends a
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1
2 sample size of at least 60 participants per group (N=120) on the assumption of two-tailed
3 testing, an alpha error $\alpha = 0.05$ and power $1-\beta = 0.90$.
4

5 6 **Statistical Analysis**

7 Patterns of missing data will be investigated, and analyses will be adjusted accordingly
8 (multiple imputation). Regarding the imputation method and predictor selection we will follow
9 the recommendations of van Buuren and colleagues [93]. It will be assumed that missing
10 values are missing at random. Analyses will be conducted on a two-sided level of significance
11 ($\alpha=0.05$). Participant characteristics will be described descriptively.
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16 All statistical analyses will be performed based on the intention-to-treat (ITT) principle.
17 Additional per protocol analyses will be conducted in order to examine associations in case of
18 patients adhering to the intervention protocol. Participants who completed at least 66% of the
19 intervention are defined as intervention completer (=per protocol).
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22
23 The primary outcome will be analysed using linear regression models at T3 as dependent
24 variable and the baseline value as covariate, adjusting for sex and age. The necessity of
25 multilevel models will be explored by interclass correlations (ICC). On substantial ICC ($>.10$)
26 multilevel models will be specified to account for the dependency in the data [94]. To analyse
27 between-group effect sizes, standardised mean differences with 95% confidence intervals will
28 be calculated for post-treatment (t3) and follow-up (t4). Secondary outcomes will be analysed
29 accordingly.
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34 Exploratory mediation and moderator analyses involving the primary and secondary outcomes
35 as well as demographic data will be conducted. Moderator and subgroup analyses are aimed
36 for in case of a sufficiently large sample size.
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41 For the planned exploratory moderator analyses, regression models will be employed. Initially,
42 each potential moderator described under "Covariates" will be analysed in a separate
43 regression model. The primary outcome psychological well-being at t3 will be the dependent
44 variable. Predictors will comprise group, the moderator variable and the interaction of group
45 and moderator. In a next step, a comprising model of all identified moderators will be tested.
46
47 Mediation analyses will be conducted according to the principles of time-lagged mediation [95].
48 Psychological well-being at t3 will be the outcome variable. Group will be chosen as
49 independent variable, whereas the variables defined in the section "Potentials mediators" will
50 constitute the respective mediating variables. No interim analyses will be applied to the data.
51
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53 54 55 **Patient and public involvement**

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57 Patient and public involvement (PPI) representatives provide input to the present study in
58 several stages. Results of the feasibility trial on SISU (DRKS-ID: DRKS00014933) were used
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60

1
2 to further develop and optimise study design and procedures. PPI representatives were
3 included in the intervention development to improve content, usability and design of SISU.
4 However, acceptance of SISU from the participants' perspective is a crucial outcome of the
5 study and both quantitative and qualitative methods are applied to capture acceptance and
6 side-effects. The dissemination plan of the study results includes presentations on international
7 conferences and publications in peer-reviewed journals.
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For peer review only

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

1
2 will be excluded. Thus, it is not possible to say whether SISU is useful in people with already
3 high psychological well-being. Furthermore, new technologies like chatbots could be especially
4 attractive to the youth, which were excluded as a population. Thus it remains unclear if SISU
5 could be useful in younger people living with low psychological well-being. Self-selection bias
6 could lead to a population which has an internet affinity. Only participants with internet-access
7 and email-address can be included in the intervention. Whereas this is probably not relevant
8 for younger people, it might still be a potential reason for selection and limited generalizability,
9 especially with regard to elder people. To rule out a potential gender bias due to a male or
10 female software agent, SISU was conceptualised gender neutral so that members of all sexes
11 feel equally addressed.
12

13
14 Usually, moderate to high dropout rates are a problem within online interventions, which needs
15 to be addressed in the planning of a study [99]. In our feasibility trial 39% of the participants
16 dropped out during study progress (assessment dropout), which could be (partly) explained by
17 organisational effort providing informed consent and unfulfilled expectations concerning the
18 intervention or the interaction with SISU. Nonetheless, the dropout rate of 14% during the
19 intervention with SISU (intervention dropout) is comparably low, which could be traced back to
20 the responsiveness/guidance by SISU. Those have been shown to improve intervention
21 adherence [100]. For the present trial we maintained these successfully tested techniques.
22

23
24 Another possible limitation is the use a waitlist control group. This can be associated with
25 overestimation of effects compared to psychological placebo or no intervention [101]. If SISU
26 shows its effectiveness compared to a waitlist control group, a next step should be to compare
27 it with an active control group like e. g. participants receiving a pamphlet with instructions for
28 doing mindfulness exercises at home. Furthermore, a potential methodological confound
29 concerns blinding. Participants are not blinded towards the primary outcome and could
30 possibly answer in a socially desirable way. However, as participants are unlikely to know the
31 study team personally, test manager effects might be low. Another methodological problem
32 could arise from assessment reactivity. Frequent assessments can trigger self-reflection which
33 can lead to an incremental effect regardless of the intervention [102]. However, this is a general
34 problem which can be particularly noticeable in control groups and in groups which receive
35 low-threshold intervention offers.
36

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38 Last but not least, the planned analyses are based on classic inferential statistics to test the
39 significance of group differences. A sample size calculation (g*power) was performed to plan
40 the sample size accordingly. However, recent evidence emphasises, that it might be fruitful not
41 to test for differences from zero. Instead, Bayesian methods could be used. They allow
42 discovering uncertainties of the effects of treatments instead of solemnly focusing on
43 dichotomising evidence into significant and not significant [103]. If this trial points towards the
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2 usefulness / effectiveness of SISU, future trials could substantiate results using Bayesian
3 methods.
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8 **Ethics and Dissemination:** This trial has been approved by the ethics committee of the
9 University of Ulm (No. 448/18, 18.02.2019) and registered in the German Clinical Trials
10 Register (DRKS-ID: DRKS00014933) on 25 April 2019. Written informed consent for
11 participation in the study will be obtained from all participants prior to their involvement.
12 Participants will receive written information on study conditions, data security, publication of
13 anonymised results, voluntariness of participation and the right to leave the study at all times.
14 They will also be informed that in case of study withdrawal, they will be able to decide whether
15 they want their data to be included in the analysis or to be deleted. Additionally, participants
16 will be asked for permission for the research team to share relevant data with people from
17 regulatory authorities, where necessary. This trial will only involve the collection and storage
18 of self-report data, not of biological specimens. Data collection will be pseudonymised and
19 data will only be accessed by authorized study personnel obliged to secrecy. After data
20 collection is completed, personalised information will be deleted and all data will be completely
21 anonymised. All participant information will be stored securely in locked file cabinets and/or
22 password-protected in a secured cloud storage with restricted access. All reports, data
23 collection, and administrated forms will be identified by a coded ID number only to maintain
24 participant confidentiality. All records that contain names or other personal identifiers, such as
25 informed consent forms (supplementary file) will be stored separately from study records
26 identified by ID number. Listings that link participant ID numbers to other identifying information
27 will be stored in separate password-protected files with limited access. According to German
28 law, data will only be shared with parties outside the project team in anonymised form. Trial
29 results will be submitted for publication in a peer-reviewed journal and presented at
30 conferences.
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49
50
51

52 **Author contributions**

53 EB had the idea of SISU. SISU was developed by the Department of Clinical Psychology and
54 Psychotherapy and the Institute of Distributed Systems at Ulm University (lead developer
55 DM, BE and EB). EB and HB designed and planned the study. EB and HB supervised the
56 study. EB and LW operatively perform the study. EB drafted the manuscript, all other authors
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58
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2 critically revised the work for important intellectual content. All authors (HB, BE, DE, A-MK,
3 NB, LW) approved the final version to be published and agree to be accountable for all
4 aspects of the work.
5
6

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8
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10 SISU and the surveys as well as for helping with study recruitment. We kindly thank Jana Moos
11 for performing the allocation procedure.
12
13

14 **Declaration of interest**

15
16 HB reports to have received consultancy fees and fees for lectures/workshops from chambers
17 of psychotherapists and training institutes for psychotherapists in the e-mental-health context.
18 A-MK has received fees for lectures/workshops from chambers of psychotherapists and health
19 insurance companies. DE reports to have received consultancy fees/served in the scientific
20 advisory board from several companies such as Minddistrict, Lantern, Schoen Kliniken and
21 German health insurance companies. He is stakeholder of the Institute for health training online
22 (GET.ON), which aims to implement scientific findings related to digital health interventions
23 into routine care.
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26 All other authors declare not to have competing interests.
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30 **Access to data and availability**

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

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4	ACT	Acceptance and commitment therapy
5	AQoL-8D	Inventory for the Assessment of Quality of Life
6		
7	BFI-10	Short version of the Big Five Inventory
8		
9	CES	Centrality of Event Scale
10		
11	CEQ	Credibility/Expectancy Questionnaire
12		
13	DRKS	Deutsches Register Klinischer Studien
14	ERQ	Emotion Regulation Questionnaire
15		
16	FAH-II	Acceptance and Action Questionnaire-II
17		
18	FS-D	Flourishing Scale
19		
20	IMI	Internet-based intervention
21		
22	IG	Intervention group
23		
24	INEP	Inventory for the assessment of negative effects of psychotherapy
25		
26	RCT	Randomised controlled trial
27		
28	TAI-SF	Inventory of Technology Alliance – Online Therapy
29		
30	TAS-20	Toronto Alexithymia Scale
31		
32	WHO-5	Well-being-Scale
33		
34	WL	Waiting List Control Group
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36	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.

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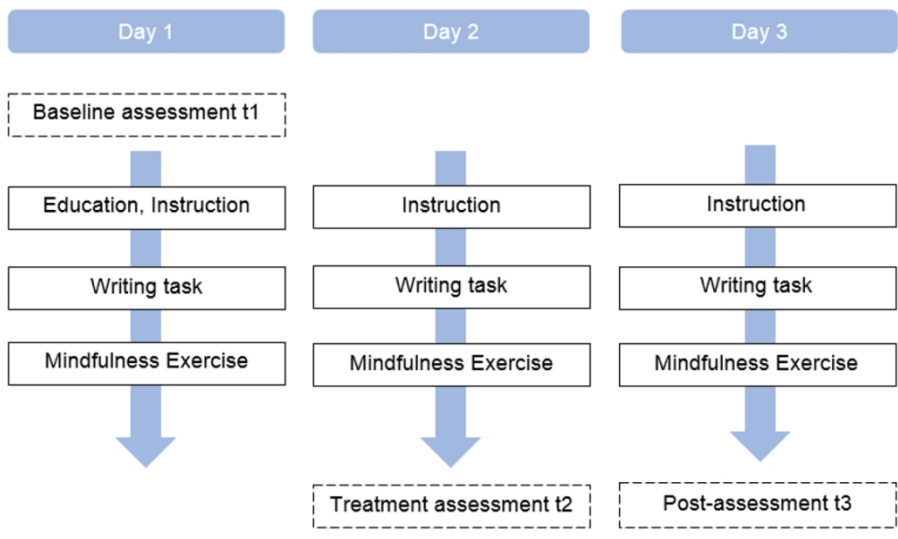


Figure 1. Content and chronological structure of the study

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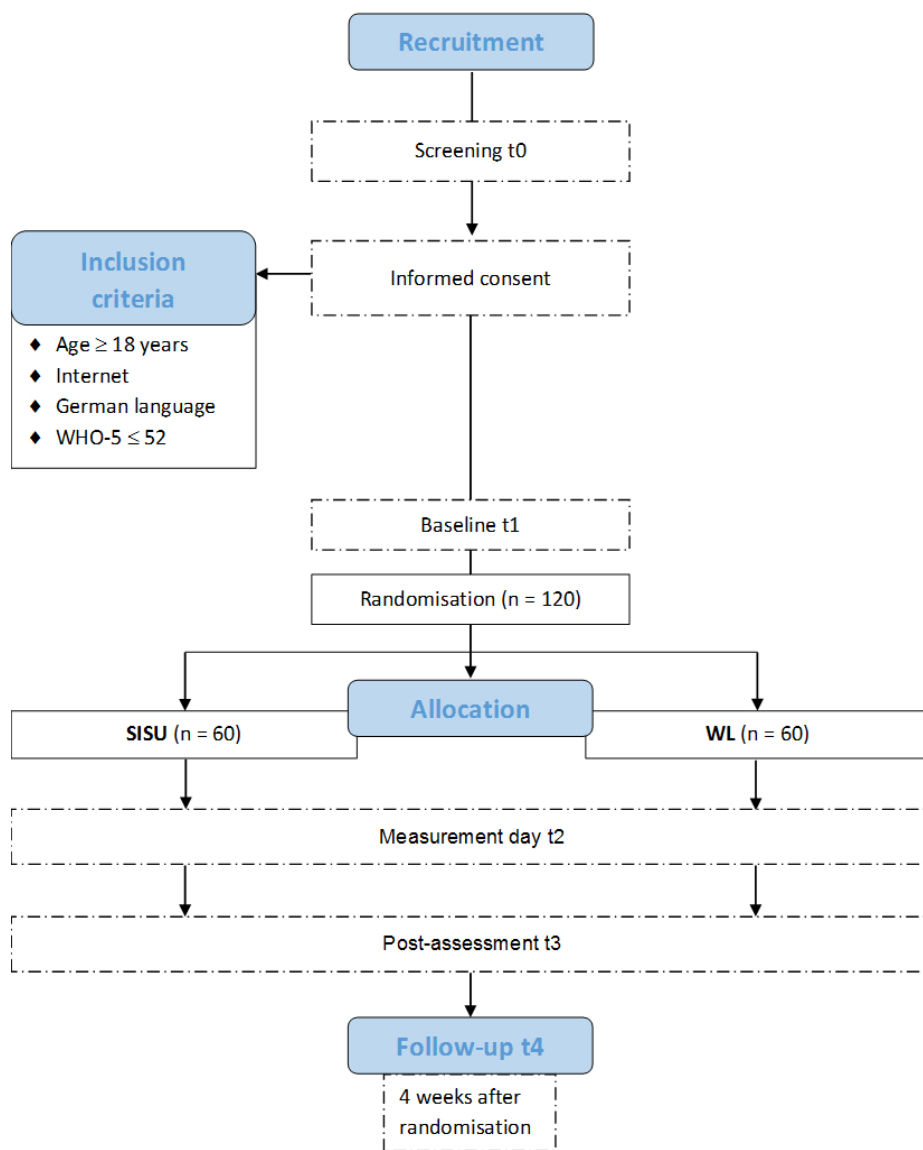


Figure 2. Flowchart of the planned study procedure.

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Teilnehmendeninformation

» SISU – Eine randomisiert-kontrollierte 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.



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.

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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:

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Universität Ulm, Helmholtzstr. 16, 89081 Ulm, Telefonnummer.: 0731 50 - 25114,
E-Mail: datenschutz@uni-ulm.de

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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



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 mirausreichend 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 SPIRIT reporting 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

1	Roles and	#5a	Names, affiliations, and roles of protocol contributors	0,19
2	responsibilities:			
3	contributorship			
4				
5				
6	Roles and	#5b	Name and contact information for the trial sponsor	n/a
7	responsibilities:			
8	sponsor contact			
9	information			
10				
11				
12				
13	Roles and	#5c	Role of study sponsor and funders, if any, in study	n/a
14	responsibilities:		design; collection, management, analysis, and	
15	sponsor and funder		interpretation of data; writing of the report; and the	
16			decision to submit the report for publication, including	
17			whether they will have ultimate authority over any of	
18			these activities	
19				
20				
21				
22				
23	Roles and	#5d	Composition, roles, and responsibilities of the	19
24	responsibilities:		coordinating centre, steering committee, endpoint	
25	committees		adjudication committee, data management team, and	
26			other individuals or groups overseeing the trial, if	
27			applicable (see Item 21a for data monitoring committee)	
28				
29				
30				
31	Introduction			
32				
33	Background and	#6a	Description of research question and justification for	3-6
34	rationale		undertaking the trial, including summary of relevant	
35			studies (published and unpublished) examining benefits	
36			and harms for each intervention	
37				
38				
39				
40	Background and	#6b	Explanation for choice of comparators	10
41	rationale: choice of			
42	comparators			
43				
44				
45	Objectives	#7	Specific objectives or hypotheses	5,6
46				
47				
48	Trial design	#8	Description of trial design including type of trial (eg,	7
49			parallel group, crossover, factorial, single group),	
50			allocation ratio, and framework (eg, superiority,	
51			equivalence, non-inferiority, exploratory)	
52				
53				
54				

Methods:
Participants,

interventions, and outcomes

1				
2				
3				
4	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
5				
6				
7				
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9				
10				
11	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
12				
13				
14				
15				
16				
17	Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8f
18				
19				
20				
21				
22				
23	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
24				
25				
26				
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28				
29				
30	Interventions: adherence	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7f
31				
32				
33				
34				
35	Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
36				
37				
38				
39	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
40				
41				
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49				
50	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
51				
52				
53				
54				
55				
56				
57	Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including	15
58				
59				

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

1			
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9	Data collection plan:	#18b	Plans to promote participant retention and complete
10	retention		follow-up, including list of any outcome data to be
11			collected for participants who discontinue or deviate from
12			intervention protocols
13			
14			
15	Data management	#19	Plans for data entry, coding, security, and storage,
16			including any related processes to promote data quality
17			(eg, double data entry; range checks for data values).
18			Reference to where details of data management
19			procedures can be found, if not in the protocol
20			
21			
22			
23	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary
24			outcomes. Reference to where other details of the
25			statistical analysis plan can be found, if not in the
26			protocol
27			
28			
29			
30	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and
31	analyses		adjusted analyses)
32			
33			
34	Statistics: analysis	#20c	Definition of analysis population relating to protocol non-
35	population and		adherence (eg, as randomised analysis), and any
36	missing data		statistical methods to handle missing data (eg, multiple
37			imputation)
38			
39			
40			
41	Methods: Monitoring		
42			
43	Data monitoring:	#21a	Composition of data monitoring committee (DMC);
44	formal committee		summary of its role and reporting structure; statement of
45			whether it is independent from the sponsor and
46			competing interests; and reference to where further
47			details about its charter can be found, if not in the
48			protocol. Alternatively, an explanation of why a DMC is
49			not needed
50			
51			
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53			
54	Data monitoring:	#21b	Description of any interim analyses and stopping
55	interim analysis		guidelines, including who will have access to these
56			
57			
58			
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1		interim results and make the final decision to terminate	
2		the trial	
3			
4	Harms	#22 Plans for collecting, assessing, reporting, and managing	13
5		solicited and spontaneously reported adverse events	
6		and other unintended effects of trial interventions or trial	
7		conduct	
8			
9			
10			
11	Auditing	#23 Frequency and procedures for auditing trial conduct, if	n/a
12		any, and whether the process will be independent from	
13		investigators and the sponsor	
14			
15			
16	Ethics and		
17	dissemination		
18			
19			
20	Research ethics	#24 Plans for seeking research ethics committee /	2, 19
21	approval	institutional review board (REC / IRB) approval	
22			
23			
24	Protocol amendments	#25 Plans for communicating important protocol	1
25		modifications (eg, changes to eligibility criteria,	
26		outcomes, analyses) to relevant parties (eg,	
27		investigators, REC / IRBs, trial participants, trial	
28		registries, journals, regulators)	
29			
30			
31			
32	Consent or assent	#26a Who will obtain informed consent or assent from	7, 17
33		potential trial participants or authorised surrogates, and	
34		how (see Item 32)	
35			
36			
37	Consent or assent:	#26b Additional consent provisions for collection and use of	n/a
38	ancillary studies	participant data and biological specimens in ancillary	
39		studies, if applicable	
40			
41			
42			
43	Confidentiality	#27 How personal information about potential and enrolled	15
44		participants will be collected, shared, and maintained in	
45		order to protect confidentiality before, during, and after	
46		the trial	
47			
48			
49	Declaration of	#28 Financial and other competing interests for principal	20
50	interests	investigators for the overall trial and each study site	
51			
52			
53	Data access	#29 Statement of who will have access to the final trial	15,20
54		dataset, and disclosure of contractual agreements that	
55		limit such access for investigators	
56			
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1	Ancillary and post trial	#30	Provisions, if any, for ancillary and post-trial care, and for	n/a
2	care		compensation to those who suffer harm from trial	
3			participation	
4				
5				
6	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate trial	19
7	trial results		results to participants, healthcare professionals, the	
8			public, and other relevant groups (eg, via publication,	
9			reporting in results databases, or other data sharing	
10			arrangements), including any publication restrictions	
11				
12				
13				
14	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of	n/a
15	authorship		professional writers	
16				
17				
18	Dissemination policy:	#31c	Plans, if any, for granting public access to the full	19
19	reproducible research		protocol, participant-level dataset, and statistical code	
20				
21				
22	Appendices			
23				
24	Informed consent	#32	Model consent form and other related documentation	n/a
25	materials		given to participants and authorised surrogates	
26				
27				
28	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of	n/a
29			biological specimens for genetic or molecular analysis in	
30			the current trial and for future use in ancillary studies, if	
31			applicable	
32				
33				
34				

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 37 tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
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Reporting checklist for protocol of a clinical trial.

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			Page Number
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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

1	Roles and	#5b	Name and contact information for the trial sponsor	n/a
2	responsibilities: sponsor			
3	contact information			
4				
5				
6	Roles and	#5c	Role of study sponsor and funders, if any, in study design; collection, management,	n/a
7	responsibilities: sponsor		analysis, and interpretation of data; writing of the report; and the decision to submit the	
8	and funder		report for publication, including whether they will have ultimate authority over any of	
9			these activities	
10				
11				
12				
13	Roles and	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee,	16
14	responsibilities:		endpoint adjudication committee, data management team, and other individuals or	
15	committees		groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
16				
17				
18				
19	Introduction			
20				
21	Background and	#6a	Description of research question and justification for undertaking the trial, including	2-4
22	rationale		summary of relevant studies (published and unpublished) examining benefits and harms	
23			for each intervention	
24				
25				
26	Background and	#6b	Explanation for choice of comparators	8
27	rationale: choice of			
28	comparators			
29				
30				
31				
32	Objectives	#7	Specific objectives or hypotheses	4
33				
34	Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial,	5
35			single group), allocation ratio, and framework (eg, superiority, equivalence, non-	
36			inferiority, exploratory)	
37				
38				
39				
40	Methods: Participants,			
41	interventions, and			
42	outcomes			
43				
44				
45	Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of	5
46			countries where data will be collected. Reference to where list of study sites can be	
47			obtained	
48				
49				
50				
51	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for	5
52			study centres and individuals who will perform the interventions (eg, surgeons,	
53			psychotherapists)	
54				
55				
56	Interventions:	#11a	Interventions for each group with sufficient detail to allow replication, including how	6f
57	description		and when they will be administered	
58				
59				
60				

1	Interventions:	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial	6f
2	modifications		participant (eg, drug dose change in response to harms, participant request, or improving	
3			/ worsening disease)	
4				
5				
6	Interventions: adherence	#11c	Strategies to improve adherence to intervention protocols, and any procedures for	7
7			monitoring adherence (eg, drug tablet return; laboratory tests)	
8				
9				
10	Interventions:	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the	n/a
11	concomitant care		trial	
12				
13				
14	Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable	9
15			(eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time	
16			to event), method of aggregation (eg, median, proportion), and time point for each	
17			outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is	
18			strongly recommended	
19				
20				
21				
22	Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts),	5f, fig.2
23			assessments, and visits for participants. A schematic diagram is highly recommended	
24			(see Figure)	
25				
26				
27				
28	Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was	13
29			determined, including clinical and statistical assumptions supporting any sample size	
30			calculations	
31				
32				
33	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5
34				
35				
36	Methods: Assignment			
37	of interventions (for			
38	controlled trials)			
39				
40				
41	Allocation: sequence	#16a	Method of generating the allocation sequence (eg, computer-generated random	6
42	generation		numbers), and list of any factors for stratification. To reduce predictability of a random	
43			sequence, details of any planned restriction (eg, blocking) should be provided in a	
44			separate document that is unavailable to those who enrol participants or assign	
45			interventions	
46				
47				
48				
49				
50	Allocation concealment	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially	6
51	mechanism		numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until	
52			interventions are assigned	
53				
54				
55	Allocation:	#16c	Who will generate the allocation sequence, who will enrol participants, and who will	6
56	implementation		assign participants to interventions	
57				
58				
59				
60				

1	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
2				
3				
4	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for	n/a
5	emergency unblinding		revealing a participant's allocated intervention during the trial	
6				
7				
8	Methods: Data			
9	collection,			
10	management, and			
11	analysis			
12				
13				
14				
15	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
16				
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18				
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21				
22				
23				
24	Data collection plan:	#18b	Plans to promote participant retention and complete follow-up, including list of any	6,7
25	retention		outcome data to be collected for participants who discontinue or deviate from intervention protocols	
26				
27				
28				
29				
30	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
31				
32				
33				
34				
35	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
36				
37				
38				
39	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
40	analyses			
41				
42				
43	Statistics: analysis	#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
44	population and missing			
45	data			
46				
47				
48	Methods: Monitoring			
49				
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51	Data monitoring: formal	#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
52	committee			
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1	Data monitoring: interim	#21b	Description of any interim analyses and stopping guidelines, including who will have	14
2	analysis		access to these interim results and make the final decision to terminate the trial	
3				
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5	Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously	11
6			reported adverse events and other unintended effects of trial interventions or trial	
7			conduct	
8				
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10	Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will	n/a
11			be independent from investigators and the sponsor	
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14	Ethics and			
15	dissemination			
16				
17				
18	Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB)	5,13
19			approval	
20				
21				
22	Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility	1
23			criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial	
24			participants, trial registries, journals, regulators)	
25				
26				
27	Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or	5, 15
28			authorised surrogates, and how (see Item 32)	
29				
30				
31	Consent or assent:	#26b	Additional consent provisions for collection and use of participant data and biological	n/a
32	ancillary studies		specimens in ancillary studies, if applicable	
33				
34				
35	Confidentiality	#27	How personal information about potential and enrolled participants will be collected,	13
36			shared, and maintained in order to protect confidentiality before, during, and after the	
37			trial	
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41	Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial	17
42			and each study site	
43				
44				
45	Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual	13,17
46			agreements that limit such access for investigators	
47				
48				
49	Ancillary and post trial	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who	n/a
50	care		suffer harm from trial participation	
51				
52	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate trial results to participants,	13,17
53	trial results		healthcare professionals, the public, and other relevant groups (eg, via publication,	
54			reporting in results databases, or other data sharing arrangements), including any	
55			publication restrictions	
56				
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1	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
2	authorship			
3				
4	Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and	13,17
5	reproducible research		statistical code	
6				
7				
8	Appendices			
9				
10	Informed consent	#32	Model consent form and other related documentation given to participants and	n/a
11	materials		authorised surrogates	
12				
13	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for	n/a
14			genetic or molecular analysis in the current trial and for future use in ancillary studies, if	
15			applicable	
16				
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 21 completed on 10. June 2020 using <https://www.goodreports.org/>, a tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
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