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Feasibility of Innovative Internet Interventions for Mental Health in Adults Living with Chronic Somatic Disease

DISSERTATION

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Abbreviations

ACT	Acceptance and Commitment Therapy
AWMF	Association of the Scientific Medical Societies in Germany
BÄK	German Medical Association
CAD	Coronary Artery Disease
CBASP	Cognitive Analysis System of Psychotherapy
CBT	Cognitive Behaviour Therapy
DBT	Dialectical-behaviour Therapy
DDG	Deutsche Diabetes Gesellschaft
DSM-5	Diagnostic and Statistical Manual of Mental Disorders
ICD-10	International Statistical Classification of Diseases
JITAI	Just-in-Time Adaptive Intervention
KBV	Kassenärztliche Bundesvereinigung
MAOI	MonoAmine Oxidase Inhibitor
MCT	Metacognitive therapy
NICE	National Institute for Health and Care Excellence
PHQ-9	Patient Health Questionnaire
RCT	Randomised Controlled Trial
SNRI	Serotonin-Norepinephrine Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
TAU	Treatment-As-Usual
TCA	TriCyclic Antidepressant
WHO	World Health Organisation

Abstract

Theoretical background: People with a chronic somatic disease are exposed to numerous stressors and suffer from mental disorders more often than people without a chronic somatic disease. The stigmatisation of mental disorders, difficulties in integrating mental health care into medical care and other barriers make access to mental health care difficult. Offering treatment via scalable internet interventions could reduce barriers and thus provide low-threshold access to psychological interventions for people with a chronic somatic disease. A flexible and adaptive mode of delivery might be essential to enable integrability into peoples' lives which are often filled with appointments due to medical therapies. This dissertation aims at exploring the feasibility of innovative internet interventions for mental health in people with a chronic somatic disease.

Structure: Research questions are investigated within six publications based on two adapted internet interventions and a developed chatbot. Two internet interventions that have already been evaluated in people with chronic pain or populations without a chronic somatic disease are adapted for people with coronary artery disease (CAD) or diabetes. (1) A meta-review provides systematic reviews and meta-analyses of internet interventions previously conducted in people with chronic somatic disease. (2) A randomised controlled feasibility trial provides information on digitised cognitive-behavioural therapy-based depression treatment for people with CAD. (3) Another randomised controlled feasibility trial provides information on a digitised acceptance and commitment-therapy based for people with diabetes and diabetes distress. (4) A narrative review systematises current concepts and the scope of fully automated software agents (so-called chatbots) delivering mental health interventions. (5) Subsequently, a chatbot is conceptualised, developed, and a pretest-posttest trial gives information about its potential to guide participants through a psychological intervention. (6) Based on (5) the chatbot “SISU“ is further developed and its effectiveness and acceptability will be evaluated in a full-scale randomised controlled trial as outlined in a study protocol.

Results: (1) The evidence base and quality of studies in specific settings is often too limited and heterogeneous to calculate effect sizes. (2) The internet-based depression treatment for people with CAD ("WIDeCAD") is not feasible to be investigated in a full-scale trial in its present format. Ideas

are presented to reach and treat people with CAD and depression. (3) The internet intervention "ACTonDiabetes" is a promising approach for reducing diabetes distress (*d* = 0.65). With minor revisions, the study procedure and intervention is feasible for the investigation in a full-scale trial in people living with diabetes and elevated diabetes distress. (4) Chatbots are practicable and acceptable to promote mental health. The evidence for the effectiveness of chatbots in mental health is heterogeneous and limited. (5) The chatbot SISU is suitable for guiding participants through an intervention but needs revision concerning delivered contents. Accordingly, the full-scale trial should also measure intervention acceptability and potential adverse effects as contents are adapted alongside the results of the feasibility trial.

Discussion: Overall, internet interventions could provide low-threshold access to mental health care for people with a chronic somatic disease by using a scalable treatment format. However, they might not be suitable without reservations across the board of chronic somatic diseases. While results of the trial in people with diabetes suggest being feasible, acceptable and potentially effective, strategies to reach and treat people with CAD and depression must be reconsidered. Further research should investigate whether and for which target groups a better understanding is needed and for which more adaptive treatment approaches might be essential. Chatbots could provide more adaptive treatments. The results of the studies on chatbots show that they are promising concerning implementing interventions. Nevertheless, research must determine their effectiveness to enable concise conclusions regarding the use of chatbots in people with chronic somatic disease. Altogether, research should further investigate innovative internet interventions by systematically digging deeper into potentially hard-to-reach, hard-to-treat populations. Studies should systematically evaluate the effectiveness and efficacy of internet interventions in different target groups to obtain robust data. At present, a 1:1 transferability of findings from the general population without a chronic somatic disease to people with a chronic somatic disease cannot be assumed.

Keywords: internet intervention, diabetes, coronary artery disease, depression, diabetes distress, chatbots

1 Prologue

1.1 Chronic Somatic Disease and Mental Health

A chronic somatic disease is a noncommunicable physical condition with a long duration and an often progressive course (World Health Organization [WHO], 2014). Living with chronic somatic disease requires ongoing treatment without which a worsening of the disease, a reduction in life expectancy or an impairment of the quality of life is expected (WHO, 2014). The most common conditions are cardiovascular disease, chronic respiratory disease, cancer and diabetes (WHO, 2021). These four make the most significant contribution to morbidity and mortality due to noncommunicable diseases globally (84%) and belong to the top 10 leading causes of death globally (WHO, 2020). The diseases impose an enormous social, psychological and economic burden with an estimated cumulative loss to the global economy of up to $47 trillion by 2030 (Bloom et al., 2011). The situation is particularly precarious in poorer countries, as related healthcare costs may quickly drain household resources (Mendenhall et al., 2017).

Besides chronic somatic diseases, mental disorders belong to the leading causes of the global health-related burden (Vos et al., 2017; Whiteford et al., 2013). Mental disorders are syndromes that disrupt people´s thinking, feeling, behaviour and the general level of functioning in a clinically significant way (American Psychiatric Association, 2013; WHO, 1993). Among 369 somatic and mental disorders, depressive disorders were the sixth leading cause of years lived with disability globally in 2019 (Abbafati et al., 2020). As a result, depression is considered one of the most burdensome disorders globally (WHO, 2008). The latest global epidemiological data reveals an average lifetime prevalence of major depression of 14.6% and a 12-month prevalence of 5.5% in high-income countries (Bromet et al., 2011).

The 12-month prevalence of mental disorders like depression is twice as high in people with a chronic somatic disease than in people without (Härter et al., 2007). In addition to the individual burden due to symptoms of depression, studies show associations between the comorbidity of mental and chronic somatic disease with increased health-related direct and indirect costs

(Baumeister, Haschke, et al., 2015; Baumeister, Knecht, et al., 2012; Hutter et al., 2010). Furthermore, this comorbidity is associated with increased morbidity, mortality, decreased treatment adherence and quality of life (Cuijpers et al., 2014; Katon et al., 2010). Addressing the comorbidity of mental and chronic somatic diseases is deemed a challenge of the 21st century (Sartorious, 2013; Scott et al., 2009).

Apart from manifest comorbid mental disorders, all diseases have both somatic and psychological components (Bundesärztekammer (BÄK) Kassenärztliche Bundesvereinigung (KBV) Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF), 2014, 2019; Deutsche Diabetes Gesellschaft (DDG), 2018). Individuals with a chronic somatic disease are frequently experiencing disease-related distress (Verhaak et al., 2005). Originally, Selye (1974) defined distress as a state of overload, such as being overtaxed by the demands of chronic somatic disease (Selye, 1974). This state can come with adverse emotional, cognitive and behavioural reactions to stressors that may cause temporary or permanent harm (Ridner, 2004). Stressors include challenging behavioural and cognitive-emotional tasks like dealing with a diagnosis or adhering to complex treatment plans (Dekker & de Groot, 2018). Disease-related distress can be attributed to the spectrum of chronic somatic disease, is to some degree normal and thus does not constitute a psychopathology per se (Fisher, Hessler, et al., 2014; Hudson & Moss-Morris, 2019; Snoek et al., 2015; Thom et al., 2019). However, elevated disease-related distress can become a disabling, clinically significant issue when present over an extended period (Atlantis et al., 2012; Barry et al., 2020; Lisy et al., 2018; Verhaak et al., 2005). Moreover, on average, individuals with a chronic somatic disease indicate lower quality of life and psychological well-being than people without (Baumeister et al., 2011; Kilian et al., 2001; Wikman et al., 2011).

When mental disorders in people with chronic somatic disease remain un- or undertreated, or elevated disease-related distress remains unaddressed, this has serious consequences.

First, comorbid mental disorders like depression have severe implications for individuals and society. On the individual level, comorbid depression is associated with worsened somatic disease-related outcomes, increased morbidity, mortality (Barry et al., 2020; Moussavi et al., 2007; Russ et

al., 2012) and reduced quality of life (Wikman et al., 2011). On the societal level, comorbid depression is associated with increased direct and indirect healthcare costs (Baumeister, Haschke, et al., 2015; Bokma et al., 2017; Hutter et al., 2010; Naylor et al., 2012; Stein et al., 2006). Economic costs exacerbate with the globally rising amount of individual years lived with chronic somatic disease due to ageing populations (Vos et al., 2017).

Second, elevated disease-related distress in people with a chronic somatic disease is common (Ferketich & Binkley, 2005; Mehnert et al., 2018; Skinner et al., 2020) and can be associated with limited quality of life (Alonso et al., 2004; Keles et al., 2007) and restricted psychological well-being (Kilian et al., 2001; Wikman et al., 2011) as well as worsened somatic disease-related outcomes (Batty et al., 2014). International and national clinical guidelines emphasise the importance of considering mental health in medical treatment of chronic somatic disease (Bundesärztekammer (BÄK) Kassenärztliche Bundesvereinigung (KBV) Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF), 2014, 2019; DDG, 2018; Knuuti et al., 2020). Nonetheless psychological interventions are often not integrated into the treatment of chronic somatic disease (Prince et al., 2007). Besides transdiagnostic commonalities across conditions (e.g. long duration, need for lifelong treatment) each chronic somatic disease comes with its own specifica (e.g. causes and associated stigma) and thus opens its own field of research. Editors of The Lancet refer to cardiovascular disease and diabetes as a global health issue (Beaglehole, 2001; Hirsch & Duval, 2013; Lancet, 2011). Starting from the overarching perspective of chronic somatic disease and mental health in general, two representatives of chronic somatic diseases will be examined in more detail.

1.1.1 Coronary artery Disease and Depression

Coronary artery disease (CAD) is a chronic somatic disease and one of the most frequent forms of cardiovascular disease (Mendis et al., 2011). Atherosclerosis in the coronary arteries characterises CAD (Mendis et al., 2011). Atherosclerosis is a pathological process that develops over time and obstructs blood vessels with deposits of fatty materials, cholesterol and other substances (Mendis et al., 2011; Rafieian-Kopaei et al., 2014). This process narrows the lumen of

the vessels and causes the arteries to become less flexible, which can subsequently restrict the blood supply to the heart (=myocardial ischemia) (Mendis et al., 2011; Rafieian-Kopaei et al., 2014). Clinical manifestations of CAD comprise acute coronary syndrome, including myocardial infarction, unstable angina and stable angina pectoris (Mendis et al., 2011). The latest global data reveals a prevalence of 197 million CAD cases worldwide in 2019, with a continuous rise since 1990 (Roth et al., 2020).

Getting a CAD diagnosis is a critical life event and can represent an unsettling experience for individuals (American Psychological Association (APA), 2007). In addition to physical symptoms like pain or shortness of breath, psychological symptoms of depression are common. About 10 to 30% of people with CAD also live with depression (Carney & Freedland, 2003; Nieuwsma et al., 2017; Rudisch & Nemeroff, 2003; Thombs et al., 2008; Tully & Baker, 2012). Sadness, feelings of emptiness or irritable mood are symptoms of depression and can be accompanied by somatic and cognitive symptoms (American Psychiatric Association, 2013). Diagnostic criteria of depression are defined by the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders fifth edition) or the ICD-10 (International Classification of Diseases, 10th revision) (American Psychiatric Association, 2013; WHO, 1993). For a diagnosis, symptoms must be accompanied by a clinically significant level of suffering or impairment of functioning (American Psychiatric Association, 2013; WHO, 1993).

A comorbid depression can worsen physical symptoms of CAD, is associated with cardiovascular morbidity, heightens the risk of CAD events like myocardial infarction and is related to all-cause and cardiac mortality (Barth et al., 2004; Lichtman et al., 2014; May et al., 2017; Van Melle et al., 2004). Research on comorbid depression in CAD consistently reveals severe implications for individuals regarding general functioning and quality of life (De Jonge et al., 2006; Parashar et al., 2006; Ruo et al., 2003). Studies indicate that reduced depression can be associated with more favourable health behaviour like medication adherence (DiMatteo et al., 2000) or the adoption of secondary prevention measures (Myers et al., 2012). The impact of comorbid CAD and depression on the individual level is accompanied by monetary consequences on the societal side. Direct (e.g. medical treatment) and indirect (e.g. work loss) costs due to the somatic condition double

with comorbid depression (Baumeister, Haschke, et al., 2015; Frasure-Smith et al., 2000; Rutledge et al., 2009; Szpakowski et al., 2017). Diabetes is a similar challenge for individuals and societies (Lancet, 2011).

1.1.2 Diabetes Mellitus Type 1 and Type 2 and Diabetes Distress

A deficient insulin production (type 1) or a poor compensatory insulin secretory response (type 2) characterises the metabolic disease diabetes (Torpy & Golub, 2011; WHO, 2016). Insulin is a hormone that regulates the plasma glucose level (WHO, 2016). Both types result in chronically increased plasma glucose levels (hyperglycaemia) if untreated (Torpy & Golub, 2011; WHO, 2016). The deficient insulin production in diabetes type 1 can be caused by autoimmune-mediated destruction of beta cells or by idiopathic destruction or failure of beta cells (Roep, 2003; Van Belle et al., 2011). Diabetes type 1 requires the daily administration of insulin (WHO, 2016). About 5 to 10% of all diabetes cases worldwide are diabetes type 1 (Maahs et al., 2010). Thus, most people with diabetes live with diabetes type 2 (90 to 95%) (Khan et al., 2020). In 2017, the prevalence of type 2 diabetes was 462 million cases worldwide (Khan et al., 2020). The individual and financial costs resulting from diabetes are rising globally, rapidly in developed countries, but lower-income countries are following suit (Khan et al., 2020).

Getting a diabetes diagnosis can be an overwhelming experience, a life-changing critical event (APA, 2007). In addition to physical aspects such as hyperglycaemia and fatigue, a life with diabetes entails numerous stressors (WHO, 2016). Stressors include the need for permanent attention to diet, self-treatment and monitoring, adhering to treatment plans and promoting coping mechanisms to deal with the disease and its consequences (American Diabetes Association, 2021a, 2021b). Individuals have to accomplish these tasks every day (American Diabetes Association, 2021a, 2021b). It must be taken into account that tasks are not static but change over time, and complications can arise (American Diabetes Association, 2021a, 2021b). Dealing with changing tasks and potential complications requires an increased commitment to building and expanding psychological resources to balance stressors and resources (Lazarus & Folkman, 1984). Psychological flexibility is an example of a psychological resource that can support individuals with

adapting to changing conditions (Dindo et al., 2017; Kashdan & Rottenberg, 2010). Ongoing imbalances between stressors and resources can lead to elevated diabetes distress (Ehrmann, 2020; Snoek et al., 2015). The definition of diabetes distress comprises emotional burdens, stresses and worries due to the chronic somatic disease diabetes (Schmitt et al., 2016). Diabetes distress is, to some extent, an expectable reaction to living with diabetes, but it can be a serious issue when distress levels are elevated (Young-Hyman et al., 2016).

Prevalence data on elevated diabetes distress in people with diabetes type 1 ranges between 20-40% (Dennick et al., 2015; Fisher et al., 2015; Sturt et al., 2015) and up to 50% (Fisher et al., 2016). Prevalence data of elevated diabetes distress in people with type 2 diabetes ranges between 20% (Fisher et al., 2008), 36% (Perrin et al., 2017) and up to 60% (Browne, Scibilia, et al., 2013). Research on elevated diabetes distress consistently reveals severe implications for individuals´ diabetes therapy and mental health (Robinson et al., 2018; Skinner et al., 2020). Elevated diabetes distress can be cross-sectionally and longitudinally associated with worsened somatic health-related self-management, glycemic control (Hessler et al., 2017; Kretchy et al., 2020; Skinner et al., 2020) and depression (Ehrmann et al., 2015). The risk of depression is twice as high in people with diabetes than in people without (Holt et al., 2014; Roy & Lloyd, 2012; Sartorius, 2018). Longitudinal studies suggest that elevated diabetes distress is associated with heightened incidence and persistence of depressive symptoms (Ehrmann et al., 2015). Depression and diabetes distress can be partially overlapping constructs (Burns et al., 2015; Snoek et al., 2015). The clinical appearance of both conditions includes irritable mood, lack of interest, drive, and weight changes (Esbitt et al., 2013; Holt et al., 2014; Snoek et al., 2015). However, elevated diabetes distress is a diabetes-specific psychological aspect of living with the disease and, therefore, causal for the emergence of diabetes distress whilst a diagnosis of depression does not imply aetiology (Snoek et al., 2015). In terms of its impact on self-management and glycaemic control, it could be similar to depression (Schmitt et al., 2021; Snoek et al., 2015). Studies show that reducing diabetes distress can lead to more favourable health behaviours (Evans et al., 2005; Hessler et al., 2014) and reduced symptoms of depression (Reimer et al., 2017), whilst improved outcomes due to the somatic condition are being

discussed (Skinner et al., 2020). Reducing elevated diabetes distress may be a central component in reducing costs on the individual level (e.g. regarding the quality of life (Schmitt et al., 2016; Snoek et al., 2015) and on the societal side as the emergence of complications and hospitalisations rise with increasing diabetes distress levels (Dieter & Lauerer, 2018; Hutter et al., 2010).

Findings suggest the relevance of treating comorbid mental disorders (Sartorious, 2013) and reducing elevated disease-related distress (Hudson & Moss-Morris, 2019) to reduce individual (Alonso et al., 2004) and societal costs (Atlantis et al., 2012; Chiu et al., 2017). Corresponding treatments include pharmacological and non-pharmacological approaches, mainly delivered face-to-face and increasingly complemented by digital solutions (Baumeister, Hutter, et al., 2012; National Institute for Health and Care Excellence (NICE), 2009; Tully et al., 2021).

1.2 Treatment of Mental Disorders and Elevated Disease-Related Distress

Pharmacotherapy can be indicated for people with a chronic somatic disease and moderate to severe depression (APA, 2019). The main types of antidepressant medication are selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) (Tully et al., 2021). An update of a Cochrane Review on antidepressants includes adults with various conditions like cardiovascular disease, diabetes and cancer (Rayner et al., 2010). Efficacy analyses include k =44 studies and N=3372 people (Rayner et al., 2010). Authors report an OR of 2.33 (95%CI 1.80 to 3.00) favouring antidepressants over placebo six to eight weeks after randomisation (Rayner et al., 2010). However, people in antidepressant groups, compared to those in placebo groups, on average experienced more side-effects like sexual dysfunction or dry mouth and were more likely to discontinue medication after six to eight weeks (Rayner et al., 2010).

SSRIs can be classified as safe and effective for people living with CAD and moderate, severe or recurrent depression, whilst TCAs and MAOIs seem to be contraindicated because of cardiac side effects (Lichtman et al., 2008). For people with diabetes, noradrenergic antidepressants and TCAs may impose a contraindication due to metabolic side effects (Deuschle, 2013). Authors of a systematic review recommend SSRIs as antidepressants among people with diabetes (Roopan &

Larsen, 2017). Nevertheless, SSRIs could increase the risk of hypoglycaemia and could be associated with weight gains in the long run (Roopan & Larsen, 2017).

A recent Cochrane Review that was conducted with my participation, investigated treatment effects of both, pharmacological and psychological interventions for depression in people with CAD (Tully et al., 2021). There is evidence that both, pharmacological and psychological approaches, may result in reduced depression symptoms at the end of treatment (Tully et al., 2021). However, the level of certainty of the evidence according to GRADE assessments (Schünemann et al., 2019) for both approaches is to be classified as low (Tully et al., 2021). Therefore, based on current evidence there might not be a universal recommendation regarding the approach of choice concerning the treatment of depression in people with CAD (Tully et al., 2021). Reflecting on indicated depression treatment approaches might be relevant for all chronic somatic diseases (Olver & Hopwood, 2013). Beyond the necessary considerations for antidepressants in physically healthy people, additional considerations must be made for people with a chronic somatic disease (Olver & Hopwood, 2013). These considerations concern the potential interactions of antidepressants with medication for physical symptoms and side effects of antidepressants, such as prolonging the QT-interval (Aronow & Shamliyan, 2020), which could be harmful to people with CAD in particular (Ostuzzi et al., 2019; Vaccarino et al., 2020).

Altogether regarding pharmacotherapy, antidepressants can effectively reduce depression in people with a chronic somatic disease, and antidepressants can interfere with the somatic condition (Baumeister, Hutter, et al., 2012; Ostuzzi et al., 2015, 2019). Whether an antidepressant can be administered should be decided on a case-by-case basis and might also depend on the duration and stage of the chronic somatic disease, potential side-effects and potential interactions with physical symptoms of the chronic somatic disease under consideration (Olver & Hopwood, 2013). The voting and weighing with respect to medication and the physical and psychological condition may be more complex than when applying non-pharmacological approaches. As polypharmacy and drug-to-drug or drug to disease interactions are common, non-pharmacological approaches may often be preferable (Scott et al., 2015).

Furthermore, pharmacological approaches may play a subordinate role in reducing elevated disease-related distress as it originates by definition from specific situational contexts and thus requires actions on a cognitive-emotional, social and behavioural level (Fisher, Gonzalez, et al., 2014). These actions can comprise psychological efforts to accept the disease as part of life and adjust to it, to face developmental tasks over time, to integrate what the disease entails into the broader (family) system and to draw courage and self-efficacy from it to carry on with life (Schmitt et al., 2016; Skinner et al., 2020; Snoek et al., 2015). There are non-pharmacological approaches to difficulties in dealing with elevated disease-related distress arising from these challenges (Chew et al., 2017). Non-pharmacological approaches can include addressing the mental health of people with a chronic somatic disease in routine care, structured group training, self-help groups, specific psychosocial services, and psychological interventions.

Psychological interventions can be effective in reducing elevated disease-related distress or treating mental disorders like depression in people with a chronic somatic disease (Baumeister, Hutter, et al., 2012; Chew et al., 2017; Harkness et al., 2010; Tully et al., 2021). Interventions can be derived from approved guideline therapies ("Richtlinienverfahren“), e.g. cognitive behaviour therapy (CBT), depth founded therapy or systemic approaches (European Association for Psychotherapy, 2021). The most studied and empirically supported representative of behavioural therapy in the last decades is CBT (David et al., 2018). Traditional CBT is a problem-oriented approach and focuses on emotional and cognitive change (Fenn & Byrne, 2013). Cognition is defined based on fundamental beliefs, dysfunctional assumptions and automatic negative thoughts that contribute to the development and maintenance of mental disorders (Beck, 1976). Core techniques of CBT comprise cognitive and behavioural strategies that target the identification and removal of maladaptive patterns of thinking, emotional reactions and behaviours (Fenn & Byrne, 2013). The approach is based on Beck´s cognitive model, which assumes that the individual perception of events influences behaviours and emotions (Beck, 1976). That is, not situational contexts determine what a person feels and does, but rather the person's interpretation of the situation (Beck, 1976).

Overall, CBT is a directive, time-limited, structured approach and belongs to the guideline procedures for depression (Fenn & Byrne, 2013).

In recent years approaches of the third wave of behavioural therapies are increasingly being researched (Hayes & Hofmann, 2017). While the first wave embraces stimulus-response mechanisms to explain human behaviour, the second wave, to which CBT belongs, switches cognitions in between (stimulus-cognition-response) (Hayes & Hofmann, 2017). Compared to the second wave of behavioural therapy, third-wave therapies emphasise contextual and experiential aspects (Heidenreich & Michalak, 2013). The third wave comprises different approaches like the acceptance- and commitment therapy (ACT), dialectical-behaviour therapy (DBT), metacognitive therapy (MCT) or the cognitive analysis system of psychotherapy (CBASP) (Heidenreich & Michalak, 2013). An increasingly researched approach of the third wave therapies in the context of chronic somatic diseases is ACT (Kuba & Weißflog, 2017; Öst, 2014).

In comparison to CBT, ACT explicitly includes techniques to foster acceptance, mindfulness and value orientation (Heidenreich & Michalak, 2013). Mindfulness involves the training of awareness for inner and outer states and experiences (Hayes, 2004). Acceptance includes adapting to unchangeable aspects in life (Hayes, 2004). In ACT, identifying values and supporting committed action towards them is more central than the removal of symptoms or disorders (Hayes & Smith, 2006). Change processes are therefore promoted in the sense of "towards-to“-strategies (e.g. towards a value and goal-oriented life) than "away from“-strategies (e.g. away from unpleasant symptoms) (Hayes & Smith, 2006). The aim of ACT is the development of higher psychological flexibility regarding one´s own positive and negative experiences (Hayes, 2004). Thereby ACT supports people to face emotional problems and unchangeable aspects in life with mindfulness and acceptance instead of experiential avoidance (Hayes, 2004). This approach seems to be a suitable approach to support the acceptance of an unchangeable condition (Kuba & Weißflog, 2017) and to address situational contexts of living with a chronic somatic disease that is associated with elevated disease-related distress (Behrouz et al., 2016; Kuba & Weißflog, 2017).

Research disciplines have emerged for somato-psychological topics like psycho-cardiology or psycho-diabetology (Hermann-Lingen, 2021; Ladwig et al., 2014; Young-Hyman et al., 2016; Zipfel et al., 2016). These disciplines deal specifically with the issues arising from co-morbidity, like the mental health in people with CAD or diabetes (Ladwig et al., 2014; Young-Hyman et al., 2016).

In Germany, the psychological care landscape for a chronic somatic disease includes inpatient, outpatient and rehabilitation services (Blümel & Busse, 2015; Tikkanen, 2020). In general, mental disorders in people who also have a chronic somatic disease can be treated using F-codes (The letter F signifies mental disorders) of the ICD-10 (WHO, 1993) (Blümel & Busse, 2015; Tikkanen, 2020). Researchers and practitioners declare that elevated disease-related distress can be an indication for treatment (Fisher, Gonzalez, et al., 2014; Schmitt et al., 2021; Snoek et al., 2015). Particular difficulties in dealing with the chronic somatic disease can be encrypted using the F54.0 diagnosis ("Psychological or behavioural factors associated with disorders or diseases classified elsewhere“) of the ICD-10 (WHO, 1993). These will also be coded in the ICD-11 ("Psychological or behavioural factors affecting disorders or diseases classified elsewhere“) (WHO, 2018). In Germany, about 30% of people with depression in need of treatment in the general population are in treatment (Engels et al., 2020). Just a small part of this 30% might be attributable to people living with chronic somatic disease and depression; thus, depression often remains un- or undertreated in this population (Serbanescu & Baumeister, 2016). For the treatment of depression in people with a chronic somatic disease, expertise in both areas, medical and mental, might be necessary (Koch-Gromus et al., 2011; Serbanescu & Baumeister, 2016). The type and number of specific, interdisciplinary services seems to vary across different chronic somatic diseases and current and comprehensive nationwide data is not available for all of them. Around 36,000 psycho-oncological services (e.g. psychosocial counselling centres, palliative care) in all sectors (in-/outpatient and rehabilitation) were identified for the year 2016 in a systematic survey (Schulz, Bleich et al., 2018). No comparable systematic data can be found for psycho-cardiological/diabetological services. Nevertheless, psycho-diabetology is certified as a further education programme for physicians, medical specialists, psychologists and psychotherapists (Kulzer, 2021). In the field of psycho-

cardiology specialists can complete courses in basic psycho-cardiological care (Hermann-Lingen, 2021). Some clinics, mainly in the rehabilitation sector, offer specialised psycho-cardiological/-diabetological or behavioural medicine concepts (Zipfel et al., 2016). In explorative comparison, there were N=1,151 registered psycho-oncologists in 2018 (Schulz, Bleich et al., 2018) and N=55 registered psycho-diabetologists in 2017 (Deutsches Ärzteblatt, 2017). Additionally, N=171 specialised diabetes psychologists were registered in 2017, meaning that they have at least completed courses in basic psycho-diabetological care (Deutsches Ärzteblatt, 2017). In psycho-cardiology, N=41 specialised cardiology psychologists or psycho-cardiologists explicitly self-registered as providers of psychocardiological services (cardiologists and members of the psychological disciplines) (Hermann-Lingen, 2021). Apart from the fact that the numbers seem to have not yet been systematised or often come about on the basis of voluntary self-registrations, numbers could reflect a heterogeneous establishment of services across different chronic somatic diseases in Germany.

Overall, it can be assumed that the mental health in people with a chronic somatic disease in general (Serbanescu & Baumeister, 2016) and elevated diabetes distress in people with diabetes (Young-Hyman et al., 2016) or depression in people with CAD in particular (Ladwig et al., 2014) often remains un- or undertreated (Bengel et al., 2003).

1.3 Barriers to Mental Health Care

Various barriers can impede access to or availability of psychological treatments (Mohr et al., 2010; Naylor et al., 2012). Against the background of the macro-societal relevance and the importance for the individual, psycho-somatic co-morbidities can be deemed a severe issue (Sartorious, 2013). Treatment barriers arise in various respects.

First, people often experience structural and individual stigmatisation or face limited mobility, time and resources (Alonso et al., 2016; Sartorious, 2013). Research suggests that people often face discriminatory behaviours or stigmatising attitudes related to diabetes (Browne, Ventura, et al., 2013; Gredig & Bartelsen-Raemy, 2017) or CAD (Merz et al., 2017), such as being blamed for the disease (Joachim & Acorn, 2000). There seems to be even more stigmatisation concerning mental

disorders in the general public (Alonso et al., 2009, 2016). People with a mental disorder seem to generally have less access to primary health care (Haussleiter et al., 2021; Miller et al., 2003) and also seem to receive inferior somatic care for their diabetes or cardiovascular disease (Desai et al., 2002; Rathore et al., 2008). In addition to stigma-associated barriers, there are system-immanent barriers to mental health care for the medically ill.

So second, social system-immanent barriers can limit access to and availability of guideline-based treatments (Bengel et al., 2003; Serbanescu & Baumeister, 2016). These can comprise the implementation of screenings, site-specific/geographic conditions and financial resources (Bengel et al., 2003; Serbanescu & Baumeister, 2016). An often discussed problem regarding the implementation of screenings is that related services may not easily cover potentially discovered needs for psychological care. On the one hand, this could be because interdisciplinary care of chronic somatic diseases does not include psychologists, psychotherapists, or psychiatrists in most cases (Chen et al., 2016; Sonnenmoser, 2009). On the other hand, referral to consultant and liaison psychosomatics/outpatient psychotherapy seems complicated (Chen et al., 2016; Deter et al., 2017).

Additionally, specialised psychologists like psycho-cardiologists or psycho-diabetologists are all together still rare in treating mental health-related issues in individuals with a chronic somatic disease (Zipfel et al., 2016). Consequently, researchers assume that psychological symptoms in people with a chronic somatic disease are often not sufficiently treated (Bengel et al., 2003). Surveys predict that the current reality of care cannot meet the further increasing demand for treatment (Bundespsychotherapeutenkammer, 2018). The situation is all the more pronounced in rural areas where the number of licensed psychologists per inhabitant is significantly lower than in urban areas (Bundespsychotherapeutenkammer, 2018). Beyond that, system-immanent barriers come especially to fruition in developing countries with lower budgets for healthcare systems (Soltani et al., 2004).

Third, barriers can also arise from health care professionals not being able to address disease-related distress or symptoms of mental disorders within routine consultations. Routine consultation times are broadly limited (Irving et al., 2017). Irving and colleagues (2017) found that in 18

economically developed and low-income/middle-income countries representing about 50% of the global population, patients on average spend 5 minutes or less with their primary care physician (Irving et al., 2017). Many vital issues regarding the chronic somatic condition need to be covered within routine consultations (Rutten et al., 2018). Issues include physical examinations, medical history evaluations, explanation of treatment methods or surgery procedures, and risk assessments (Knudtson et al., 2006; Ojeifo & Berkowitz, 2015). Consequently, consultation models often do not include time for psychological aspects (Irving et al., 2017).

While health care has traditionally been delivered face-to-face, digitisation is expanding the possibilities of care (Olayiwola et al., 2016; Wasfy et al., 2016). The use of internet-based services in medical fields enables online held consultations (Olayiwola et al., 2016; Wasfy et al., 2016), apps to support medication adherence (Peng et al., 2020) or fully automated software agents, so-called chatbots, which deliver health-related information to individuals in a conversational style (Lim et al., 2021). Digitised applications such as internet interventions can be the key to sustainably reducing many barriers to psychological treatment (Naslund et al., 2017; Paganini et al., 2016).

1.4 Psychological Internet Interventions

An internet intervention can be defined as "a primarily self-guided intervention program that is executed by means of a prescriptive online program operated through a website and used by consumers seeking health- and mental-health related assistance. The intervention program itself is designed to create positive change or enhance knowledge, awareness, and understanding with regard to mental health (Barak et al., 2009, p.5).“ Sound health-related education materials and interactive web-based components are used for this purpose (Barak et al., 2009). Internet interventions can be characterised by the central components of guidance, technical implementation, theoretical foundation and area of application (Paganini et al., 2016).

Guidance refers to the amount of human support with processing through the intervention (Baumeister et al., 2014). As a component of internet interventions, guidance can vary, ranging from unguided interventions to thoroughly guided support (Baumeister et al., 2014). Guidance includes human interactions focusing on feedback on user progress and is usually provided by an eCoach

(e.g. psychologist/physician) (Baumeister et al., 2014). Guidance is a presumed mechanism to foster treatment adherence, thus keeping users in the intervention (Moshe, Terhorst, Philippi, et al., 2021). Systematic reviews show that guided interventions can lead to better outcomes than unguided interventions (Moshe, Terhorst, Philippi, et al., 2021; Richards & Richardson, 2012; Spek et al., 2007). At the same time, guidance can hamper the cost-effectiveness of interventions as it increases the overall cost of the intervention (Baumeister et al., 2014). In that, guidance can relativise the effectiveness advantage of guided over unguided interventions when costs exceed the benefits (Baumeister et al., 2014). Guidance could be more relevant for people with a chronic somatic disease and significant co-morbid psychological issues (Jernelöv et al., 2012; Meeuwissen et al., 2011) than for people with one disease or fewer associated issues like chronicity or disease severity (Christensen et al., 2009). One reason for this is that the overall load might be higher as people do not only need to adhere to the psychological treatment but also to somatic treatment (e.g. adhering to medication regimen, regular appointments with physicians and specialists). At this point, the rapidly advancing digitalisation can be used to find technical solutions.

This leads to the second component by which internet interventions can be characterised: the technical implementation (Paganini et al., 2016). Intervention contents, user feedback, ratings and regular assessments can be delivered on a website, via E-Mail, video(-conference), app or audio (Paganini et al., 2016). New technologies like chatbots, that were not well conceptualised or established in the field of mental health care at the start of this doctorate in 2017 (Fitzpatrick et al., 2017; Ly et al., 2017) could play an essential role as a mode of delivery of psychological interventions in the future (Lim et al., 2021). Technical solutions that e.g. mimic a human-like feedback could enable fully automated guidance and thus provide a high level of support at low cost (Titov et al., 2013).

The third component of internet interventions is the area of application (Paganini et al., 2016). Depending on the time of administration of the intervention, different areas can be distinguished, namely prevention, treatment and aftercare (Baumeister et al., 2017). In the area of prevention, the focus could be on low-threshold services for people with a chronic somatic disease regarding the

development of a mental disorder (Kampling et al., 2021). The adjacent area of an application refers to the administration of internet interventions to treat manifest, clinically relevant mental disorders like depression (Sander et al., 2016). In aftercare for example, psychological interventions can contribute to the maintenance of treatment effects following an inpatient stay (Lin et al., 2013).

Finally, internet interventions can be described by their underlying theory (Paganini et al., 2016). Various psychotherapeutic orientations are possible as theoretical foundations (Paganini et al., 2016). To date, internet interventions are most often based on CBT (Ebert et al., 2018). Reasons are good empirical evidence regarding CBT-based interventions and easy transferability into the online format (Sander et al., 2016). Transferability benefits from CBT´s high levels of structure and psychoeducation (Sander et al., 2016). Other theoretical approaches that extend CBT, like ACT, are becoming increasingly popular for translation into online formats in the field of chronic somatic diseases (Öst, 2014). In ACT, advantages of CBT regarding the transfer into an online format can be combined with the theoretically emphasised focus on accepting disease-related challenges (Lin et al., 2017).

Taken together, internet interventions could be offered on a large scale, at low cost and at different stages of a chronic somatic disease (prevention, treatment, aftercare) (Lin et al., 2013). Advancing digitalisation enables scalable, flexible forms of service delivery, facilitating access to services for highly stressed target groups as they do not come with substantial cost or time-spatial requirements (Ebert et al., 2018; Titov et al., 2013). Internet interventions could be incorporated into existing in- or outpatient care and rehabilitation of a chronic somatic disease (Lin et al., 2013). The potentials of internet interventions in the field like a high level of scalability and flexibility could be the key to downsize treatment barriers (Ebert et al., 2018). The high degree of integrability into everyday life and standard care could enable specialists to better address mental health during routine consultations (Wasfy et al., 2016). For the future, it is conceivable that specialists prescribe psychological internet interventions when detecting elevated disease-related distress or when recognizing symptoms of depression in routine care (Titov et al., 2018). An increased availability of internet interventions could help to achieve a better integration of body and mind when treating a

chronic somatic disease (Sartorious, 2013). Whether and to what extent potentials of internet interventions can be harnessed in terms of providing treatments in this population still needs to be investigated (Baumeister et al., 2021; Carlbring et al., 2018; Ebert et al., 2018).

1.5 Evidence of Internet Interventions for People with Chronic Somatic Disease

In comparison to research on internet interventions for mental disorders in physically healthy populations, little research exists in populations with a chronic somatic disease (Andersson, 2018; Baumeister et al., 2021). Systematic reviews suggest that research in the field seems to have long focused internet interventions for behavioural aspects such as improving self-management, physical activity or decreasing smoking and alcohol consumption (Mehta et al., 2019; Van Beugen et al., 2014). Although this is undoubtedly very important as several chronic somatic diseases share these behavioural (risk) factors (WHO, 2021), the number of studies that evaluated internet interventions for mental health in this population is comparatively small (Charova et al., 2015).

Three studies systematically reviewed this body of research on internet interventions for mental health in people with a chronic somatic disease. First, van Beugen and colleagues (2014) evaluated the effectiveness of guided CBT-based internet interventions compared to passive control groups. The authors reported small short-term effect sizes for anxiety (d = 0.17, 95%CI 0.01 to 0.32, p = .03, k = 10), depression (d = 0.21, 95%CI 0.08 to 0.34, p = 0.01, k = 15) and disease-related distress (d = 0.17, 95%CI 0.03 to 0.31, p = .02, k = 6) (Van Beugen et al., 2014). Second, Charova and colleagues (2015) found small short-term effects of mainly CBT-based, (un-)guided internet interventions on depression in people with a chronic somatic disease (d = 0.36, 95%CI 0.20 to 0.52, p < 0.01, k = 9). Third, Mehta and colleagues (2019) found small effects of CBT-based internet interventions on anxiety (SMD = 0.45 ± 0.09, p < 0.001, k = 25) and depression (SMD = 0.31 ± 0.04, p < 0.001, k = 25). However, reviews included relatively few studies with a mostly unclear or high risk of bias (Charova et al., 2015; Mehta et al., 2019; Van Beugen et al., 2014). Data on long-term effects are missing, and studies mostly included populations with chronic somatic diseases other than diabetes or CAD (Charova et al., 2015; Mehta et al., 2019; Van Beugen et al., 2014).

In conclusion, only a few randomised controlled trials (RCT) investigated internet interventions for mental health in people with diabetes (Schmidt et al., 2018) or CAD (Tully et al., 2021). Nevertheless, pioneering work in the field was done by several research groups.

Regarding diabetes, Nobis and colleagues (2015) evaluated a guided CBT-based internet intervention for people with type 1 or type 2 diabetes. The primary outcome was depression, secondary outcome, amongst others, was diabetes distress. Within secondary analyses, authors found a significant reduction of diabetes distress post-treatment (d = 0.58, 95%CI 0.33 to 0.83, p < 0.001). This effect persisted after six month (d = 0.50, 95%CI 0.04 to 0.54, p < 0.001) (Ebert et al., 2017). Also, on the level of secondary analyses, van Bastelaar and colleagues (2011) found a significant effect on diabetes distress in a group receiving a CBT-based internet intervention compared to a waitlist control group. Likewise, on the level of secondary analyses, Newby and colleagues (2017) found large short-term between-group differences in the intervention group receiving a CBT-based treatment in comparison to a treatment-as-usual control group on diabetes distress (g = 0.80, 95%CI 0.32 to 1.27, p < 0.05). However, this trial assessed multiple primary outcomes, and only people with major depression were included.

Results of these RCTs suggest that CBT-based internet interventions could effectively reduce diabetes distress, but existing studies were not powered for this outcome (Newby et al., 2017; Nobis et al., 2015; van Bastelaar et al., 2011). All studies investigated CBT-based interventions, but ACT may be of particular interest as a theoretical framework for the population because it explicitly includes the acceptance of unchangeable aspects of living with diabetes (Gregg et al., 2007).

To my knowledge, at the beginning of this doctorate in 2017, studies neither investigated diabetes distress as the primary outcome of an internet intervention nor were there sufficient studies on online or face-to-face ACT-based interventions for people with type 1 and type 2 diabetes. Since then this has not changed much but first steps have been taken towards evidence on ACT-based interventions for people with diabetes. A recent systematic review and meta-analysis investigates face-to-face ACT-based interventions for people with diabetes type 2 (Ngan et al., 2021). Meta-analyses reveal a small pooled effect size of SMD = -0.37 (95% CI -0.63 to -0.12, p < 0.01, k = 5)

for the reduction of diabetes distress in intervention groups compared to (enhanced) treatment-as-usual control groups (Ngan et al., 2021). Additionally, authors report reductions in HbA1c-levels (MD = -0.35 95% CI -0.67 to -0.04, $p < 0.03$, $k = 3$) up to four weeks post-intervention (Ngan et al., 2021). Analogous to a recent systematic review on CBT-based internet interventions for people with diabetes (Yap et al., 2021), the next step could be to systematise evidence on ACT-based internet interventions for people with diabetes and diabetes distress.

The research situation regarding internet interventions for people with diabetes is similar to that for people with CAD, but pioneering has already been done in this area as well. Regarding CAD, Norlund and colleagues (2018) investigated a 14-week CBT-based internet intervention in comparison to a treatment-as-usual control group in people who have had a recent myocardial infarction (<3 month ago) and symptoms of depression or anxiety (HADS >7) (N = 239). There were no significant differences between groups post-treatment (β = -0.47, 95% CI -1.95 to 1.00, $p = 0.53$) (Norlund et al., 2018). Schneider and colleagues (2020) investigated a CBT-based internet intervention for depression and anxiety in people who had an acute coronary event in the last 24 months. Results showed significant between-group improvements for the intervention group compared to the control group on anxiety ($d = 1.62$ 95%CI 1.00 to 2.24) and depression ($d = 1.09$ 95%CI 0.51 to 1.66) (Schneider et al., 2020). However, the trial was underpowered due to recruitment difficulties (N = 53 instead of the planned N=70 participants) (Schneider et al., 2020). To date, studies in the field are rare and inconclusive, and it seems particularly remarkable that many report recruitment difficulties (Norlund et al., 2018; Schneider et al., 2020). More research is needed to gain knowledge about internet interventions for people with CAD and depression. Linked to this is the question of which psychotherapeutic approach should be chosen. Taken together, CBT belongs to the guideline procedures for the treatment of depression (European Association for Psychotherapy, 2021), and it is the approach with the most evidence in the field of internet interventions (Sander et al., 2016). Additionally, CBT can be an effective treatment for reducing depression in people with CAD (SMD = -0.55 95%CI -0.80 to -0.31) (Tully et al., 2021). Considering

previous trials in the field of CAD and internet interventions, evidence is needed on whether using a CBT-based internet intervention for people with CAD is feasible.

Overall, it can be stated that research on internet interventions for mental health in adults with chronic somatic disease in general and CAD or diabetes in particular still benefits from going through clinical study phases to determine if, how and when an intervention would be beneficial for a specific population (Park et al., 2020). Feasibility trials can be implemented to put innovative intervention techniques to test before they are used on a large scale and to reinforce the development of full-scale trials (Eldridge et al., 2016). Therefore, the focus of feasibility trials is not on effectiveness or efficacy (Eldridge et al., 2016). Primarily, randomised controlled feasibility trials can be used to assess essential parameters that are needed to properly design a definitive trial (Eldridge et al., 2016). Thus, a focus can lie on evaluating study recruitment (e.g. willingness of participants to be randomised, number of eligible participants) and the acceptability of an intervention (e.g. satisfaction, adherence) (Eldridge et al., 2016). Feasibility trials can also include assessments of characteristics of intended outcome measures and the assessment of negative effects due to treatment (Eldridge et al., 2016).

Internet Interventions for people with a chronic somatic disease are a promising area of research as they offer opportunities to reduce gaps in mental health services (Vaidyam et al., 2019). Research on needs and preferences regarding the mental health care of people with a chronic somatic diseases emphasises the importance of adaptive and flexible delivery modes (Roberge et al., 2016). This makes digital implementation options particularly interesting for increasing access to and easing integration of psychological interventions into the care of people with chronic somatic disease (Baumeister et al., 2021). Systematic reviews and meta-analyses show that internet interventions can be a suitable format to provide adequate psychological treatment in physically healthy populations (Andersson, 2018). First systematic reviews suggest that this also holds for people with a chronic somatic disease (Carlbring et al., 2018), but the evidence is still rare or inconclusive in the field of CAD or diabetes (Baumeister et al., 2021; Charova et al., 2015; Cotter et

al., 2014; Tully et al., 2021). The research area faces challenges that need to be tackled to reduce research gaps.

1.6 Research Gaps and Challenges

Diabetes and CAD are among the most costly diseases worldwide (Bloom et al., 2011). Persons concerned are often experiencing elevated disease-related distress or symptoms of depression (Koch-Gromus et al., 2011). Both societal and individual costs can increase with comorbid mental health issues in terms of, e.g. declines in quality of life (Baumeister et al., 2011) or increased health care costs (Chiu et al., 2017; Haschke et al., 2012; Katon & Ciechanowski, 2002). People with a chronic somatic disease are about twice as likely to suffer from a mental disorder than those without (Härter et al., 2007). In addition, a high proportion of people with a chronic somatic disease also lives with increased disease-related distress (Ferketich & Binkley, 2005; Mehnert et al., 2018; Skinner et al., 2020). This fact is all the more pronounced as recent studies indicate that people with a chronic somatic disease are amongst the most vulnerable populations regarding mental health in times of the COVID-19 pandemic (Sayeed et al., 2020). Consequently, researchers state the need for additional mental health resources for people with chronic somatic disease due to the COVID-19 pandemic (Sayeed et al., 2020). Effective treatments for mental disorders exist, but most of them are time and place-bound, are too few in number or bear drug-to-drug or drug-disease interactions (Baumeister, Hutter, et al., 2012; Tully et al., 2021). So, mental disorders often remain un- or undertreated, elevated disease-related distress often unaddressed, due to various barriers. Internet interventions can help overcome treatment barriers (Paganini et al., 2016). Further evidence at the interface of internet interventions for mental health in people with a chronic somatic disease could help to pave the way towards widespread availability and use (Serbanescu & Baumeister, 2016).

The rapid progress of digitalisation makes the field of research a fast-growing and changing one, facing theoretical, methodological and practical challenges and in particular the following at the beginning of this doctorate in 2017.

First, a theoretical challenge comprises capturing and and mapping evidence of internet interventions for people with chronic somatic disease. Systematising existing knowledge regarding

the current state-of-the-art of internet interventions for people with a chronic somatic disease helps to identify areas to work on. Previous research indicates that people with a chronic somatic disease could benefit from particular flexible modes of delivery that are easily integrable in medical treatment (Roberge et al., 2016). At this point it is important to generate knowledge on innovative ways to provide this. Consequently, another theoretical challenge emerges with regard to chatbots and their use in the context of mental health. A definition of chatbots can be taken from computer sciences, where chatbots are defined as computer programmes that enable access to information and services through automated text- or voice-based natural language dialogues (Abdul-Kader & Woods, 2015). This technology allows people to converse with a technical system regardless of the availability of human, time and place-bound resources (Abdul-Kader & Woods, 2015). Compared to accessing content on an online platform, this delivery format consists of synchronous interactions (Abdul-Kader & Woods, 2015). Technical approaches like chatbots could automatically guide participants through internet interventions or even fully deliver psychological interventions with a high degree of flexibility and adaptability to individual needs. The use of chatbots for mental health-related issues is not a new idea, with Joseph Weizenbaum conducting rudimentary tests with the chatbot ELIZA in 1966, but promising attempts to provide adequate psychological treatment have only emerged with advancing digitisation recently (Fitzpatrick et al., 2017; Ly et al., 2017). So second, the acquisition of a better understanding of concepts, evidence and role of chatbots in mental health care is another theoretical challenge in the field (Fitzpatrick et al., 2017; Ly et al., 2017).

Methodologically, research needs to determine to what extent internet interventions for people with CAD and depression (Johansson, Westas et al., 2019) or diabetes and elevated diabetes distress (Schmidt et al., 2018) are feasible, as the number of studies in the field is low (Johansson, Westas et al., 2019; Schmidt et al., 2018). Feasibility trials are indicated to answer whether and how intended methodologies are applicable for the use in large randomised controlled trials in certain populations (Eldridge et al., 2016). Additionally, they help to test innovative technologies, especially in fields with a scarce and heterogeneous scientific landscape and ethical responsibilities due to the often elevated level of individual suffering and involvement of societal resources (Oxman, 2004).

This need is all the more pronounced when it concerns innovative treatment concepts like chatbots (Guyatt et al., 2008; Oxman, 2004). Results of feasibility trials should then be used to inform decisions of study design, intervention contents or safety procedures (Eldridge et al., 2016). These considerations lead to practical challenges in the field.

It is vital to different stakeholders like researchers, funders, or patients to implement resource-efficient projects (Guyatt et al., 2008). Testing whether a planned study design and intervention work prior to its investigation on a large scale can help ensure this for all involved parties (Eldridge et al., 2016). Results of smaller-scale studies may point to necessary adjustments regarding the internet intervention or study design and may help to identify and reduce negative effects of treatment (Eldridge et al., 2016). In that, results may be helpful to identify improvement potentials regarding the implementation of resource-efficient projects (Eldridge et al., 2016). Overcoming this practical challenge of the field might 1) support the development of safe and sound internet interventions, 2) support the conduct of high-quality studies that yield robust results on effectiveness, 3) provide the best possible interventions to patients, and 4) help decision-makers in the field decide effectively and most reasonably which and how related projects can be funded (Eldridge et al., 2016). This thesis attempts to address these challenges and to reduce some of the research gaps.

1.7 Scope of the Dissertation

The prologue of the present dissertation describes why innovative internet interventions should be considered a component of the treatment of people with chronic somatic disease.

In a nutshell, people with a chronic somatic disease in general and CAD or diabetes in particular are often experiencing elevated disease-related distress and are at high risk of also living with a mental disorder (Levenson, 2007). Various barriers hamper access to and uptake of psychological treatment (Mohr et al., 2010; Naylor et al., 2012). Internet interventions can contribute to overcoming these barriers (Paganini et al., 2016). A crucial research gap is the sparse and not yet conclusive evidence base, which limits the potentials of internet interventions in these populations (Serbanescu & Baumeister, 2016). This bottleneck was the starting point of the present dissertation.

Proceeding from this, research shows that psychological treatments for people with a chronic somatic disease need to fit into a complex structure of daily routines and medical care (Roberge et al., 2016). In light of the findings of the systematic overview (publication IV of this dissertation), other cutting-edge research (Fitzpatrick et al., 2017; Ly et al., 2017) and technological advances in various sectors (e.g. in the economic domain) it is evident that chatbots could meet this need.

At this point, theoretical research gaps tie up to methodological and practical ones. So within the scope of this dissertation, first, a better understanding of the current evidence on (chatbot-based) internet interventions for chronic somatic diseases is needed. Secondly, two trials are being conducted to investigate the feasibility of psychological internet interventions for people with CAD or diabetes. Third, feasibility studies provide practical implications on how to generate high-quality evidence and on how to use individual and societal resources responsibly. Fourth, innovative technologies like chatbots could expand mental health services for people with a chronic somatic disease in the future, but in the beginning of this doctorate in 2017 they are not well-defined, conceptualised, investigated or widely available in the field at all. This dissertation will contribute to reducing these research gaps.

2 Aim and Dissertation Programme

The dissertation programme comprises the investigation of the feasibility of innovative internet interventions for mental health in adults with a chronic somatic disease. Each publication investigates specific research questions dedicated to this topic. Thereby, the dissertation programme aims to reduce identified research gaps in the field. Figure 1 demonstrates the central elements and studies of the dissertation. Within the framework of the dissertation programme, six publications cover the following superordinate research questions:

1) What is the state-of-the-art of internet interventions for people with a chronic somatic disease?

2) Is a guided CBT-based internet intervention for individuals with coronary artery disease and elevated symptoms of depression feasible?

3) Is a guided ACT-based internet intervention for individuals with diabetes and elevated diabetes distress feasible?

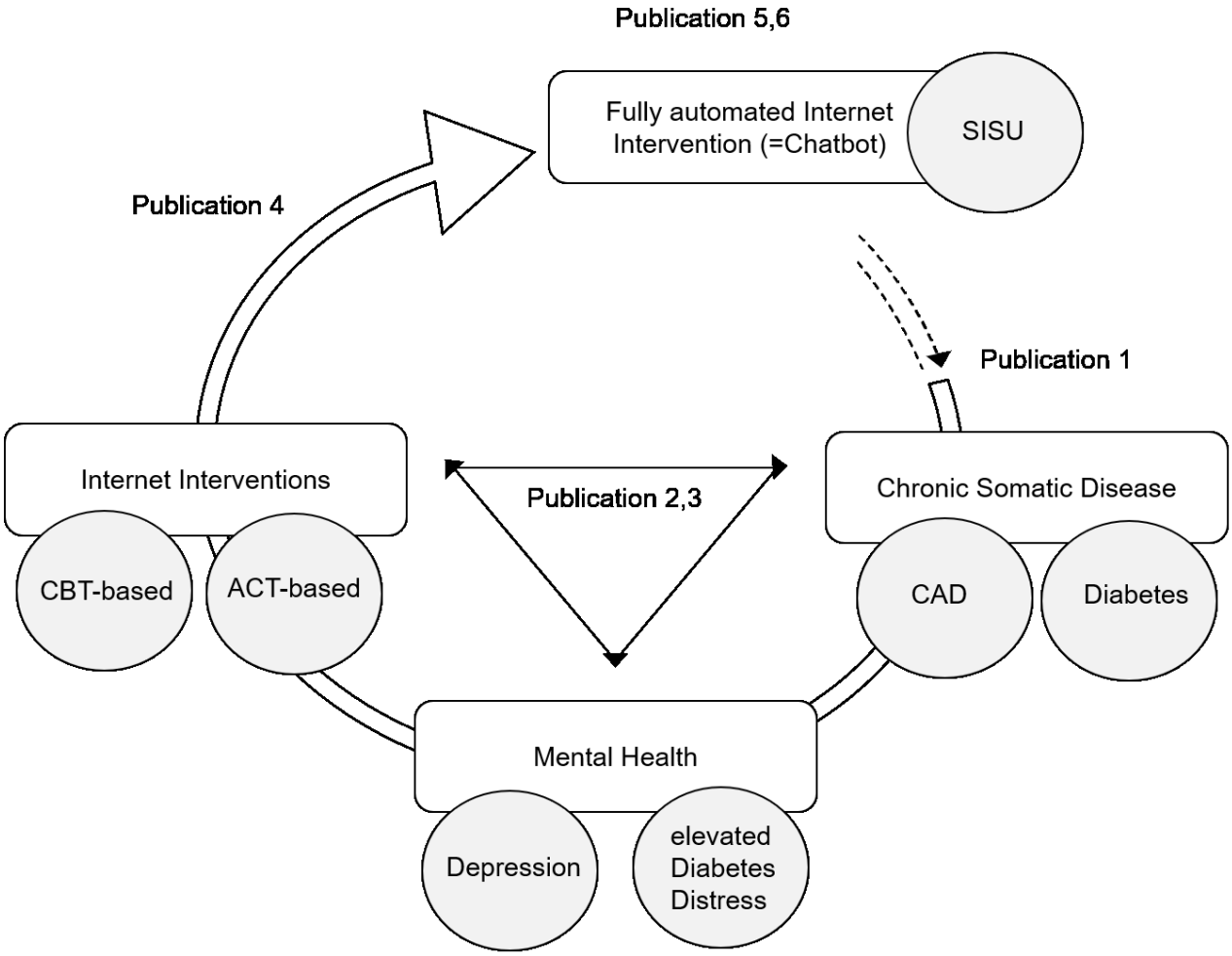
4) How could chatbots be conceptualised and systematised in the field of mental health care and what is the current evidence on chatbots for mental health-related issues?

5) Is the developed chatbot ("SISU“) feasible to guide participants through a psychological intervention?

6) How can SISU be optimised and investigated within a full-scale randomised controlled trial?

Figure 1

Overview of Central Elements and Studies of the Dissertation



Note. Abbreviations CAD = Coronary artery disease, CBT = Cognitive Behaviour Therapy, ACT = Acceptance and Commitment Therapy, SISU = Software-Agent providing a brief Intervention for Self-help to Uplift psychological well-being.

3 Overall Context of the Publications

3.1 Publication I: Internet Interventions in Chronic Somatic Disease

Bendig, E., Bauereiß, N., Ebert, D. D., Snoek, F., Andersson, G., & Baumeister, H. (2018). Internet-based interventions in chronic somatic disease. *Deutsches Ärzteblatt International, 115*(40), 659-665. https://doi.org/10.3238/arztebl.2018.0659

The first publication focussed on conceptualising and mapping the research landscape of existing internet interventions for people with a chronic somatic disease. Therefore, a meta-review approach was chosen, including systematic reviews and meta-analyses which included RCTs that compared internet interventions to waitlist-control/minimal intervention/no intervention control groups. The meta-review supports insight into the thematically broad scope of existing literature. The article defines internet interventions and presents current evidence in the field of chronic somatic disease. The systematic overview suggests that internet interventions are used for a wide range of topics regarding behaviour change. The article discusses the field's current limitations, highlighting the need for further research as findings are promising but not yet generalisable to specific chronic somatic diseases like CAD or diabetes.

Consequently, the focal point of the subsequent two studies was to investigate internet intervention for these two populations specifically. Therefore, two randomised controlled trials were conducted (study two and three). Within these trials, two different internet interventions that were successfully evaluated in other contexts were further developed and adapted to coronary artery disease (CAD) or diabetes. The primary outcome of both studies was feasibility.

3.2 Publication II: Internet Intervention for People with CAD

Bendig E., Bauereiß, N., Buntrock, C., Habibović, M., Ebert, D. D., Baumeister, H. (2021). Lessons learned from an attempted randomized-controlled feasibility trial on “WIDeCAD” - an internet-based depression treatment for people living with coronary artery disease (CAD). *Internet Interventions, 24*, 100375. https://doi.org/10.1016/j.invent.2021.100375

Specifically, in the second publication, results on the guided internet intervention "WIDeCAD“ for adults with CAD are reported. WIDeCAD was investigated within a two-arm parallel RCT compared to a waitlist-control group. The theoretical foundation of the intervention was cognitive CBT. The trial included N=34 adults with CAD (self-report) and at least mild symptoms of depression (Patient Health Questionnaire [PHQ-9], sum-score ≥ 5). Data were collected at baseline (T1) and post-treatment (T2, eight weeks after randomisation). Overall, the study teaches lessons for future studies in the population. Intense recruitment efforts were made and the recruitment period

comprised 25 months. Nevertheless, this trial did not recruit a sufficient number of participants. Participants who started the intervention showed low adherence to the intervention. Consequently, it can be concluded WIDeCAD is not feasible to be evaluated in a full-scale trial in the present format. Against the background of existing literature, the results of this trial imply the necessity of testing other or new ideas to reach participants and, therefore, the necessity of conducting more studies to explore open questions. Whether therapeutic approaches other than traditional CBT might be more appropriate for people with CAD is being discussed. One such approach under discussion is ACT, used as the basis for the intervention in the subsequent study.

3.3 Publication III: Internet Intervention for People with Diabetes

Bendig E., Bauereiß, N., Schmitt, A., Albus, P., Baumeister, H. (2021). ACTonDiabetes: a guided psychological internet intervention based on Acceptance- and Commitment Therapy (ACT) for adults living with type 1 or 2 diabetes – Results of a randomised-controlled feasibility trial. *BMJ Open, 11*(7), e049238. http://dx.doi.org/10.1136/bmjopen-2021-049238

The third publication relates to the investigation of the guided internet intervention "ACTonDiabetes“ for adults with diabetes type 1 or type 2. ACTonDiabetes was investigated compared to a waitlist-control group. The intervention was theoretically based on ACT (Hayes, 2004). N=42 adults consented to participate within seven months, and data was collected formative, at baseline (T1) and post-treatment (T2, eight weeks after randomisation). Participants accepted the intervention, and linear regression models revealed that the intervention was potentially suitable to reduce diabetes distress. Results show that the intervention and study procedures are feasible to be evaluated in a full-scale trial with content revisions alongside participants´ formative feedback. For a definitive trial, increasing mechanisms to foster intervention adherence is desirable to raise the average treatment dosage per person. One mechanism known to have the potential to foster adherence is guidance (Baumeister et al., 2014). In this regard, research literature discusses whether guidance may be more critical for people with chronic somatic disease than for people without this co-morbidity (Jernelöv et al., 2012; Meeuwissen et al., 2011). Since a high level of guidance is associated with higher costs and thus can limit the cost-effectiveness of interventions

(Baumeister et al., 2014), the question arises of whether there are alternatives to increase guidance without increasing costs. Innovative technologies like chatbots could provide guidance on low cost. However, the current state-of-the-art of chatbots for clinical psychological and psychotherapeutic research questions was unclear at that time in the course of the doctorate in 2017/2018.

3.4 Publication IV: Chatbots in Clinical Psychology and Psychotherapy

Bendig, E., Erb, B., Schulze-Thuesing, L., & Baumeister, H. (2019). The Next Generation: Chatbots in Clinical Psychology and Psychotherapy to Foster Mental Health – A Scoping Review. *Verhaltenstherapie*, 1-13. https://doi.org/10.1159/000501812

Thus, within the fourth publication a definition of chatbots in clinical psychology and psychotherapy was elaborated and the landscape of chatbots for clinical psychological research questions was systematised. Therefore, the narrative review aimed at identifying findings in the field and summarise the current evidence base. All k=6 included studies mainly sought to investigate practicability, usability or feasibility of psychological interventions delivered via chatbot. Although, on the one hand, there has been an enormous growth of available chatbot applications in the field recently, on the other hand, results indicate that the evidence base is heterogeneous and high-quality studies are still rare. However, the growing interest in chatbot-delivered psychological interventions will lead to more evidence in the future. Although research attempts have been rapidly increasing recently, the field is heterogeneous, and the quality of studies is often low. Findings point to research desiderata and current pitfalls of the field. Taking desiderata and current pitfalls into account, a chatbot for psychological well-being was being designed and developed in a junior team consisting of two persons from the Institute of Distributed Systems at the Ulm University (Dr. Benjamin Erb, Dominik Meißner) and me (the author of this dissertation). From an ethical point of view, it was necessary to test the innovative technology prior to a large-scale use in potentially vulnerable target groups (Balcombe & De Leo, 2021; Shivayogi, 2013). Consequently, the developed chatbot was first tested in a non-clinical population (study five) and subsequently in people with low psychological well-being (study six).

3.5 Publication V: Feasibility of the Chatbot "SISU"

Bendig, E., Erb, B., Meißner, D., Bauereiß, N., Baumeister, H. (2021). Feasibility of a Software agent providing a brief Intervention for Self-help to Uplift psychological well-being ("SISU“). A single-group pretest-posttest trial investigating the potential of SISU to act as therapeutic agent. *Internet Interventions, 24*, 100377. https://doi.org/10.1016/j.invent.2021.100377

The fifth publication deals with current recommendations/desiderata of the field identified in publication four. Therefore, the chatbot "SISU“ was developed in a multidisciplinary team. The study's primary aim was to test the potential of SISU to act as a therapeutic agent. Research questions were investigated within a single group pretest-posttest design. The pilot trial included N=30 adults that processed through a two-day chatbot-delivered intervention. Data were collected at baseline (T1), during the intervention (T2) and after the intervention (T3). Intervention contents delivered by the chatbot were based on therapeutic writing techniques that aimed at fostering emotional disclosure in participants. The conversational style of the chatbot and exercises were based on principles of Acceptance and Commitment Therapy (Hayes, 2004). Results indicate that the innovative technology can act as a therapeutic agent guiding participants through the investigated intervention. Nevertheless, the chatbot could not prevent participants from negative short-term effects due to the intervention content (increase in anxiety over time, negative affect), which were found in prior studies (Herbert et al., 2019). Related content and technical adjustments are needed prior to the evaluation of SISU in a confirmatory trial. This was accomplished for the subsequent publication.

3.6 Publication VI: Outline of the RCT on the Chatbot SISU

Bendig, E., Meißner, D., Erb, B., Weger, L., Küchler, A.-M., Bauereiß, N., Ebert, D. D., Baumeister, H. (2021). 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. *BMJ Open, 11*(2), e041573. https://doi.org/10.1136/bmjopen-2020-041573

For the sixth publication, contents, as delivered by the chatbot in preceding publication, were revised and developed according to the findings of the previous empirical study. A full-scale RCT was planned with N=120 adult participants based on the results of the fifth study. Thus, the sixth publication is a study protocol which shows the design of a study that aims at evaluating the clinical effectiveness and acceptance of a chatbot-based intervention. The primary outcome is psychological well-being. The Chatbot SISU relies on therapeutic writing in combination with acceptance and commitment therapy-based principles. Results regarding the effectiveness of SISU will provide evidence regarding the acceptability and effectiveness of a chatbot for psychological well-being.

4 Publication I

Internet-based interventions in chronic somatic disease

Reference:

Bendig, E., Bauereiß, N., Ebert, D. D., Snoek, F., Andersson, G., & Baumeister, H. (2018). Internet-based interventions in chronic somatic disease. *Deutsches Ärzteblatt International*, *115*(40), 659-665. https://doi: 10.3238/arztebl.2018.0659

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Review Article

Internet-Based Interventions in Chronic Somatic Disease

Eileen Bendig, Natalie Bauereiß, David Daniel Ebert, Frank Snoek, Gerhard Andersson, Harald Baumeister

Summary

Background: Clinical guidelines recommend psychosocial care as an integral part of medical treatment, but access is often limited. Technology-based approaches provide an attractive opportunity to optimize health outcomes and quality of life in people with chronic somatic diseases e.g. by means of Internet- and mobile-based interventions (IMIs). The present article provides an overview on the basics of IMIs, applications and their evidence base for people living with chronic somatic diseases.

Methods: We conducted a selective literature search in the PubMed and Cochrane databases. Reviews which included randomized controlled trials investigating psychological IMIs were discussed pertaining to their relevance for the population described.

Results: IMIs lead to a change in unfavorable behavior connected to chronic somatic diseases. IMIs can foster protective factors like balanced physical activity or risk factors like smoking or alcohol consumption. However, studies reveal small effect sizes of d=0.25 for physical activity and an averaged effect size of d=0.20 for smoking and alcohol consumption. Additionally, IMIs can be used for the (co-)treatment of chronic somatic diseases, for instance to increase disease-specific self-efficacy in patients with diabetes (d=0.23). Studies included in meta-analyses are often highly heterogenous and are investigated in research contexts with limited health care services relevance.

Conclusion: IMIs are potentially effective when aiming at lifestyle changes and supporting medical treatment in people with chronic somatic diseases. However, results are still heterogenous and the evidence base is limited regarding specific settings, compounding the discussion of possible ways of implementing IMIs into our health-care systems.

Cite this as:
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On average, 70% of adults globally die from chronic somatic diseases and their complications (1) such as coronary artery disease, heart failure, cancer, asthma, chronic obstructive pulmonary disease (COPD), diabetes mellitus or human immunodeficiency virus (HIV). People with chronic somatic diseases might be confronted with a threat to their life, threats to independence and autonomy and threats to life goals, future plans, relationships and economic well-being (2). They often are confronted with a multitude of self-management challenges, including adhering to complex treatment plans, coping with the daily challenges due to their condition as well as dealing with mental health issues such as depression, anger or anxiety (2).

From health care services research it is well-known that adherence to treatment regimens often falls short (3). However, there are several barriers to psychosocial support like limited mobility, time constraints and stigmatization as well as limited availability of evidence-based interventions (4). Internet- and Mobile-Based Interventions (IMIs) might be an innovative and economically attractive way to lower these barriers and improve the health status and well-being of people with chronic somatic diseases (5).

The present review provides an overview on the evidence of psychosocial IMIs in people with chronic somatic diseases, as well as conclusions and future perspectives on applying IMIs to these patients.

Characterizing Internet- and Mobile-Based Interventions

IMIs are mostly standardized self-help programs, provided via a website (6). IMIs can be characterized with regard to

- the extent of human support,
- theoretical foundations,
- technical implementation,
- objectives and
- areas of application (7).

They can be an integral part of the medical treatment or provided as stand-alone intervention. Areas of application comprise prevention, initiation of medical/psychological treatment, components of the medical/psychological treatment or follow-up as exemplified in the *Box*. Various evidence-based psychotherapeutic techniques can build the basis for IMIs aiming at behavior change, increasing

BOX

Area of application and phases of an Internet- and Mobile-Based Intervention (IMI)

- **Prevention**
  - smoking cessation
  - alcohol consumption
  - healthy diet
  - sexual behavior
- **Initiation of Treatment**
  - treatment expectations, treatment motivation
  - negative emotions
- **Component of Treatment**
  - treatment/medication adherence
  - distress
  - depression
  - anxiety
- **Follow-Up**
  - transfer to daily life
  - disease-management
  - stabilization of treatment effects

health-related knowledge, awareness and understanding in users as well as fostering adherence to medical treatment (8), coping with the disease and tackling feelings of depression and anxiety (9,10).

Pertaining to the extent of human support, IMIs can be classified by the degree of guidance (e.g. minimally, intensively, unguided) (6). For guided IMIs, e-coaches (e.g. psychologist/physician) guide participants through a modular program by sending short messages or feedbacks to the participant after each session. If the IMI is unguided, participants complete an instructive program by themselves.

A wide range of studies across lifestyle factors (e.g. physical activity, smoking) and psycho-social (co-)treatment of medical conditions indicate the potential of IMIs for the prevention, treatment and follow-up in general *(Figure)*. IMIs designed to promote behavior change can be effectively used to influence various health-related behaviors, including physical activity, smoking, alcohol consumption, diet, sleep, or sexual behavior (11), all of which are key risk factors for chronic somatic diseases. Reviews and meta-analyses on IMIs aimed at changing lifestyle factors show small to medium effect sizes comparable to cognitive-behavioral face-to-face interventions (12).

Psychosocial IMIs for the (co-)treatment of chronic somatic diseases can be used for a large variety of problem areas. Psychological IMIs might aim at preoperative treatment expectations (13), coping skills, self-management, treatment/medication adherence and patient empowerment (10). Tackling problem areas of people with chronic somatic diseases might help to reduce limitations due to disability and to improve quality of life (10).

The following paragraphs describe the current evidence on IMIs for changing lifestyle factors and (co-)treating medical conditions in people living with chronic somatic disease.

Methods

Studies included in this selective review were identified by expert knowledge and a comprehensive literature search in the databases PubMed and Cochrane Library in November 2017 and April 2018 following the structure of a meta-review. The meta-review approach was selected given the broad scope of the present review.

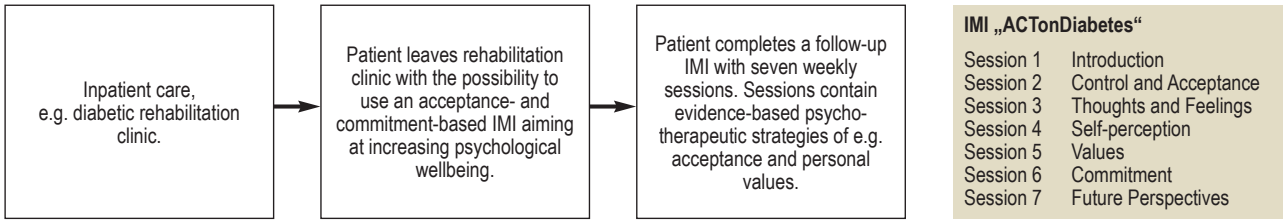
Systematic reviews and meta-analyses of randomized controlled trials (RCTs) which compared Internet- and mobile-based psychosocial interventions to waitlist-control/minimal intervention/no intervention were selected by one of the authors (EB) and discussed in their relevance for people living with chronic somatic diseases. The search strategy was based on a combination of MeSH terms pertaining to IMIs for differenct chronic somatic diseases and different problem areas. The search strategy combined ("internet" OR "mobile-based" OR "web-based" OR "online-intervention" OR "e-health" OR m-health) AND ("chronic disease" OR "cardiovascular disease" OR "diabetes" OR "human immunodeficiency virus" OR "cancer" OR "respiratory disease") AND ("self-management" OR "empowerment" OR "behavior change" OR "alcohol consumption" OR "smoking" OR "sleep" OR "physical activity" OR "adherence") AND publication type ("meta-analysis" AND "systematic review").

State of the evidence for Internet- and Mobile-Based Interventions (IMIs)

Changing lifestyle factors

Well-balanced physical activity can be considered as independent protective factor and cornerstone for all causes of burden and mortality (e.g. risk factors for obesity, type 2 diabetes, coronary artery disease) (14, 15). IMIs can reduce cardiovascular risk factors in high-at-risk adults by increasing physical activity (Standardized mean difference [SMD] = 0.25, 95% CI [0.10; 0.39]) (16). Foster et al. (17) reviewed IMIs versus control with low risk of bias at 12-month follow-up, finding significant effects on cardiovascular fitness (SMD=0.40, 95% CI [0.04; 0.76], n=2; high quality evidence) and on self-reported physical activity (SMD=0.20, 95%CI [0.11; 0.28]; moderate quality evidence, n=9). These effects might hold true for the population of people with chronic somatic diseases, e.g. people with diabetes (18), cancer (19) or COPD (20). However, the heterogeneity of studies within these populations is high and hampers the calculation of effect sizes. Additionally, limited information due to obstacles, moderators and users´ experience (21) highlight the need for a more

FIGURE



Example for the use of an Internet- and mobile-based Intervention (IMI) in the context of patient aftercare (e15).

differentiated view on how, when, why and for which population physical activity IMIs are indicated.

Smoking and drinking are core risk factors for developing a chronic somatic disease. IMIs can help to reduce tobacco use (21–23) and alcohol consumption (23, 24). Meta-analyses indicate smoking cessation IMIs being superior control groups with no intervention, with a reported relative risk (RR) between 1.15 (95% CI: [1.02; 1.30]) and 2.16 (95% CI: [1.77; 2.62]) (21, 22, 25, 26).

For adult problem drinking, meta-analyses comparing IMIs to a passive control group revealed a small to medium effect size (g = 0.39, 95% CI: [0.23; 0.57]) in favor of the IMI to reduce alcohol consumption (27) (Hedges'g corresponds approximately Cohens'd; subsequent effects are interpreted based on (28) with g=±.2 indicating small, ±.5 medium, ±.8 large effects). Another review reveals that participants using IMIs drank approximately 23g pure alcohol less than participants of passive control groups or participants receiving minimal intervention (24). Additionally, one meta-analysis across alcohol and tobacco use revealed a weighted average effect size of d=0.20 ($p<0.001$) (23). Several studies included populations with HIV or other chronic somatic diseases (10). Thus, there is good reason to assume that IMIs aiming at smoking cessation and reduced alcohol consumption will work in people living with chronic somatic diseases as well.

Sleep disorders are associated with negative health outcomes and chronic somatic diseases (15). Individuals facing chronic somatic diseases are frequently affected by sleep disorders relative to the general population and simultaneously, insomnia is a risk factor for developing chronic somatic diseases (29, 30). Recent systematic reviews and meta-analyses revealed that in mixed populations, i.e. people with and without chronic somatic diseases, IMIs for insomnia have the potential to improve multiple indices of sleep with effect sizes comparable to cognitive-behavioral face-to-face therapy for insomnia, ranging from g=0.21 to g=1.09 (31). Sleep indices included the overall sleep duration, subjective sleep quality and the number of nightly awakenings. The effects were maintained at 4–48 week follow-up with g= 0.58 to g=0.68 ($p<0.05$, n=5) (31). In people who survived cancer, sleep-efficiency was improved due to cognitive-behavioral IMIs with a medium effect size of d=0.53 (95% CI: [0.39; 0.68]) in comparison to control (32). This effect persisted at a 6-month follow-up (small effect size d=0.33) (32). Thus, IMIs aiming at healthy sleep in people with chronic somatic diseases might bear the potential to substantially improve peoples' well-being and physical health.

Similar results can be found for other risk and health behaviors such as sexual behavior (33) or a healthy diet in people with chronic somatic diseases (34). A statistically significant but not necessarily clinically meaningful (i.e. treatment effects that reach practically important impact on rates of behavioral risk factors) overall effect size (g=0.17, 95% CI: [0.14–0.19]) can be found across different behaviors (smoking cessation, physical activity, receiving regular mammography screening or eating a healthy diet) (35). Similarly, weight in people with chronic somatic diseases can be significantly reduced by IMIs compared to usual care or waitlist-control (weighted MD= –1.32 kg/m^2, 95% CI: [–2.59;–0.06]) (36). Nevertheless, weight loss of one kg/m^2 will hardly be regarded as clinically meaningful, irrespective of statistical significance (37). More information is needed on the differential effects of lifestyle IMIs and sustainability of effects in order to optimize their potential for people living with chronic somatic diseases.

The (co-)treatment of chronic somatic diseases

Self-management is a crucial factor for the adequate coping with chronic disease. Recent meta-analyses of self-management interventions for adults with metabolic diseases showed that IMIs aiming at improving self-management significantly improved adults' HbA_{1c}-levels (MD= –0.43%, 95%-CI: [–0.68; –0.19%], n=10), body weight and quality of life (38). The number of readmissions due to heart failure and emergency visits due to asthma might be reduced too (39) and asthma-control can be improved by IMIs (40). A recent review on internet-delivered self-management support for improving

TABLE 1

Effectiveness of IMIs in high-at-risk groups and people with chronic somatic diseases based on selected meta-analyses.

Target population	SMD	[95-%-KI]	N
Lifestyle Factors			
Alcohol (23, 27, e16)	0.39	[0.23; 0.57]	7
	0.22	[0.14; 0.29]	28
	0.20	[0.13; 0.27]	16
Smoking (23)	0.14	[0.06; 0.23]	13
Physical activity (16)	0.25	[0.10; 0.39]	14
Overweight (36)	MD: 1.32 kg/m^2	[0.06; 2.59]	5
Diet (34)	0.22	[0.09; 0.34]	25
Sleep*[1] (31)	1.09	[0.74; 1.45]	8
(Co-)treatment of chronic medical conditons			
Diabetes (e3)	0.61	[0.29; 0.94]	2
Cardiovascular Disease (16,40)	MD: 2.66 mm Hg	[1.52; 3.81]	47
	Scoping Review*[2]		18
Cancer (32)	0.53	[0.39; 0.68]	8
HIV (33)	Scoping Review*[2]		23
COPD (20)	Scoping Review*[2]		9
Asthma (40)	0.25	[0.12; 0.37]	3

Estimates of SMD are based if available on systematic reviews and meta-analyses in the population of people with chronic somatic diseases or populations high at risk for developing a chronic disease.
*[1]Several outcomes due to sleep indices were measured; selected outcome: insomnia severity
*[2]Scoping review = Systematic reviews on IMIs for specific medical conditions with only partly meta-analytic data aggregation on plenty medical and psycho-social outcomes.
CI = Confidence interval; N = number of included RCTs in the meta-analysis; MD = mean difference; SMD = standardized mean difference (Cohens' d / Hedges' g).

coronary heart disease (CHD) and self-management-related outcomes, revealed significant effects especially for the improvement of lifestyle-related behaviors (e1). However, data is too scarce or inconsistent to draw conclusions pertaining to clinical outcomes like morbidity or mortality in this population (e1, e2). However, other indices for improved self-management such as adherence to treatment and management of distress have been shown as well (e1).

Patient empowerment, that is, enhancing the involvement of patients in their own care, is another crucial factor in coping effectively with chronic disease. A systematic review which included various chronic somatic diseases (e.g. diabetes, heart failure, COPD) found, that IMIs significantly improved patient empowerment (SMD=0.61, 95% CI: [0.29; 0.94], n=2) and disease-specific self-efficacy (SMD=0.23, 95% CI: [0.12; 0.33], n=9) (e3).

Finally, IMIs might improve adherence to treatment or medication. Medication plans as well as treatment plans can often not develop their full potential, for approximately 50% of patients do not adhere to them as prescribed (3). A recent systematic review of IMIs on treatment adherence across different medical populations revealed significant improvements ($p<0.05$ to $p<0.001$) in 56% of the 27 included RCTs, while 37% revealed no significant results and 7% reported mixed results (8). These results demonstrate that the potential of IMIs to increase treatment adherence is high, but content and quality of investigated IMIs varies considerably between studies.

A systematic review and meta-analysis in persons with cardiovascular disease found significantly increased adherence to medical therapy (odds ratio [OR] 4.51, 95% CI: [2.38; 8.57], $p<0.0001$) as well as pharmacological and non-pharmacological therapy (OR 3.86, 95% CI: [1.35; 10.03], $p<0.01$) in the IMI group compared to usual care (e4). Besides promising results, its important to mention that data on plenty medical and psychosocial outcomes are missing for most somatic diseases. Nevertheless, the research landscape in this field is growing. Reported effect sizes are selectively recapped in *Table 1* while *Table 2* gives an overview of selected IMIs.

Conclusion

The present review provides evidence on the potential effectiveness of IMIs when targeting lifestyle factors and supporting medical treatment. Currently, the usage of IMIs in routine care increases globally, most often realized as (guided) stand-alone self-help interventions. Reported systematic reviews included RCTs that compared IMIs with at least one non-intervention control (31) as well as active control groups (e.g. minimal intervention, face-to-face intervention) (17, 21, 24).

Some systematic reviews did not find any evidence of publication bias (17, 32) while others tried to minimize publication bias by searching a wide

TABLE 2

Selected Internet- and Mobile-Based Interventions (IMIs)

Name	Population	Goal	More information
Selected Tried and Tested Internet- and Mobile-Based Interventions.			
Stepathlon	general	physical activity	www.stepathlon.com
SHUTi	general	insomnia	www.myshuti.com
QuitCoach	smokers	cessation	www.quitcoach.org.au
ACTonPain	chronic pain	psychological flexibility	www.geton-training.de/chronischeSchmerzen.php
Currently under investigation.			
WIDeCAD / W-Decide	Coronary artery disease/ Cancer	increasing psychological wellbeing	www.geton-training.de/WIDeCAD.php www.geton-training.de/W-Decide.php

range of databases as well as sources of unpublished literature (24) and adjusted for potential publication bias (31) or reported insufficient numbers of studies impeding the assessment of publication bias (21).

In summary, the evidence base and quality of studies in the population of people with chronic somatic diseases is often too scarce and heterogenous to calculate effect sizes (18, 19). Substantial heterogeneity emerged between included studies e.g. with regard to quality and scope of interventions, comparison conditions, participants characteristics, theoretical foundations and outcomes. It is important to mention, that systematic reviews and meta-analyses indicate that the positive effects of interventions on psycho-social outcomes are not easily translatable into physical outcomes (e.g. reduced HbA_{1c}-levels in diabetes (e5), high-density lipid-protein or reduced colesterol in people with cardiovascular disease (e2). More research is needed on the question of to what extent IMIs can help to improve disease-related physical outcomes as well as clinical outcomes like hospitalization, morbidity and mortality-rates.

Furthermore, most of the included RCTs were carried out in selected research settings. Further research must show to what extent the results can be transferred into the specific health-care services context. Future RCTs should investigate if a similar picture can be drawn from research conducted in specific routine health-care settings. In this context, sustainability of intervention effects and cost-effectiveness analyses need to become more prominent (e6, e7). Similarly, negative effects of IMIs should be examined more carefully, investigating if patients might deteriorate or undergo adverse events (e8).

One systematic review on cognitive-behavioral IMIs for psychological distress in people living with chronic somatic disease highlighted that none of the 29 included studies reported a negative effect on any outcome measures (e9). Still, little is known about rare but serious adverse events that might be caused by largely automated interventions (e8).

Finally, some studies showed that the acceptance of IMIs in the respective target populations such as people with diabetes is relatively low (53.8% reported low acceptance) (e10, e11), questioning the current public health relevance of IMIs. The same might apply to health-care providers who are skeptical regarding the integration of IMIs into their everyday practice. However, targeted information can increase acceptance considerably (e10–e12) and acceptance is known to increase with IMIs becoming part of routine care (e12).

Thus, it might be safe to say that IMIs provide the possibility to further improve our health care systems, particularly if embedded in a systematic health care plan to support a digitally enabled and integrated patient-centered health-care like in Australia, where an established 10-year program aims at implementing statewide technology foundations for eHealth (e13). Thereby, IMIs could target lifestyle factors, the underlying or preventable medical conditions as well as mental comorbidities, a well studied topic (e14) beyond the scope of the present review.

Conflict of interest statement

Prof. Andersson received honoraria for the authorship and co-authorship of a publication related to the topic of this review. (Author fee paid by Book Royalty).

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Key messages

- Chronic diseases are the leading cause of death and disability worldwide.
- Research investigating innovative internet- and mobile-based interventions (IMIs) is growing rapidly.
- Evidence-based IMIs might be an innovative way to improve the health-status of people living with chronic somatic diseases.
- Practitioners should be informed about possibilities and limits of IMIs to make informed decisions on if, how when and why incorporating IMIs into their routine-care.

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► **Supplementary material**
For eReferences please refer to:
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CLINICAL SNAPSHOT



Figure: 3D volume rendering of the CT angiography of the proximal humerus fracture and the traumatic dissection of the brachial artery (arrows)

Traumatic Dissection of the Brachial Artery as the Result of a Proximal Humerus Fracture

A 79-year-old woman was brought to our surgical emergency department by ambulance after tripping and falling on her left side. She presented with pain in the left shoulder and weak peripheral pulses in the left upper extremity (radial artery, ulnar artery). There was also hypesthesia in the area supplied by the ulnar nerve (digits (IV and V).

Conventional radiography of the left shoulder showed a proximal fracture of the humerus. CT angiography of the left upper extremity, carried out because of the clinical findings, revealed traumatic dissection of the brachial artery in the fracture zone.

The patient was immediately taken to the operating room for treatment by an interdisciplinary team (vascular surgery, trauma surgery). Access was gained via an extended deltopectoral incision. The brachial artery was repaired using an interposition graft, while the fracture was managed by internal plate fixation.

Postoperatively the peripheral pulses were stronger and the hypesthesia was in regression. Five days after surgery the patient was discharged with intact peripheral perfusion and normal motor and sensory function.

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5 Publication II

Lessons learned from an attempted randomized-controlled feasibility trial on “WIDeCAD”- An internet-based depression treatment for people living with coronary artery disease (CAD)

II

Reference:

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Lessons learned from an attempted randomized-controlled feasibility trial on "WIDeCAD" - An internet-based depression treatment for people living with coronary artery disease (CAD)

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ABSTRACT

Background: Despite the high prevalence of comorbid depression in people living with coronary artery disease (CAD), uptake of psychological treatment is generally low. This study was designed to investigate the feasibility of an internet-based cognitive-behavioral (iCBT) depression intervention for people with CAD and depressive symptoms. Methods: People with CAD and depressive symptoms (PHQ-9 $\geq$ 5) were randomly assigned to the eight modules comprising iCBT ($N = 18$), or waitlist-control ($N = 16$). Measures were taken at baseline (t1) and at post-treatment (eight weeks after randomization, t2). Feasibility-related outcomes were recruitment strategy, study attrition, intervention dropout, satisfaction, negative effects as well as the potential of the intervention to affect likely outcomes in a future full-scale trial (depression, anxiety, quality of life, fear of progression). Data analyses were based on intention-to-treat principles. Linear regression models were used to detect between group differences. Linear Mixed Models were used to model potential changes over time. Results: This trial was terminated prior to a-priori defined sample size has been reached given low recruitment success as well as high intervention dropout (88%) and study attrition (23%). On average, participants in the intervention group completed $M = 2.78$ ($SD = 3.23$) modules. Participants in the waitlist control group barely started one module ($M = 0.82$, $SD = 1.81$). The satisfaction with the intervention was low ($M = 20.6$, $SD = 0.88$). Participants reported no negative effects attributed to the iCBT. Differences between groups with regard to depression, anxiety, fear of progression and quality of life remained non-significant ($p > 0.05$). Conclusion: This trial failed to recruit a sufficient number of participants. Future work should explore potential pitfalls with regards to the reach and persuasiveness of internet interventions for people living with CAD. The study gives important indications for future studies with regard to the need for new ideas to reach and treat people with CAD and depression.

1. Introduction

Coronary artery disease (CAD) is the leading cause of death worldwide (Naghavi et al., 2015). Advances in medical treatment have resulted in a decrease of mortality rates (Mensah et al., 2017; Lopez and Adair, 2019), subsequently resulting in an increase in years lived with CAD (Vos et al., 2017; James et al., 2018). Besides the need of medical treatment, CAD is often accompanied by depression and anxiety

Abbreviations: APOI, Attitudes towards Psychological Online Interventions Questionnaire; AQoL-8D, Inventory for the Assessment of Quality of Life; CAD, Coronary artery disease; CBT, Cognitive Behavioral Therapy; iCBT, internet-based cognitive behavioral therapy; WIDeCAD, **W**eb- and mobile-based **I**ntervention for **DE**pression in people with **CAD**; CG, waitlist control group; CSQ, Client Satisfaction Questionnaire; EG, intervention group; GAD-7, Generalized Anxiety Disorder 7-item Scale; HADS, Hospital Anxiety and Depression Scale; INEP, Inventory for the assessment of negative effects of psychotherapy; ITT, intention-to-treat; FOP-Q-SF, Fear of Progression Questionnaire; PHQ-9, Patient Health Questionnaire; SMS, short message service.

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(Rudisch and Nemeroff, 2003; Todaro et al., 2007), with every fifth person living with CAD is also living with depression and/or anxiety (Rudisch and Nemeroff, 2003; Lett et al., 2004; Rothenbacher et al., 2007; Air et al., 2016). Depression can worsen CAD-related outcomes (Lett et al., 2004) and is associated with cardiovascular morbidity and all-cause mortality (Härter et al., 2007; Baumeister et al., 2010, 2011, 2015; Haschke et al., 2012; Watkins et al., 2013; Smith and Kneebone, 2016; Stenman et al., 2016). Depression can be considered as a recurrent risk factor for CAD events (Brown et al., 2009; Dhar et al., 2016).

Research on comorbid depression reveals serious implications for individuals with regard to individual functioning and quality of life (Dickens et al., 2012; Palacios et al., 2016) as well as hampering health-related outcomes (Meijer et al., 2011; Tully and Baker, 2012; Pedersen et al., 2017; Palacios et al., 2018).

Depression can compromise health behaviors (Tully and Baker, 2012) like medical adherence (DiMatteo et al., 2000; Kronish et al., 2006) and adherence to cardiac rehabilitation programs (Dhital et al., 2018). Studies show that eliminating depressive symptoms might lead to better health behaviors such as lower alcohol consumption, less smoking and higher physical activity (DiMatteo et al., 2000; Lett et al., 2004). Apart from the consequences of living with CAD and symptoms of depression on the individual level, monetary consequences for the society at large due to indirect costs like work loss and direct costs due to medical treatment further increase with comorbid depression (Härter et al., 2007; Haschke et al., 2012; Robert-Koch-Institut, 2015). Therefore, effective depression treatments are needed.

Pharmacological (Carney et al., 1999; Zellweger et al., 2004; Pizzi et al., 2011) and non-pharmacological treatments like psychotherapy can improve depressive symptoms in people with CAD (Richards et al., 2017). Whilst pharmacological interventions can have small to moderate effect sizes on short-term depression remission and response (e.g. SSRIs) (Tully et al., submitted), pharmacological treatment can also interfere and even worsen conditions in CAD (e.g. use of tricyclics for antidepressant treatment) (Vaccarino et al., 2020). Psychological interventions which are based on Cognitive Behavioral Therapy (CBT) have a medium effect on short-term depression in people living with CAD (SMD = −0.55, 95%CI -0.80 to −0.31) and a small effect on medium term depression scores (SMD = −0.20, 95%CI -0.28 to −0.12) (Tully et al., submitted). There are multiple barriers towards mental healthcare offers, including stigmatization, limited mobility, time and resources as well as limited access and availability (Messerli-Bürgy et al., 2012; Andrade et al., 2014; Nübling et al., 2014; Groschwitz et al., 2017).

Internet Interventions could be a flexible approach for patients and might help to overcome various barriers in a cost-effective way by delivering low-threshold healthcare offers on a large scale and wide roll-out (Bendig et al., 2018). Internet interventions are (guided) self-help programs, provided on a website (Barak et al., 2009) and can be complemented by mobile-based features. Recent meta-analyses indicate, that guided internet interventions can be as effective in treating mental and somatic disorders as face-to-face psychotherapy (Carlbring et al., 2018). Guidance refers to the extent of human support by eCoaches (e.g. psychologist/physician) (Barak et al., 2009), with at least a minimum of guidance shown to be a beneficial feature of internet interventions (Baumeister et al., 2014).

There is a growing body of well-conducted research on internet interventions for the treatment of depression in cardiovascular populations (e.g. Lundgren et al., 2016; Habibović et al., 2017). However, overall research is still scarce on the interface of cardiovascular disease and psychological depression treatment in general (Nygårdh et al., 2017; Johansson et al., 2019) and even more scarce at the interface of internet interventions for people living with CAD and depression.

There are two studies which investigated a CBT-based IMI (iCBT) in people with a recent acute coronary event (Norlund et al., 2018; Schneider et al., 2020). Norlund and colleagues (Norlund et al., 2018) investigated a 14-week iCBT ("U-CARE") in comparison to a treatment-as-usual control-group (CG) in people who have had a recent (<3 month ago) myocardial infarction and symptoms of depression and/or anxiety (HADS >7) (N = 239). Primary outcome was depression and anxiety (HADS). There were no significant differences between groups (beta = −0.47, 95% CI -1.95 to 1.00, p = 0.53). Schneider and colleagues (Schneider et al., 2020) investigated an iCBT ("Cardiac wellbeing course") for depression and anxiety in people who experienced an acute coronary event in the last 24 month (unstable angina or myocardial infarction). Authors planned to recruit $N = 70$ participants, but ended up with N = 53 participants. Results showed significant between-group improvements for the intervention group (n = 25) compared to the control-group (n = 28) on general anxiety (Cohen's d = 1.62 95% CI 1.00 to 2.24) and depression (Cohen's d = 1.09 95%CI 0.51 to 1.66). Norlund et al. (Norlund et al., 2018) as well as Schneider et al. (Schneider et al., 2020) both reported considerable difficulties with study recruitment/uptake. In this manner, Messerli-Bürgy and colleagues (Messerli-Bürgy et al., 2012) had to stop the Interherz project which sought to investigate an Internet-based intervention ("Deprexis") for cardiac participants living with depression.

People with CAD and depression are seemingly not only difficult to reach, but also partly challenging to keep engaged. The U-Care study (Norlund et al., 2018) reported low intervention adherence rates with only 15.4% of participants in the IG completed more than the introductory module (Wallin et al., 2018). Adherence was investigated in depth by the help of machine learning algorithms (Wallert et al., 2018). Adherent participants were more frequently female with a higher level of cardiac-related anxiety (Wallert et al., 2018). Schneider and colleagues (Schneider et al., 2020) reported a good intervention adherence rate with 92% of participants completing at least four of eight modules. Also Johansson et al. (Johansson et al., 2019) found good adherence rates in a population with different cardiovascular diseases (heart failure, CAD, atrial fibrillation). A total of 60% (n = 43) of the iCBT group completed all seven modules (Johansson et al., 2019). As reasons for greater intervention adherence than in previous studies, authors discussed that iCBT contents were adapted for cardiovascular diseases and feedback was provided from medical staff (Johansson et al., 2019).

The current study was designed to evaluate the feasibility and potential effectiveness of an iCBT for people living with CAD and depression (**W**eb- and mobile-based **I**ntervention for **DE**pression in people with **CAD** "WIDeCAD") in a German-speaking population (Germany, Switzerland, and Austria). Thereby, the trial aimed to test a wide range of recruitment strategies that can be considered fruitful (e.g. multipliers (=persons who contribute to the dissemination of information) in clinics and self-help organizations, advertisements of heart institutions, social media) (Treweek et al., 2013). An already existing iCBT, ICARE Prevent (Weisel et al., 2019) was adapted to the population. The iCBT is optimized for desktop/notebook applications but also runs on mobile-based applications like smartphones/tablets. WIDeCAD aims at reducing depression, applies mechanisms to foster adherence, comprises highly personalizable contents and can be individually tailored to individual preferences of participants. Moreover, it targets anxiety symptoms, which are frequently present in people with CAD and depression (Rudisch and Nemeroff, 2003; Lett et al., 2004; Rothenbacher et al., 2007; Air et al., 2016). Specifically, the WIDeCAD study aimed to:

1. Explore the feasibility of the iCBT, specifically recruitment, dropout and satisfaction with the intervention.
2. Examine potential negative effects of the iCBT.
3. Examine if the intervention potentially affects depression and other intended outcomes of a future full-scale trial.

2. Materials and methods

2.1. Participants

Participants were eligible to take part in this study if they were 18

years of age or older, had a self-reported lifetime diagnosis of CAD and depressive symptoms (PHQ-9 $\geq$ 5) (Kroenke and Spitzer, 2002; Johansson et al., 2019), internet access, sufficient German language skills and provided informed consent. Participants received the consent forms after expressing their interest to participate digitized or printed and had to send them back signed. Exclusion criteria comprised increased suicidality (PHQ-9 item 9: "Thoughts that you would rather be dead or want to harm yourself" on more than half of the days) or lifetime diagnoses of a psychotic, schizophrenic or bipolar disorder.

2.2. Study design and assessment

This parallel group randomized-controlled feasibility trial was conducted from June 2017 to July 2019. The intervention group (IG), which received the guided iCBT, was compared to a waitlist control group (CG) which started the unguided iCBT 8 weeks after randomization.

This trial was conducted in compliance with the Declaration of Helsinki and good scientific practice. The trial is registered at the WHO International Clinical Trials Registry Platform via the German Clinical Studies Trial Register (DRKS): DRKS00012546 (date of registration: 17.07.2017). All procedures involved in the study are consistent with the generally accepted standards of ethical practice approved by the ethics committee of the Friedrich-Alexander University Erlangen-Nuremberg (No. 46_17 B). The present study was reported in accordance with the CONSORT 2010 guidelines for RCTs (Eldridge et al., 2016) and the guidelines for executing and reporting internet interventions research (Barak et al., 2009).

All surveys were conducted online via the "Unipark" platform (www.unipark.de). Data was collected at baseline (t1) and at eight weeks after randomization (posttreatment; t2). Data obtained from the online-platform included: number of modules completed and number of intervention completers. Outcomes, measurements and points of assessment are shown in Table 2.

2.3. Recruitment

Recruitment took place in German-speaking countries (Germany, Switzerland and Austria). Various recruitment strategies and methods to improve recruitment were applied (Treweek et al., 2013). We recruited via 1) medical specialists in clinics (departments for internal medicine/cardiology), 2) volunteers in heart foundations 3) waiting rooms of cardiac specialists' practices, 4) self-help organizations for people living with CAD, 5) cardiac groups 6) heart institutions and foundations 7) social media (specialized groups/information websites) 8) talks and workshops on conferences for cardiologists 9) articles in cardiologic patient magazines as well as 10) advertisements directly on the landing page for trial recruitment. Interested people approached through these channels signed up on the landing page or expressed their interest via E-Mail. Those who met inclusion criteria and provided informed consent were randomly allocated to one of the two groups. All participants had full access to treatment-as-usual care during the study. For an overview of applied channels see Table 2.

2.4. Randomization

Randomization was performed on an individual level by a not otherwise in the study involved university staff (Tim Dretzler, TD). There was no way that researchers involved in the study could foresee allocation of individual participants. Not otherwise to the study associated staff enrolled and assigned participants (Laura Simmelbauer, LS and Karolin Bauer, KB). A permuted block randomization with 2 and 4-block size and an allocation ratio of 1:1 was used. The randomization list was created by an automated web-based program, sealed envelope (https://www.sealedenvelope.com).

2.5. Intervention

2.5.1. Development and central elements

The iCBT was adapted on the basis of the already evaluated ICARE prevent-intervention (Weisel et al., 2019). Originally, Weisel and colleagues (Weisel et al., 2019) built on evidence-based modules from a range of internet interventions which have shown to be effective in treating depression (e.g. Buntrock et al., 2016; Ebert et al., 2017). Weisel and colleagues (Weisel et al., 2018) then further developed ICARE prevent contents alongside the results of a small-scale study. ICARE prevent was designed as a transdiagnostic intervention (Weisel et al., 2018). The contents of the modules focus on depression and also include contents on symptoms of anxiety. Central elements of the iCBT are *addressing needs* (module 1), where treatment motivation, goals, the cognitive triangle and activity plans are addressed. *Behavioral activation* (module 2) comprises mood stabilizing, reinforcing positive activities and dealing with difficulties with achieving planned activities. *Psychoeducation* (module 3) includes information on depression and anxiety with the aim to mediate a better understanding for these mental aspects in participants. *Cognitive Restructuring* (module 4) and *Problem solving* (module 5) include basic CBT-based techniques and skills as well as exercises on structured behavioral analyses. In the last module (*Future Plans*) participants are supported to reflect on the past modules and to focus on strategies for the maintenance of learned techniques in the future. A *Booster session* (module 8) addresses the implementation efforts and successes so far and again focusses on the maintenance of learned techniques. More detailed descriptions of central elements can be found elsewhere (Weisel et al., 2019).

ICBT contents were personalizable and tailored to individual specific needs throughout the intervention. Participants could choose which psychoeducational contents they wanted to intensify and which skills and exercises they wanted to enhance (e.g. further practice and strengthen problem solving skills and/or practicing with fear-inducing stimuli). Moreover, participants were able anytime to choose if they wanted to read text passages themselves or if contents should be read to them. An overview of contents can be seen in Table 1.

Participants were able to choose additional modules in accordance to specific needs. Additional modules comprised e.g. healthy sleep, self-worth, rumination and worries, alcohol consumption and affect regulation or acceptance (detailed information on additional modules can be found elsewhere (Weisel et al., 2019).

Case vignettes (i.e. written patient narratives) underpinned iCBT contents for a variety of clinical purposes like psychoeducation, building relationships, support, decision making and problem solving. Different exercises and tasks based on CBT-techniques are integrated with the aim to support the transfer of knowledge and CBT-based strategies into the people's daily lives.

The iCBT incorporates a high degree of mechanisms to foster adherence. This includes a high level of interactive material like tasks and quizzes. Contents are illustrated by multi-media components, e.g.

Table 1
Content and techniques of the iCBT.

Module title	Module content
1 Addressing needs	Treatment motivation, goals, cognitive triangle, activity plans adapted to people living with CAD
2 Behavioral activation	Mood stabilizing, reinforcing positive activities, difficulties with achieving planned activities
3 Psychoeducation	Structured information on depression and anxiety
4 Cognitive restructuring	CBT-techniques and skills, structural behavioral analyses
5 and 6 Problem solving	Problem solving skills and optional exposition practice with fear-inducing stimuli
7 Future plans	Reflection and maintenance strategies
8 Booster session	Implementation efforts and successes, maintenance of learned strategies and techniques

Notes. CAD=coronary artery disease.

text, audio, video. After each module, participants of the IG receive feedback on tasks and contents from an eCoach. As soon as the participants read the feedback, they were enabled to continue with the next module. An optional SMS-coach was integrated to foster intervention adherence. The SMS-coach sent motivational messages to the mobile device of participants.

2.5.2. WIDeCAD version

Modifications were made to the original iCBT (Weisel et al., 2019), including 1) disease-specific information and psychoeducative elements as well as case vignettes of people living with CAD and depression. 2) Longer text passages of the original iCBT were structurally simplified and shortened. The iCBT in the WIDeCAD study consisted of seven modules and a booster session.

The iCBT was delivered on the online-platform Minddistrict®. If participants did not process through the next module within one week and did not react to reminder per Email, there were telephone reminders up to three times. Processing through a module was conceptualized to last approximately 45–60 min. However, there was no time limit and participants could take breaks, whenever they wanted and were encouraged to do so. Participants were recommended to complete one module per week. Four weeks after completing the seventh module, participants could process through a refresher module to repeat contents and support the participants to transfer learned contents and strategies into daily routines (Weisel et al., 2019).

2.6. Procedure

For participants in the IG, an account on the online-platform minddistrict® was created and an eCoach was assigned to the participant by KB or LS. Next, an automated E-mail was sent to the participant with the link for account activation. After creating a personal password, participants were enabled to login and start with the first module. The eCoach received a message whenever the participant finished a module. Within two working days, the eCoach provided a standardized feedback on the minddistrict®-platform. The feedback consists of standardized, predefined and minimally personalized text modules. Participants could start the next module after reading the feedback. Participants who missed to process through their next module within the following week were reminded three times. If the participant did not answer the third reminder, the current module was disabled by the eCoach. Participants were told that they can reactivate their module by messaging the eCoach.

In module 1, all participants (IG and CG) could choose if they wanted to be supported by none, three or five automated daily short messages (SMS). These SMS were standardized and had motivating and supportive content (tiny-tasks corresponding to intervention contents, reminders to practice).

Participants of the CG received the unguided iCBT eight weeks after randomization. All procedures were the same as for the IG but participants processed through the intervention without receiving feedback. Participants were a-priori informed about this difference between IG and CG and were able to contact their assigned eCoach anytime if they had any questions.

Throughout the intervention, participants were encouraged to apply newly learned strategies and supported by tasks (keeping a sleep-, activity-, thought-, challenge-, or alcohol consumption-diary). All eCoaches were Master's level students in clinical psychology that received a training for eCoaching from EB, supervised by HB. All eCoaches used a detailed manualized protocol throughout the intervention for all processes: Giving feedback to participants, reminding participants to move on with the intervention or complete measurements, plot and react when emergencies occur. All eCoaches were regularly (at least once a month) inter- (EB) and supervised (HB) and were regularly encouraged to ask questions whenever there were insecurities, irregularities or signs of suicidality in participants.

2.7. Outcome: feasibility

2.7.1. Recruitment, dropout and satisfaction with the intervention

To answer the research questions, we investigated study flow and recorded access routes. In order to learn about characteristics of the population reached by the recruitment strategies, we assessed demographic variables (age, gender, nationality, marital status and former psychotherapy/counselling experiences) and recorded the severity of the CAD (New York Heart Association (NYHA) classification). Study attrition was operationalized by missing questionnaire data for one or both points of assessment. Every person who did not complete the intervention (module 1 to 7) was defined as intervention dropout. Participants who dropped out from the intervention where called and asked to give reasons for not continuing with the intervention.

To measure treatment satisfaction, we used the Client Satisfaction Questionnaire (CSQ-8; Schmidt and Nübling, 2002). Participants rated their satisfaction with the WIDeCAD intervention on a 4-point Likert-scale for each of the 8 items. Higher scores indicate higher satisfaction. For psychosomatic contexts, a mean of $M = 23.5$ $SD = 5.0$ is reported (Kriz et al., 2008). Values >23 are being classified as good treatment satisfaction (Kriz et al., 2008).

2.7.2. Negative effects and potential of the intervention to affect intended outcomes

To assess experienced negative effects due to the intervention, the 15-item version of the Inventory for the Assessment of Negative Effects of Psychotherapy (INEP; Ladwig et al., 2014) was employed. Items are rated on a 4-point-Likert scale (0 = "no agreement" to 3 = "total agreement") or a bipolar 7-point scale. The INEP also allows to inquire whether participants attribute changes to the intervention or other life circumstances (e. g. "Since I attended WIDeCAD I feel better (+3)… worse (-3)"). Topics are negative effects in the social environment, intrapersonal factors or work-related situations.

To assess the potential for the intervention to affect likely outcomes in a future definitive RCT, we measured depression (PHQ-9), anxiety (GAD-7), quality of life (AQoL-8D) and fear of progression (FOP-Q-SF).

2.7.2.1. Depressive symptoms. Depressive symptoms are recorded by the Patient Health Questionnaire (PHQ-9; Kroenke and Spitzer, 2002). Nine items are rated on a 4-point-Likert scale (0 = "not at all" to 3 = "almost every day"). There is an additional item which asks if functionality is limited in daily life. A meta-analysis concluded that scores of more than ten points indicate increased depressiveness and values over seven points at least a mild depressive episode (Manea et al., 2012).

2.7.2.2. Anxiety symptoms. The Generalized Anxiety Disorder 7-item Scale (GAD-7) measures anxiety symptoms or disorders (Spitzer et al., 2006). There are seven Items to rate on a 4-point-Likert scale (0 = "never" to 3 = "almost every day"). A sum score is computed. Sum scores of fifteen points or higher at severe anxiety symptoms.

2.7.2.3. Quality of life. We measured quality of life with the Assessment of Quality of Life scale (AQoL-8D) (Richardson et al., 2014). The AQoL-8D measures 8 dimensions of quality of life (independent living, senses, pain, mental health, happiness, self-worth, coping and relationships), that result in overall physical and psychosocial quality of life scores. The total score ranges between 35 and 176 points with higher values indicating lower quality of life.

2.7.2.4. Fear of progression. The short form of the Fear of Progression Questionnaire (FOP-Q-SF) worries and fear of disease progression can be captured within people with chronic diseases (Mehnert et al., 2006). The response to twelve Items is documented on a 5-point-Likert scale (1 = "never" to 5 = "very often").

2.8. Data analysis

The data was analyzed by means of SPSS 26 and R (Core Team, 2017) software and Excel. Quantitative data were analyzed by means of descriptive statistics (frequency, percentage, mean, standard deviation).

The present analyses follow the ITT principle. To handle missing values multivariate imputation by chained equations were performed to create 20 complete datasets (Enders, 2010). Missing data was assumed to be missing at random (van Buuren et al., 1999). Predictive mean matching was used as imputation method (van Buuren and Groothuis-Oudshoorn, 2011). Imputation models were defined following the recommendations by van Buuren and colleagues (van Buuren et al., 1999; van Buuren and Groothuis-Oudshoorn, 2011). Imputation models include variables defined for the primary analysis and auxiliary variables. Analyses were conducted for each imputed dataset and pooled using Rubin's rule (Rubin, 1996, 2004).

Potential group differences were explored by linear regression models. Baseline values were defined as predictors in regression models (van Buuren and Groothuis-Oudshoorn, 2011). For these computations, mean, standard deviation, standardized regression coefficient, and the corresponding 95% CI as well as Cohen's *d* (corrected for small sample size, $d = \frac{M1-M2}{Sample\ SD\ pooled} * \left(\frac{N-3}{N-2.25}\right) * \sqrt{\frac{N-2}{N}}$ (Cohen, 1977; Durlak, 2009)), were reported. These cross-sectional analyses were enriched by longitudinal analyses. Linear mixed models consider that assessments are nested within persons and the resulting dependency between variables. In this study, the repeated measurements (level 1) are nested within person (level 2) (Luke, 2004; Nezlek et al., 2006). For all analyses the significance level was set to $p < 0.05$.

3. Results

3.1. Recruitment, dropout and satisfaction with the intervention

3.1.1. Recruitment

In total, $N = 72$ people living with CAD expressed their interest to participate in the study and were invited for the screening. $N = 62$ participants were screened for eligibility. $N = 34$ people (55%) fulfilled the inclusion criteria and provided informed consent during the 25-month recruitment period. The main reasons for exclusion was not providing informed consent (53%, $n = 18$). Post-assessment was completed by $n = 26$ (76%) participants, with a higher percentage of completers in the control group ($n = 13$, 81%) compared with the intervention group (n = 13, 72%). An overview of recruitment channels can be seen in Table 2. Participant flow can be seen in Fig. 1.

On average, participants were $M = 56.4$ years of age (SD = 10.2), 35% ($n = 12$) were woman. The highest education level of 50% ($n = 17$) of participants was secondary school level, 50% (n = 17) indicated A-levels. With regard to employment status, 21% ($n = 7$) indicated to work full-time. About one third indicated absenteeism (permanently unable to work, $n = 6$, 18%; or currently in sick leave, $n = 5$, 15%), 23% ($n = 8$) were retired. Net household income was <60.000 € in 82% ($n = 28$) of participants. Nearly half of the participants have had prior experiences with psychotherapy (41%, $n = 14$), whilst 21% (n = 7) currently received psychotherapy and $n = 3$ (9%) were on a waiting-list for psychotherapy. One third (29%, $n = 10$) never received any psychotherapeutic treatment. One third of participants (32%, $n = 11$) was taking antidepressant medication, with n = 6 in the IG and n = 5 in the CG. With regard to risk factors, 21% (n = 7) indicated to have an arterial hypertension, 24% (n = 8) indicated a lipometabolic disorder, 18% (n = 6) indicated to have diabetes type 2, 50% (n = 17) indicated to live with any additional chronic disease. More than half of the participants identified as smoking formerly, but currently absent (53%, $N = 18$), 12% ($n = 4$) were smokers. With regard to the self-reported severity of CAD (New York Heart Association (NYHA) classification), 27% ($n = 9$) indicated Stadium I (No restrictions on physical performance), 50% (n = 17) Stadium II, 18% (n = 6) Stadium III and 6% (n = 2) Stadium IV. Average BMI was $M = 31$, $SD = 6.66$. For further details see Table 3.

Table 2
Addressed recruitment channels.

	N contacted	N shared information/ accepted posts[a]
German heart institutions/organizations	35	15
Austrian heart institutions/organizations	17	2
Swiss heart institutions/organizations	2	1
Self-help organizations	26	12
Facebook groups	23	11
Facebook sites	6	4
Cardiological practices	6	2
Clinics	25	9
Forums for self-help	7	4
Heart training group	1	1
Conference workshops on WIDeCAD and talks on cardiological conferences	3	n.a.
Specialized patient magazines	4	0
Psychologists in cardiac clinics	2	1
Psychocardiologists	1	0
Volunteers which are committed to a heart foundation	10	2
Banner on CAD informational web pages/ landing page	5	4

[a] Numbers from organizations etc. we know for sure (through feedback) that they have forwarded information on WIDeCAD/helped recruiting by means of sharing flyers, clinics sending follow-up letters to their patients and included information on the WIDeCAD study.

3.1.2. Study attrition, intervention dropout and satisfaction

Intervention dropout was high (88%, $n = 16$), with 41% (n = 7) of the intervention group not completing the introductory module, 18% (n = 3) completing the introductory module only, and 30% (n = 5) completing additional modules. Furthermore, only 18% (n = 3) adhered to the treatment by completing all modules within eight weeks. On average, participants in the intervention group completed $M = 2.78$ ($SD = 3.23$) modules. Participants in the waitlist control group barely started one module ($M = 0.82$, $SD = 1.81$). Nearly one quarter of questionnaire data was missing (23%, n = 8). Participants' satisfaction with the intervention (CSQ-8) was low with $M = 20.6$, $SD = 0.88$. Interested participants who provided informed consent but did not start the intervention (n = 7) most often indicated (71%, n = 5) that other life circumstances kept them from participation. Participants which discontinued the intervention most often indicated that the contents were too difficult to understand/involved too much text (n = 7 of n = 11 participants indicated dropout reasons) or that they did not feel that the intervention was helpful to them/provided additional support (n = 4).

3.2. Negative effects and potential of the intervention to affect intended outcomes

At post-measurement (t2) effects on depression ($\beta = -0.40$, 95% CI -1.07 to 0.27, $p = 0.24$), anxiety ($\beta = 0.03$, 95% CI -0.60 to 0.66, $p = 0.91$), fear of progression ($\beta = 0.12$, 95% CI -0.55 to 0.78, $p = 0.72$) and on quality of life ($\beta = -0.05$, 95% CI -0.82 to 0.72, $p = 0.89$) were statistically insignificant (Table 4).

Longitudinal analyses revealed no significant change over time in anxiety, depression, quality of life and fear of progression (ps > 0.05). The intervention had no main effect on the outcomes (ps >0.05) and there was no significant effect on the change over time (all interaction effects; ps >0.05).

None of the participants reported negative effects attributed to the intervention (t2). One participant indicated suicidal thoughts and plans (participant indicated that he or she would kill her/himself if she/he could) but did not attribute these thoughts to the iCBT but to other life circumstances.

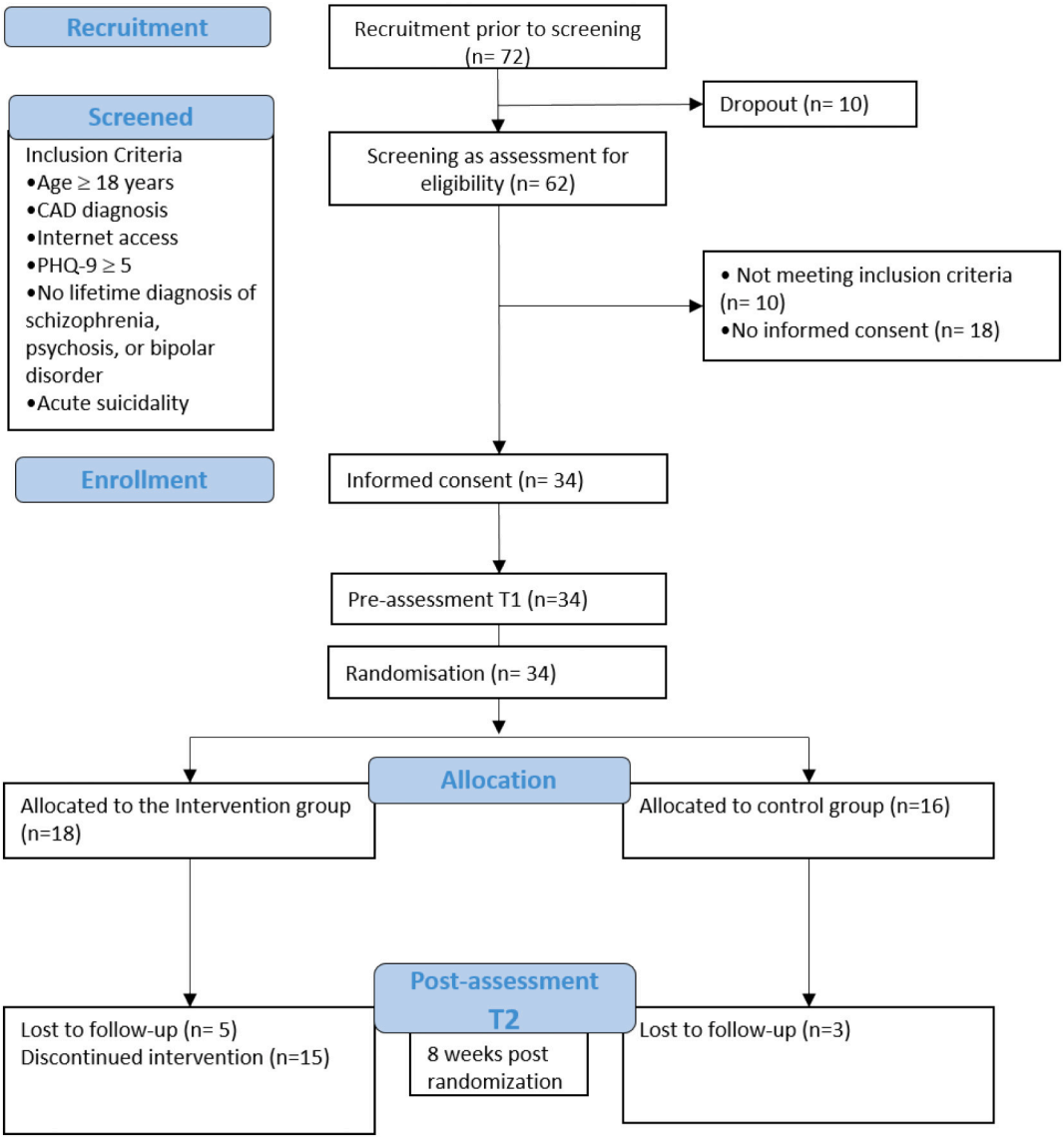

Fig. 1. Participant flow.

4. Discussion

In this RCT, we evaluated the feasibility of a guided, tailored iCBT compared to a waitlist control-group in participants living with CAD and depressive symptoms. On average, participants in the intervention group completed $M = 2.78$ ($SD = 3.23$) modules. Participants in the waitlist control group barely started one module ($M = 0.82$, $SD = 1.81$). Intervention adherence was comparatively low in comparison to meta-analytically evaluated studies on iCBT for depression and anxiety (Păsărelu et al., 2017) indicating a high percentage of participants allocated to the iCBT received a small intervention dosage. The satisfaction with the intervention was low ($M = 20.6$, $SD = 0.88$, CSQ-8). Participants reported no negative effects attributed to the intervention. Differences between groups with regard to depression, anxiety, fear of progression and quality of life remained non-significant ($p > 0.05$). Study recruitment was difficult. Additionally, one third of the few people who signed up for screening were excluded due to not providing informed consent. Based on these findings, the administered study procedures and iCBT cannot be deemed feasible to be investigated in a full-scale trial in the present form.

This trial failed to achieve higher uptake and intervention adherence albeit self-referral, adaption of already evaluated contents and enhanced mechanisms to foster adherence. In the following we will discuss possible reasons and solutions for both uptake and intervention adherence as lessons learned from this trial.

Findings are in line with previous trials on depression in people with CAD with a low uptake rate (Messerli-Bürgy et al., 2012; Norlund et al., 2018; Schneider et al., 2020). Based on prior trials we aimed at a broad recruitment strategy in order to examine ways of reaching people living with CAD. However, neither of the online and on-site recruitment strategies (Table 2) proved their value. Various reasons could explain this.

First, there could be a need to address certain subgroups within the population of people living with CAD. Recent studies suggest that people with mild depressive symptoms do often not need additional support shortly after an cardiac index event like MI (Herrmann-Lingen et al., 2016) or implantable cardioverter defibrillator implantation (Habibović et al., 2017) whilst there might be other subpopulations which do. Relevant subpopulations could comprise e.g. people with persisting depressive symptoms after a cardiac event (Davidson et al., 2010).

Second, 53% of the people who expressed their interest did not provide informed consent. The informed consent process could have been too complicated or the described requirements for study participation might have been perceived as too demanding (7 weekly modules, 2 measurements, 1 booster module, technical demands). However, these

Table 3
Sociodemographic characteristics.

Variable		N	%
Relationship status			
Single		4	11.8%
In a relationship		6	17.6%
Married (living together)		22	64.7%
Married (living apart)		1	2.9%
Divorced		1	2.9%
Children			
Yes		20	58.8%
No		14	41.2%
Highest educational level (ISCED-97-level)[a]			
Level 2 (secondary education first stage)		17	50.0%
Level 3 (secondary education second stage)		6	17.6%
Level 4 (post-secondary non tertiary education)		1	0.03%
Level 5 (first stage of tertiary education)		9	26.5%
Level 6 (second stage of tertiary education)		1	0.03%
Employment			
Yes	Full-time	7	20.6%
	Part-time	7	20.6%
No	Seeking work	1	2.9%
	On medical leave	5	14.7%
	Occupational disability	6	17.6%
	Retirement	8	23.5%
Income			
<1300€		4	11.8%
1300€ - 2600€		7	20.6%
2600€ - 3600€		10	29.4%
3600€ - 5000€		7	20.6%
5000€ - 18,000€		4	11.8%
Not specified		2	5.9%
Details on the CAD condition			
Myocardial infarction			
Yes		12	35.3%
No		22	64.7%
NYHA classification			
Stadium I: no limitation of physical capacity		9	26.5%
Stadium II: complaints in case of increased physical strain		17	50.0%
Stadium III: complaints during light physical strain		6	17.6%
Stadium IV: complaints at rest		2	5.9%
Treatment			
Medical treatment			
Treatment completed		11	32.4%
Currently under treatment		20	58.8%
Treatment is paused		3	8.8%
Implantable defibrillator converter			
Yes		9	26.5%
No		25	73.5%
Operation			
No		11	32.4%
Yes	Bypass surgery	11	32.4%
	Percutaneous coronary intervention	12	35.3%
Psychotherapy or -intent			
Yes	Currently in treatment	7	20.6%
	Treatment more than 3 months ago	14	41.2%
	Currently on waiting list	3	8.8%
No		10	29.4%
Cardiac rehabilitation			
Yes		23	67.6%
No and none planned		8	23.5%
Currently not, but planned		3	8.8%
Antidepressants			
Yes, stable dose for at least 3 months		10	29.4%
Yes, dose was changed in the last 3 months		1	2.9%
No		23	67.6%
Somatic (risk) factors			
Arterial hypertension		7	20.6%
Lipometabolic disorders (cholesterol)		8	23.5%
Coagulation disorders		2	5.9%
Unknown		5	14.7%
Type 2 diabetes		6	17.6%
Cancer		1	2.9%
Other chronic conditions		17	50.0%
No other somatic problems		15	44.1%
Nutrition (Fruit and vegetables in the last month)			
>5× a day	1	2.9%	1× a day	6	17.6%
4–5× a day	2	5.9%	5–6× per week	4	11.8%
3× a day	5	14.7%	3–4× per week	1	2.9%
2× a day	13	38.2%	1–2× per week	2	5.9%
Risk behavior					
Alcohol consumption (Alcoholic drinks in the last month)					
Never				13	38.2%
1-2× per month				10	29.4%
1-2× per week				7	20.6%
3-4× per week				3	8.8%
5-7× per week				1	2.9%
Physical activity					
Never				3	8.8%
1–2× per week				10	29.4%
3–4× per week				9	26.5%
Daily				12	35.5%
Tobacco use					
Yes				4	11.8%
No, but smoked in the past				18	52.9%
No, never smoked				12	35.3%
Screening for psychosocial aspects					
Following European guidelines (Piepoli et al. (2016)/German translation of Albus et al. (2018), multiple answers possible)					
Critical life events just before problems with the heart occurred					
Death of a loved one				4	11.7%
Divorce				1	0.03%
Serious illness in the family				6	17.6%
Job loss				4	11.7%
No				16	47.0%
Other critical life events				10	29.4%
Bond between parents and children					
Yes				21	61.8%
No				8	23.5%
Unknown				5	14.7%
Social support					
Yes				14	41.2%
Rather yes				10	29.4%
Rather no				8	23.5%
No				2	5.9%
Do you often feel annoyed by the habits of other people?					
Yes				25	73.5%
No				9	26.5%
Do you often get annoyed about little things?					
Yes				25	73.5%
No				9	26.5%
Chronic diseases in the family (multiple answers possible)					
Coronary artery disease				24	70.6%
Type 2 diabetes				10	29.4%
Cancer				16	47.1%
Other chronic conditions				7	20.6%

Notes.
[a] International Standard Classification of Education (ISCED).

obstacles to successful clinical trials in patients with somatic diseases and depression were also present in other trials of the present research group using similar interventions (Nobis et al., 2015; Bauereiß et al., 2017; Baumeister et al., 2020; Sander et al., 2020). All of these trials have been successfully completed and showed mostly promising results regarding uptake and effectiveness (Nobis et al., 2015; Bauereiß et al., 2017; Baumeister et al., 2020; Sander et al., 2020). Thus, whilst the informed consent process has likely an impact on uptake, this alone does not explain the recruitment problems seemingly specific to psychotherapy trials on patients with CAD.

A third reason for low uptake could be that the target group might be unaware of or ambivalent towards opportunities and necessities of mental health care (Pols et al., 2018). In people with CAD the focus might rather be on the management of the somatic symptoms (Scherer et al., 2007), subordinating the role of psychological aspects, sometimes perceived as stigmatizing (Pols et al., 2018). It has been only a few

Table 4
Linear regression analysis of changes from pre- to post-treatment.

Measurement	Baseline T1 IG M (SD)	Post-measurement IG T2 M (SD)	Baseline CG M (SD)	Post CG M (SD)	Standardized coefficient β	SE β	95% CI	*p*-Value	Cohen's d
Depression, PHQ-9	11.61 (3.94)	9.04 (5.16)	10.69 (4.67)	10.73 (5.31)	−0.40	0.33	−1.078 to 0.2787	0.24	0.31
Anxiety, GAD-7	10.00 (5.01)	8.21 (5.52)	10.38 (4.41)	8.29 (4.72)	0.03	0.30	−0.5973 to 0.6630	0.91	0.02
Quality of life, AQoL-8D	61.27 (12.52)	63.87 (16.43)	60.06 (12.81)	63.78 (14.42)	−0.05	0.36	−0.8191 to 0.7155	0.89	0.00
Fear of progression, FOP-Q-SF	38.50 (10.22)	39.54 (11.55)	39.63 (12.16)	39.00 (8.77)	0.12	0.32	−0.5467 to 0.7805	0.72	0.05

Notes. Data are M (SD), regression coefficients and Cohen's d; SE = standard error; PHQ-9 = Patient Health Questionnaire-9; GAD-7 = Generalized Anxiety Disorder 7-item Scale; AQoL-8D = Assessment of Quality of Life scale; PA-F-F-KF = Fear of Progression Questionnaire.

decades since "psychocardiology" as an emerging field at the interface between cardiology, psychiatry and psychology is becoming more prominent in the clinical field (Halaris, 2013; Koch, 2013). Researchers call it a challenge of our time to bring different disciplines together to optimize the treatment of CAD towards a more holistic understanding and treatment of disease (Davidson et al., 2018). Thereby, attitudes of both patients and health care providers might need to be tackled (Magaard et al., 2018; Pols et al., 2018) in order to reach patients with CAD and depression. Attitudes and mental health literacy regarding psychological aspects and their treatment in CAD could be subject of future research. This might be even more important for women as the health literacy regarding cardiovascular disease seems generally lower (e.g. Merz et al., 2017) and different (Bucciarelli et al., 2020) than in men. A promising, holistic approach is the collaborative care model (Katon et al., 2010). It integrates services of somatic and mental health professionals (Katon et al., 2010; Tully and Baumeister, 2015). The approach can be feasible and effective as a depression treatment in CAD (Katon et al., 2010; Tully and Baumeister, 2015). So far, there is insufficient evidence to determine the superiority of one of the depression treatments in CAD (standalone psychological or pharmacological or collaborative care) (Tully et al., submitted). To combine advantages of treatment approaches, future studies could investigate an internet intervention like WIDeCAD in a collaborative care framework.

Fourth, our approach did possibly not sufficiently address the social and economic characteristics of the target population. The sample deviates from usual sampling characteristics in the sector of internet intervention utilization, where well educated middle-aged woman are often overrepresented (Andersson and Titov, 2014; Karyotaki et al., 2017). Characteristics in the present sample are related to a lower educational level, lower income and complex disease (multi-morbidity, moderate lifestyle regarding risk factors). This finding concords with prior research, documenting a socioeconomic gradient in CAD with higher morbidity and mortality due to CAD in lower educated, lower income populations (Janati et al., 2011). Thus, this could play an enormous role in driving health disparities as a whole, suggesting that we need to increase our efforts of tackling the difficult to reach difficult to treat people in need of mental health care.

These considerations raise the question of underlying mechanisms of utilization behavior in psychological interventions for people with CAD. A limited action-control belief (Hoebel et al., 2013; Fournier, 2020; Green et al., 2020) or more existential needs than the future mental health due to a lower socioeconomic status (Hoebel et al., 2013) could culminate in the belief that health-related actions or their maintenance do not make sense (Hoebel et al., 2013; Moor et al., 2017). A more need- and motive-oriented approach might then be indicated in order to increase uptake towards evidence-based depression interventions such as Internet Interventions for depression.

However, low uptake was only part of the reasons for why we label WIDeCAD a failed trial. Participants who signed up for the trial also showed low intervention adherence.

As challenges regarding intervention adherence is already known from prior studies (e.g. Norlund et al., 2018), we used an iCBT developed to maximize intervention adherence. Moreover, participants had to sign up to the intervention themselves as research indicates that intervention adherence is higher in self-referral health care models compared to internet interventions integrated into primary care settings (Newby et al., 2013; Allen et al., 2016; Norlund et al., 2018). Furthermore, the iCBT contents were already evaluated in prior studies (Weisel et al., 2019, 2020) and adapted to the population with CAD, which was both discussed as reason for comparatively good intervention adherence in prior studies (Johansson et al., 2019; Schneider et al., 2020). Again, based on the low intervention adherence, we have to conclude that all these mechanisms and measures might still not be sufficient to treat people with CAD and depression.

One possible explanation for the low intervention adherence is, that intervention content was insufficiently engaging. The text comprehensibility of the iCBT at hand could have been too complex, as some participants stated problems with intervention contents. This could have reduced task-related self-efficacy (Schwarzer, 1992). Future studies could examine whether there are associations between perceived text comprehensibility (e.g. readability index), self-efficacy and adherence in people living with CAD.

Second, participants had to complete 7 weekly modules of 45–60 min duration each within 8 weeks to meet the criteria for intervention adherence. This might have been challenging and difficult to integrate into the peoples' daily lives. As intervention usage can continue beyond post-treatment, it is possible that the number of processed modules could rise with further measurement points. Future studies could explore if a pragmatic intervention usage over a longer time period beyond the post-assessment could be more appropriate (Braun et al., 2020). A corresponding operationalization of adherence might then be indicated.

Third, we might also learn from the one study which included people living with CAD and did not report problems with intervention adherence (Johansson et al., 2019). This study built on an intervention which was developed by an interdisciplinary team of psychologists, cardiologists and specialized nurses and thus could have better matched needs, motives and educational level of participants (Johansson et al., 2012; Lundgren et al., 2016). Thereby, future attempts of developing interventions might benefit from an interdisciplinary professional focus, but might even more profit from taking the patient perspective into account (Merlin et al., 2017). The present intervention is based on professional and patient feedback, however, not specific to CAD. Thus, we still need to examine whether there is a need of depression interventions tailored to patients' conditions (Nobis et al., 2015; Baumeister et al., 2020; Sander et al., 2020) or whether a more generic transdiagnostic intervention approach is sufficiently effective.

A core limitation for interpreting the study findings is the small sample size due to recruitment difficulties. It is not possible to draw conclusions regarding the iCBTs effect on depression. However, the

feasibility trial was neither designed to nor appropriately powered to test a hypothesis (Arain et al., 2010; Shanyinde et al., 2011). Online assessment leads to a heterogenous sample limiting the internal validity of findings. For example online assessments are associated with uncertainties concerning diagnostic status of participants as it was based on self-report. Including medical data and applying standardized clinical diagnostic interviews would have been desirable to clarify the mental and somatic status of participants. Additionally, the current sample does not reflect real-life uptake of patients already in the health care system. In order to investigate this a pragmatic trials would have to be conducted which systematically recruit participants from routine care settings like e.g. Johansson et al. (2019). Although generalizability of results is arguably limited, an important strength of this trial is the provision of deeper insights into often encountered difficulties regarding reach and engagement in this population. This might prove to be fruitful for future research in the field as it provides various starting points for future trials.

5. Conclusions

In a nutshell, there is a health policy mandate to provide interventions for people with CAD and depression (Dickens et al., 2012; Haschke et al., 2012; Naghavi et al., 2015). ICBT can be effective, but its reach is not always sufficient and its effectiveness at the patient level cannot yet be determined consistently (Messerli-Bürgy et al., 2012; Norlund et al., 2018; Schneider et al., 2020). It is from utmost importance to further investigate how interventions could effectively reach and support people living with CAD and depression (Nygårdh et al., 2017; Johansson et al., 2019). This is not the first CAD-trial that didn't succeed recruiting a sufficient number of participants (e.g. Messerli-Bürgy et al., 2012). Future trials on internet-based depression treatment could strive towards a better understanding of the people behind the diagnosis "CAD" in order to address them more effectively (Habibović et al., 2017; Herrmann-Lingen et al., 2016). One idea could be to use recommendations of The European Association of Cardiologists e.g. regarding psychosocial screening questions (Piepoli et al., 2016) to understand and involve the patients' perspectives and needs more inherently. Then, further investigations regarding persuasive e-health design are needed, supporting people with uptake and regular use of interventions (Baumeister et al., 2019). Overall, new ideas are needed to reach and treat people with CAD and depression since the struggle is real.

Declaration of competing interest

HB received consultancy fees, reimbursement of congress attendance and travel costs as well as payments for lectures from Psychotherapy and Psychiatry Associations as well as Psychotherapy Training Institutes in the context of E-Mental-Health topics. He has been the beneficiary of study support (third-party funding) from several public funding organizations. DDE possess shares in the GET.On Institute GmbH, which works to transfer research findings on Internet- and mobile-phone-based health interventions into routine care. DDE has received payments from several companies and health insurance providers for advice on the use of Internet-based interventions. He has received payments for lectures from Psychotherapy and Psychiatry Associations and has been the beneficiary of third-party funding from health insurance providers.

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CRediT authorship contribution statement

HB and DDE had the idea to investigate the CBT-based intervention in people living with CAD and depression. Intervention contents were originally developed by the university of Erlangen-Nuremberg in cooperation with others (see Weisel et al., 2019). EB adapted contents to the target population. EB and HB planned and designed the study. HB supervised the study. EB operatively performed the study. EB drafted the manuscript, all other authors critically revised the work for important intellectual content. All authors approved the final version to be published and agree to be accountable for all aspects of the work.

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6 Publication III

ACTonDiabetes: a guided psychological internet intervention based on Acceptance- and Commitment Therapy (ACT) for adults living with type 1 or 2 diabetes – Results of a randomised-controlled feasibility trial

III

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BMJ Open

ACTonDiabetes—a guided psychological internet intervention based on Acceptance and Commitment Therapy (ACT) for adults living with type 1 or 2 diabetes: results of a randomised controlled feasibility trial

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ABSTRACT

Objectives This two-group randomised controlled trial evaluates the feasibility of an Acceptance and Commitment Therapy (ACT)-based internet intervention for diabetes distress in people with diabetes type 1 or type 2. Participants were assigned to a guided self-help intervention (EG) or waitlist control group (CG).

Setting Recruitment took place following an open recruitment strategy including different diabetes centres, self-help groups and social media platforms.

Participants Eligibility criteria comprised being 18 years of age or older, self-reported diagnosis of type 1 or type 2 diabetes, internet access, sufficient German language skills and written informed consent.

Intervention ACTonDiabetes is an internet-based and mobile-based intervention and comprises an introduction and seven modules (one module per week, processing time about 45–60 min). Intervention contents are based on ACT.

Primary and secondary outcome measures Participants were assessed before and 8 weeks after randomisation. Primary outcome was feasibility (trial recruitment, acceptability). Potential group differences in diabetes distress and other outcomes at follow-up were analysed using linear regression models with baseline values as predictors. All analyses were based on an intention-to-treat principle, potential negative effects were analysed on per-protocol basis.

Results From October 2017 to April 2018, N=42 people with diabetes consented and were randomised (EG n=21, CG n=21). Forty-three per cent of the EG completed all treatment modules within 8 weeks. Across modules, formative user feedback revealed that contents could be optimised regarding comprehensibility (34%), individualisation (20%) and text amount (21%). Overall, 57% of participants dropped out prior to full treatment completion. There were reductions of diabetes distress in the EG (d=0.65, p=0.042).

Conclusions Modifications of the intervention content according to the user feedback will be performed to further improve acceptability. Mechanisms to foster intervention adherence should be considered for lowering the attrition rate. ACTonDiabetes is feasible for the implementation in a confirmatory trial.

Trial registration number WHO International Clinical Trials Registry Platform via the German Clinical Trials Register (DRKS) (DRKS00013193).

Strengths and limitations of this study

- This is the first trial on an Acceptance and Commitment Therapy-based internet intervention for people with diabetes.
- The intervention was adapted from a previously evaluated treatment concept for people with a chronic somatic disease.
- This feasibility trial promotes a responsible use of resources and a high standard of quality in a confirmatory trial.
- Attrition was high in both comparison groups.
- Formative user feedback is used to further improve the ACTonDiabetes intervention.

INTRODUCTION

The prevalence and incidence rates of diabetes are increasing worldwide.[1] For Germany, there is an assumed increase of between 10.7 million (+54%) and 12.3 million (+77%) type 2 diabetes cases until 2040.[2] Additionally, the rate of individual years lived with diabetes is rising globally.[1] Against the background of these developments, the editorial of The Lancet speaks of a 'diabetes pandemic'.[3] Diabetes care constitutes an enormous economic burden for healthcare systems as well as an enormous burden on the level of individuals due to years lived with the disease.[1 4] Living with diabetes type 1 or 2 is challenging.[5] It comes along with a multitude

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of requirements that need to be considered and mastered in everyday life.[5] Requirements comprise permanent self-treatment and monitoring,[5–7] adhering to complex treatment plans,[8 9] and promoting coping mechanisms to deal with diagnosis and disease.[10] Consequently, the prevalence of diabetes distress is high. Diabetes distress is defined as experiencing negative emotions and burden due to the demanding and progressive conditions of living with diabetes.[11 12] It involves negative emotional reactions[5] such as feeling overwhelmed by the demands of living with diabetes, worries and fears about possible complications, frustration due to perceived limitations regarding lifestyle or suboptimal treatment outcomes.[13 14] About 36% of people with type 2[12] and 41% of the people with type 1 diabetes[15] report elevated diabetes distress. This has consequences in many respects.

Diabetes distress has been associated with impaired psychological well-being, reduced treatment adherence,[14] reduced glycaemic control[16] and common comorbid mental disorders like depression.[17] In relation to this, a longitudinal study shows that diabetes distress can be associated with a higher incidence and persistence of depressive symptoms.[18] Clinical treatment guidelines recommend the assessment of and interventions for reducing diabetes distress as integral part of diabetes care.[19–21] However, elevated diabetes distress often remains untreated or undertreated due to various barriers.[20–22] Barriers include fear of stigmatisation, limited mobility of patients, time and resources as well as limited access and availability of psychological interventions.[23 24] Barriers can also arise on the part of healthcare professionals not detecting or being not able to address diabetes distress within routine consultations.[25]

Innovative technologies can help to overcome these barriers by delivering low-threshold digitised interventions on a large scale.[26 27] In this context, internet interventions have been considered a cost-effective and flexible approach to provide psychological interventions to people with diabetes.[28 29] Internet interventions are (guided) self-help programmes which can be provided on a website[30] and complemented with mobile-based applications like apps.[26 27] Guidance refers to human support from e-coaches (eg, psychologist/physician).[30] Evidence suggests that at least a minimum of guidance can constitute an effect-facilitating factor.[31 32] A recent meta-analysis investigating internet interventions for people with mental disorders and/or chronic somatic conditions suggests that guided internet interventions can be as effective as traditional face-to-face interventions.[33] Internet interventions have been effectively used to support behaviour change (weight loss,[34] physical activity,[35] glycaemic control,[36] smoking cessation,[37] alcohol consumption[38]). Additionally, they were effectively used for treating comorbid mental disorders in people with diabetes[28 39] and clinically relevant diabetes distress.[28 29] Nevertheless, overall evidence in the field is still very limited with regard to quantity and quality of studies.[26] To date, interventional studies have not focused on diabetes distress as primary outcome in this field of research.

Nobis *et al*[40] evaluated a guided internet intervention for people with diabetes type 1 or 2 with depressive symptom severity as primary outcome. Authors compared the treatment group with an active control group receiving psychoeducation. On the level of secondary outcomes of this trial, results indicated a significant effect of d=0.58 (95% CI 0.33 to 0.83, p<0.001) for the reduction of diabetes distress post-treatment which persisted after 6 months (d=0.50, 95% CI 0.04 to 0.54, p<0.001).[41] Likewise, van Bastelaar *et al*[29] found significantly greater reductions of diabetes distress in the treatment group receiving internet-based depression treatment compared with a waitlist control group. The evaluated interventions were both based on cognitive–behavioural therapy (CBT).[29 40]

While most previously studied internet interventions are theoretically based on CBT,[42] people with chronic somatic conditions might benefit from interventions that focus less on aspects of 'change' and more on 'acceptance' of the unchangeable condition as in Acceptance and Commitment-based Therapy (ACT).[43 44] ACT aims at increasing psychological flexibility by fostering acceptance of unchangeable aspects in life[43 44] like living with diabetes.[45] Recent studies show positive effects of ACT in this population regarding self-management.[45 46] Gregg *et al*[45] as well as Shayeghian *et al*[46] found that people receiving an ACT intervention performed better diabetes self-care and had more optimal glycated haemoglobin (HbA1c) values after the treatment than the active control group which received a structured education workshop on diabetes control. However, one study of Maghsoudi *et al*[47] did not find significant reductions in diabetes distress following a group-based ACT intervention (eight weekly 90-minute sessions) in comparison with a treatment-as-usual control group. Further studies are being initiated recently.[48]

To our knowledge, this is the first study on an ACT-based internet intervention aiming at reducing elevated diabetes distress. Notably, the effectiveness and cost-effectiveness of the internet intervention 'ACTonPain' aiming at reducing pain-related burden in people with chronic pain were supported in studies by Lin *et al*.[49–51] ACTonDiabetes was built on the ACTonPain treatment programme to develop a widely practicable, local and temporal flexible, low-threshold internet intervention to reduce diabetes distress in people with type 1 and type 2 diabetes.

The present study evaluates the feasibility of the programme ACTonDiabetes. Therefore, trial recruitment, acceptability and preliminary results regarding the effectiveness of the intervention are investigated. Results will inform decision processes concerning study procedures, potential amendments and the design of a future definitive trial. User feedback will be used to further improve and refine the ACTonDiabetes intervention. Specifically, this study aimed to:

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1. Explore the feasibility of trial recruitment and acceptability of the internet intervention.
2. Examine if the intervention potentially affects diabetes distress and other intended outcomes of a future full-scale trial.

METHODS

Participants

People were eligible to participate in this study if they were 18 years of age or older, had a self-reported diagnosis of type 1 or type 2 diabetes, had internet access, sufficient German language skills and provided written informed consent. Participants received the consent forms digitised or printed and were asked to sign and return them. Participants were excluded if they had other forms of diabetes (eg, gestational diabetes).

Study design and assessment

This parallel group, randomised-controlled feasibility trial enrolled participants from October 2017 to April 2018. The intervention group (EG) received the guided ACTonDiabetes intervention and was compared with a waitlist control group (CG) which started the unguided intervention 8 weeks after randomisation. This trial was conducted in accordance with the Declaration of Helsinki and good scientific practice. The present report follows the Consolidated Standards of Reporting Trials (CONSORT) 2010 guidelines for feasibility randomised controlled trials (RCTs).[52]

Recruitment

Recruitment took place following an open recruitment strategy. Different methods were administered: research staff in diabetes centres and diabetes self-help groups who informed potential participants of the offer, flyers in medical practices and social media posts in diabetes-related groups. Interested people signed up on the ACTonDiabetes homepage or expressed their interest via email to the study mail address. Those who met the inclusion criteria and provided written informed consent were randomised.

Randomisation and blinding

Randomisation was performed on an individual level by a person not otherwise involved in the study (Lena Storz). The randomisation list was created by an automated web-based program called 'sealed envelope' (https://www.sealedenvelope.com). Lioba Fluhr enrolled the participants. A permuted block randomisation with variable 2 and 4 block size (randomly arranged) and an allocation ratio of 1:1 was used.

ACTonDiabetes intervention

The guided internet intervention was delivered on the online platform Minddistrict. The theoretical base is the ACT. Contents were adapted to the population of people with diabetes from the already evaluated ACTonPain intervention.[49–51] The intervention consists of seven modules. The content of the intervention involves psychoeducation underpinned by fictional peer support (a woman with recently diagnosed type 2 diabetes, a younger man with type 1 diabetes, an older man with long-standing, insulin-treated type 2 diabetes). The narratives of the peers address typical problems and burdens, worries, needs and experiences with strategies and resources as well as topics covered in the intervention. Contents are provided by means of texts, video sequences, audio files or illustrations of various ACT models and metaphors. A description of the intervention contents can be found in table 1. Participants are advised to process through the intervention in 7 weeks, completing one module per week. The processing time for each module is scheduled to take approximately 45–60 min. ACTonDiabetes is based on three assumed effect factors: the intervention contents, guidance and daily exercises. Guidance was provided by an e-coach (psychologist) who provided standardised feedback after each module. To support transfer into everyday life, specific ACT-based exercises and tasks (eg, keeping a diabetes distress diary) were included. Furthermore, participants received short message service (SMS) coaching with motivational prompts and mindfulness tasks. A schematic depiction of the intervention can be seen in figure 1.

Measures

All surveys were conducted online via the Unipark platform (unipark.de).

Measurement time points were at baseline (T1) and at 8 weeks after randomisation (T2) (ie, after the treatment should normally be completed). An overview of outcomes, measurements and points of assessment is shown in table 2.

Study aims were operationalised as follows:

1. Trial recruitment and acceptability.
   - Access routes, study flow, baseline characteristics.
   - User attitudes, formative user feedback, negative effects, adherence.
2. Potential of the intervention to affect intended outcomes in a confirmatory trial.
   - Diabetes distress, depression, anxiety, self-management, diabetes acceptance, quality of life, fear of progression.

Trial recruitment and acceptability

Recruitment

Access routes were recorded by an open-ended question asking how participants got to know about the study. With regard to study flow, early participant attrition was investigated to determine if mechanisms sufficiently bridged the gap between eligibility/consent and actual trial uptake, as recommended.[53 54] For this purpose, we measured the participation rate (number of participants divided by the number of eligible people). Recruitment was deemed successful if the participation rate was at least 70% of all eligible participants (in hoc sensu early attrition maximum 30%).[54 55] In order to learn about

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Table 1 Overview of contents and techniques of all sessions

Module	Key module contents	Focused ACT techniques
0	Introduction to the structure and basic ideas of the ACT training, explanation of the SMS coach, presentation of accompanying case vignettes of the training; sources and evidence	Psychoeducation*
1	Fostering of treatment expectations and motivation, psychoeducation on diabetes and its complications, diabetes distress and associations between diabetes and mental health; development of the individual diabetes history and coping mechanisms; introduction to the ideas of ACT; elaboration of a good reason for processing through ACTonDiabetes; clarification of individual objectives for the training; introduction to mindfulness and conscious breathing; elaboration of the individuals' previous handling of diabetes distress, previous strategies with short-term and long-term success; presentation of possible different approaches alongside ACT	Psychoeducation* Acceptance Generation of creative hopelessness
2	Introduction to the concepts of control and acceptance, development of the idea of mindfulness: the body; introduction of the diabetes diary within which the focus is on components of the SORC-model[95] (Behavioral analysis model, acronym: Situation, Organism, Reaction, Contingency/ Consequence); diabetes distress and (un-)influenceable variables in life; primary and secondary suffering; introduction to behavioural experiments, self-observation tasks, homework, ACT metaphors and mindfulness exercises. Further optional diaries are offered to support self-observational processes/tracking behaviour (eg, acceptance diary, mindfulness diary)	Experiential acceptance* Recognising malfunctions of control strategies; acceptance as alternative concept
3	Elaboration of and differentiation between thoughts and feelings; development of the idea of mindfulness regarding thoughts; dealing with negative thoughts and feelings; language processes and vocabulary tips to support defusion processes	Defusion,* recognising the meaning of language; creating distance from own thoughts
4	Self-conceptualisations; three senses of self; being the observing self; development of the idea of mindfulness regarding all senses	Self as context* Defusing from implicit evaluations; getting to know the observing self
5	Introduction to values; values as chosen life directions; choosing values; goal-setting strategies, mindfulness regarding feelings	Values;* developing value awareness
6	Commitment and its influence on a value-driven life, mindfulness in the everyday life, ACT formula; begin to take action	Committed action, ACT formula;* learning ways to act in accordance to values
7	Development of the way forward; commitment; conclusion and future perspective, skills overview and maintenance	Committed action, mindfulness;* sustainable anchoring of the learning content in everyday life

Every module starts with a review of key elements from the last session and ends with a summary and outlook.
*Inclusion of metaphors (eg, man in the fountain; playing tug of war with unchangeable aspects in life), tasks and exercises to make contents experienceable.
ACT, Acceptance and Commitment Therapy; SMS, short message service.

characteristics of the population reached by applied recruitment strategies, we assessed age, gender, diabetes type and former psychotherapy/counselling experience. Additionally, we explored if participants who signed up had a certain level of burden, thus elevated symptoms of diabetes distress, depression or anxiety at baseline (T1).

Acceptability

Acceptability refers to reactions of participants regarding the ACTonDiabetes intervention.[56] Collected data include attitudes towards internet interventions (Attitudes towards Psychological Online Interventions Questionnaire (APOI)[57]), as well as information acquired through the online platform Minddistrict on usage and engagement (number of modules completed, length of processing time per module, number of intervention completers and formative user feedback). Formative user feedback was collected to gain knowledge of the users' acceptance of the intervention. Therefore, we assessed comments and critiques of the participants as well as the perceived appropriateness of the intervention contents. Furthermore, we assessed perceived negative effects of the intervention (Inventory for the Assessment of Negative Effects of Psychotherapy (INEP)[58]), as well as treatment satisfaction (Client Satisfaction Questionnaire (CSQ-8)[59]) using validated questionnaires.

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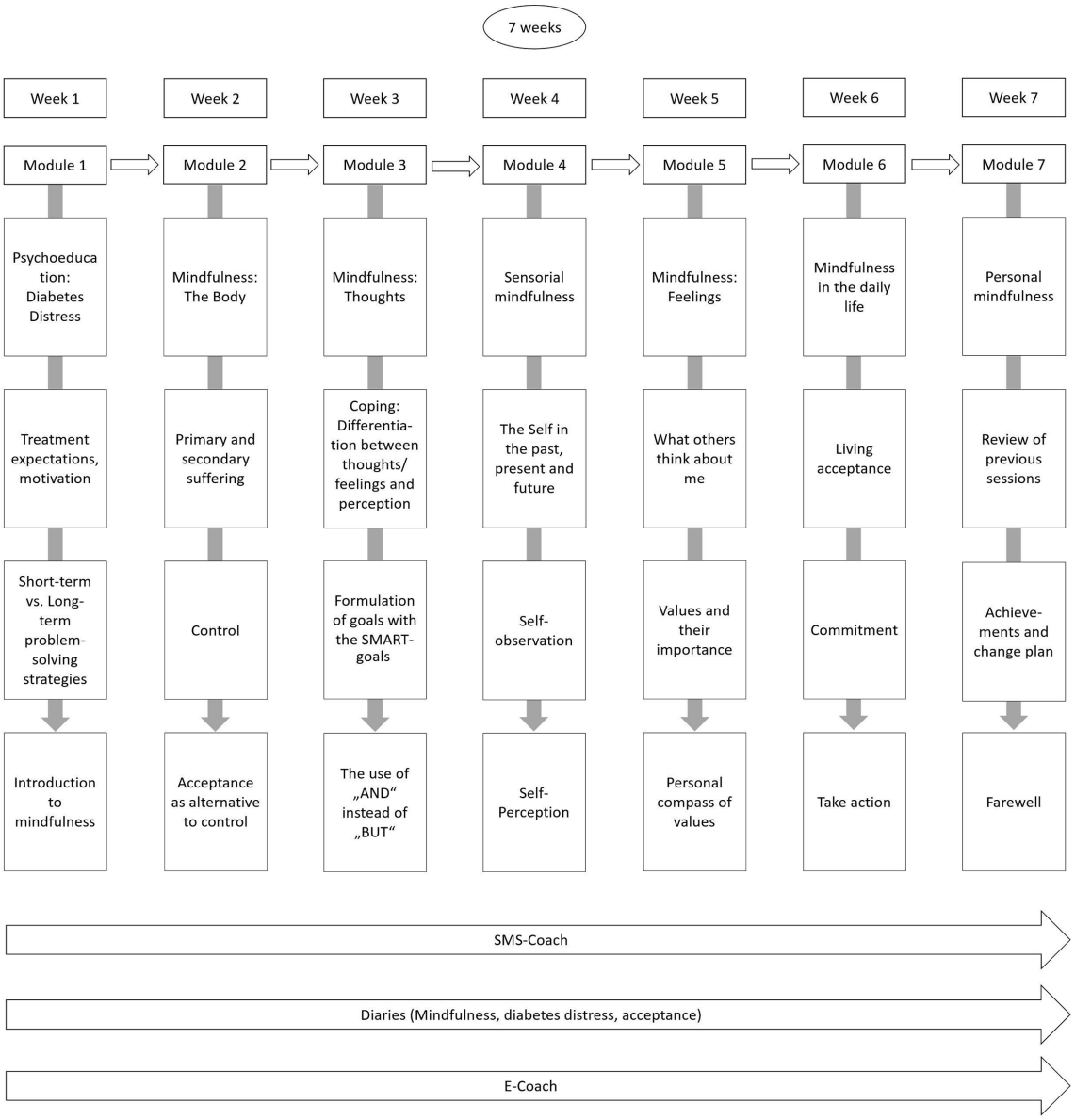

Figure 1 Intervention structure of ACTonDiabetes. SMS, short message service. SMART, specific, measurable, achievable, relevant, time-limited

Attitudes towards internet interventions

The APOI[57] consists of 16 items (eg, 'I think ACTonDiabetes could help me') which are rated on a 5-point Likert scale (1='I do not agree at all' to 5='I agree completely'). The tool estimates four subscales (four items each): scepticism and perception of risks (SCE), threat due to technology (TET), confidence in effectiveness (CON) and anonymity benefits (ABE). Higher scores on CON and ABE indicate more positive attitudes, while higher values on SCE and TET indicate more negative attitudes towards internet interventions. Subscale scores can be added to a total score (range 16–80). A higher total score indicates a more positive attitude.[57] A low level of acceptance of the internet-based delivery format has been associated with a lower uptake rate.[60] Thus, an at least medium level of acceptance may be required for the implementation on a larger scale.[61 62] Understanding attitudes towards internet interventions may help allocating dissemination and recruitment resources for a larger RCT efficiently.[62]

Formative user feedback

Participants in the EG received a voluntary feedback questionnaire after each module. Questions aimed at rating the length and comprehensibility for each module on a 3-point scale (too short, just right, too long). Additional open questions were administered to gather information on certain intervention contents (exercises, techniques or metaphors) per module ('What was the most/least helpful exercise for you within this module?').

Negative effects

Potential negative effects were assessed using the 15-item version of the INEP.[58] Participants rated possible negative effects which occurred during or

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Table 2 Overview of constructs, measurement instruments and points of assessment

Construct	Instrument	Point of assessment	
		T1	T2
Trial recruitment			
Recruitment strategy		X	X
Demographics	Self-report	X	X
Dropout	Study attrition rate	X	X
Acceptability			
Satisfaction	(CSQ-8)	X	X
Negative effects	INEP		X
Attitudes and expectations	APOI	X	X
Protocol adherence	Treatment dropout		X
Formative user feedback	Feedback per module		X
Outcome data			
Diabetes distress	PAID	X	X
Depressive symptoms	PHQ-9	X	X
Anxiety symptoms	GAD-7	X	X
Fear of progression	FoP-Q-SF	X	X
Acceptance and Action Diabetes Questionnaire	AADQ	X	X
Diabetes Self-Management Questionnaire	DSMQ	X	X
Quality of life	AQoL-8D	X	X

T1=baseline; T2=post-measurement.
AADQ, Acceptance and Action Diabetes Questionnaire; APOI, Attitudes towards Psychological Online Interventions Questionnaire; AQoL-8D, Assessment of Quality of Life 8-item Questionnaire; CSQ-8, Client Satisfaction Questionnaire; DSMQ, Diabetes Self-Management Questionnaire; FoP-Q-SF, Fear of Progression Questionnaire–Short Form; GAD-7, Generalized Anxiety Disorder 7-item Scale; INEP, Inventory for the Assessment of Negative Effects of Psychotherapy; PAID, Problem Areas In Diabetes Scale; PHQ-9, Patient Health Questionnaire-9.

after the intervention on a 4-point Likert (0='no agreement' to 3='total agreement') or a bipolar 7-point scale (−3='worse' to 3='better'). Participants then indicate if they attribute negative effects to the intervention or other circumstances (eg, 'I feel better (+3)…worse (−3) since the start of the intervention'; 'I put this effect down to the intervention' (1), 'other circumstances' (2)). Topics include possible negative effects in the fields social environment, intrapersonal factors and work-related situations.

Treatment satisfaction

The CSQ-8[59] measures satisfaction with the intervention using eight items and a 4-point Likert scale. Higher scores indicate higher treatment satisfaction. For psychosomatic populations, a mean of M=23.5 (SD=5.0).[63] Thus, values close to M=23.5 were classified as sufficient satisfaction with the ACTonDiabetes treatment to be investigated in a larger trial.

Adherence

Study attrition as well as intervention adherence was evaluated 8 weeks after randomisation. Adherence was operationalised by the percentage of participants who completed the majority of modules. That is, participants at least processed through the introduction and the initial four of the seven core modules within 8 weeks.

Outcome data

Diabetes distress

The 20-item Problem Areas In Diabetes (PAID) Scale[64] was used to measure diabetes distress. The scale requests diverse emotional problems due to living with the chronic condition. Responses are given on a 5-point Likert scale (0='no problem' to 4='serious problem'). The raw sum score is multiplied with 1.25 to calculate the total score (range 0–100). Higher scores indicate higher diabetes distress. Values of 40 and above are considered to indicate elevated, thus clinically relevant diabetes distress.[65]

Depression

The Patient Health Questionnaire-9 (PHQ-9[66]) was used to measure symptoms of depression. Its nine items assess the key symptoms of depression according to the Diagnostic and Statistical Manual of Mental Disorders; responses are given on a 4-point Likert scale (0='not at all' to 3='almost every day'). The total score ranges from 0 to 27 with values of 10 or higher suggesting elevated depressive symptoms.

Anxiety

The Generalized Anxiety Disorder 7-item Scale (GAD-7[67]) was used to measure symptoms of anxiety. Seven items are rated on a 4-point Likert scale (0='never' to 3='almost every day'). Higher total scores (range 0–21) indicate higher levels of anxiety.

Self-management

Overall, diabetes self-management was measured using the Diabetes Self-Management Questionnaire (DSMQ[68]), consisting of 16 items which describe aspects of self-management. Items are rated on a 4-point Likert scale (0='does not apply to me' to 3='applies to me very much'). The raw sum score is transformed to a scale from 0 to 10 with higher scores suggesting better self-management.

Acceptance

The Acceptance and Action Diabetes Questionnaire[69] was used to measure diabetes acceptance. Acceptance of diabetes-related feelings, thoughts and its impact on

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valued action is measured on 11 items on a 5-point Likert scale (1='never' to 5='nearly always').

Quality of life

The Assessment of Quality of Life 8-item Questionnaire[70] was used to measure quality of life on eight dimensions (independent living, senses, pain, mental health, happiness, self-worth, coping and relationships). Sum score measures indicate overall physical and psychosocial quality of life. The total scores range between 35 and 176 points with higher values indicating higher quality of life.

Fear of progression

The short form of the Fear of Progression Questionnaire[71] measures worries and fear regarding disease progression and development of diabetes complications using 12 items and a 5-point Likert scale (1='never' to 5='very often'). The total score ranges from 0 to 60, higher scores indicate higher fear.

Sample size

As this trial was intended to help revise/finalise the intervention and select suitable outcome measures for the full-scale trial, the target of this trial was to recruit at least 40 participants with 20 participants per arm. In accordance with the extended version of the CONSORT statement for feasibility trials,[52] investigators decided to proceed with the recruitment of participants until enough information was reached to decide whether or how to continue with a future definitive trial. Online supplemental table 1 comprises formal feasibility criteria with regard to trial recruitment, acceptability and outcome data following standard recommendations.[56 72]

Data analysis

The data were analysed with R.[73] Quantitative data include descriptive statistics (frequency, percentage, mean, SD, median) and linear regression models for investigating potential group differences. Regression models were used to investigate group differences (dummy coded predictor: EG=1). Baseline values were used as covariate in all regression models.[74] Analyses are based on an intention-to-treat principle. Multivariate imputation by chained equations were performed to create 20 complete datasets.[74] Missing data were assumed to be missing at random.[75] Predictive mean matching was used as imputation method.[74] Imputation models were defined following the recommendations by van Buuren *et al*,[74 76] that is, including variables defined for the primary analysis and auxiliary variables. Analyses were conducted for each imputed dataset and pooled using Rubin's rule.[77 78] For all outcomes, mean, SD, standardised regression coefficient and the corresponding 95% CI are reported. The significance level was set to $p<0.05$ for all analyses.

Patient and public involvement

Patient and public involvement (PPI) representatives provide input to the present study in several stages. The intervention was further developed in a multidisciplinary team comprising psychologists, psychotherapists, diabetes specialists and people with diabetes. PPI representatives were included in the intervention development to improve content, usability and design of ACTonDiabetes.

RESULTS

Trial recruitment and acceptability

Recruitment

The study was closed after N=42 participants had been randomised. N=61 individuals were assessed for eligibility and informed about the study. N=18 people did not consent, two participants were excluded for not meeting inclusion criteria (figure 2). Forty-two people with diabetes were randomised (participant flow, figure 2), equalling to a participation rate of 71%. Sixty-four per cent of people assessed for eligibility got to know about the study from specialised diabetes centres, 30% were recruited via social media, 6% from other sources.

Baseline participant sociodemographic and clinical characteristics are presented in table 3. Mean age of the sample was M=46.9 (SD=14.4), 50% were female. The majority, 76%, of the participants were diagnosed with type 1 diabetes.

Baseline diabetes distress was elevated with a mean PAID score of M=43.9 (SD=13.7). Furthermore, the mean PHQ-9 and GAD-7 scores at baseline suggested mild depressive (M=8.40, SD=5.11; PHQ-9) and anxiety symptoms (M=6.62, SD=4.34; GAD-7).

Acceptability

Attitudes towards internet interventions

The assessment of attitudes towards internet interventions using the APOI revealed values of M=39.7 (SD=7.1) at T1 and M=41.7 (SD=11.25) at T2 in the EG, and M=40.1 (SD=9.4) (T1) and M=42.6 (10.0) (T2) in the CG (see table 3). Attitudes were not significantly different between EG and CG at post-measurement (b=−0.04, p=0.86). Participants' mean satisfaction with intervention according to the CSQ-8 total score was M=25.8 (SD=5.6) (table 3).

Formative user feedback

We received N=89 feedback forms from n=21 participants across the seven modules regarding processing time per module. Much feedback (75%, n=16) indicated that the processing time per module was just right. Minddistrict data revealed that processing through modules took on average M=84 min (SD=36) per module. Open questions revealed that mindfulness and acceptance-based interventions were perceived as particularly positive across modules (46% of 89 feedback, n=41). Across the modules, open-ended questions indicated that contents were not always easy to understand (34%, n=30), not sufficiently individualised (20%, n=18) and too text intensive in overall amount (21%, n=19).

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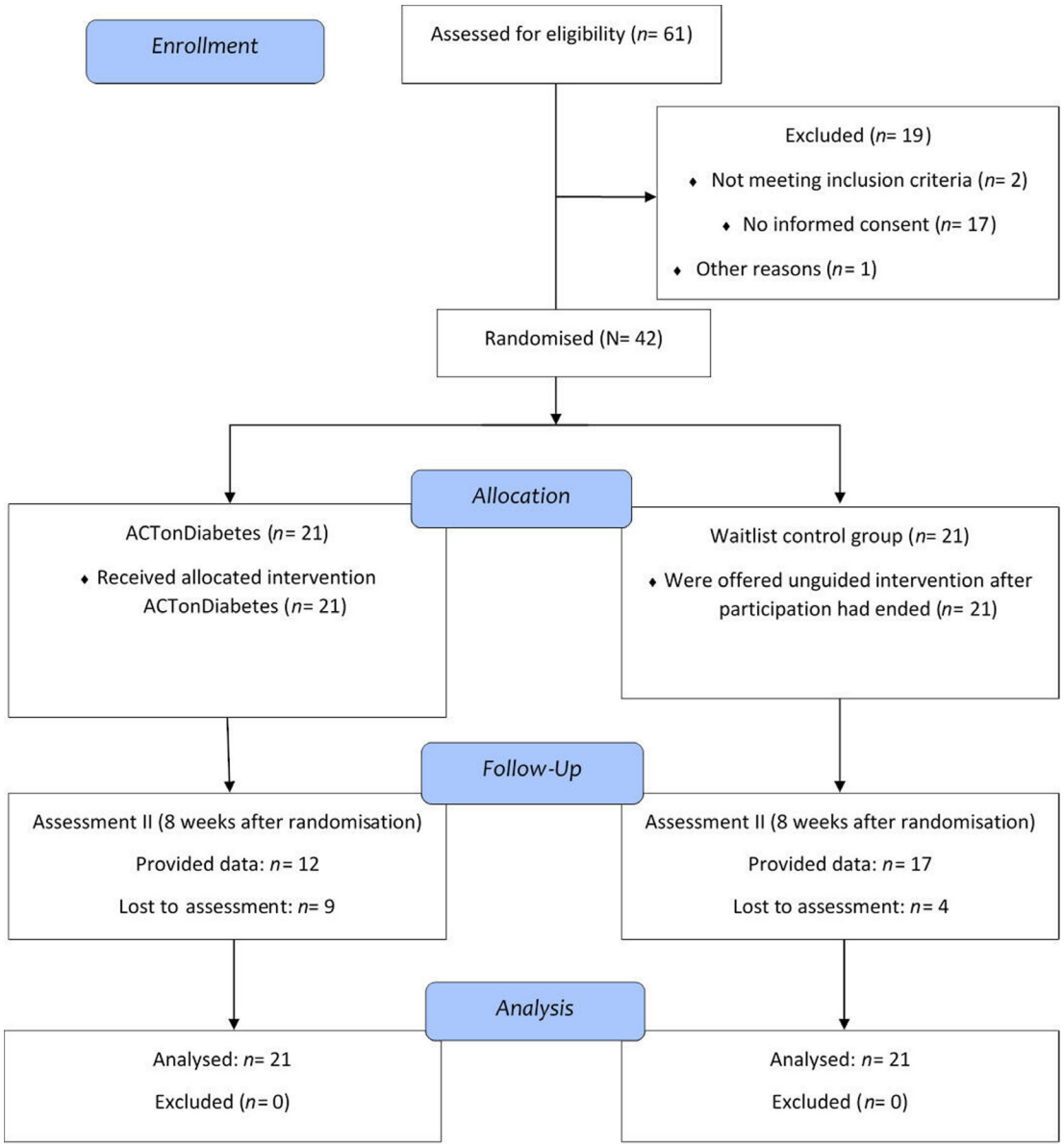

Figure 2 Participant flow.

Negative effects

At post-treatment, none of the participants of the EG indicated to feel worse than before ACTonDiabetes. About one-third of participants reported no change in their subjective well-being (33%, n=7), while two-thirds (66%, n=14) reported that their well-being improved since the start of the intervention. All participants who reported improvements attributed their experienced positive changes to the intervention. Four participants (14%) reported to suffer more from past experiences than before the intervention; one of them attributed this change to the intervention, while the others attributed it to other circumstances. One person reported a more increased number of relationship conflicts than before the intervention. However, this was not attributed to the intervention. Two participants (6.8%) reported worsened relationships with their families and three regarding friends (10.3%) since the intervention, but none of them attributed these changes to the intervention. Four persons (19%) of the EG worried that colleagues or peers might get to know about their participation in the study/receiving treatment. Three persons (10.3%) indicated to worry about possible future trouble with insurance; one of them attributed this to the intervention. Six persons (20.7%) indicated to have more financial worries than before the intervention. One of them attributed this to the intervention. Eight persons (27.5%) indicated feeling dependent on the intervention. Eleven persons (37.8%) reported greater difficulties to make decisions on their own after finishing the intervention, but only one of them attributed this to the intervention. Finally, five persons (17.2%) reported that they did not feel well for longer periods after attending the intervention but attributed this to other life circumstances.

Overall, N=16 participants of the EG (76%) reported at least one negative change in social, intrapersonal or

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Table 3 Baseline sample characteristics by group

	ACTonDiabetes, n=21 M (SD)	Waitlist, n=21 M (SD)
Age	47.6 (12.7)	46.1 (16.2)
Diabetes distress (PAID)	45.1 (13.8)	42.58 (13.4)
Quality of life (AQoL-8D)	68.99 (13.0)	66.06 (11.5)
Depression symptoms (PHQ-9)	7.38 (5.3)	9.43 (4.8)
Anxiety symptoms (GAD-7)	6.24 (4.2)	7.00 (4.6)
Fear of progression (FoP-Q-SF)	34.33 (8.9)	32.24 (9.9)
Diabetes acceptance (AADQ)	41.62 (7.1)	41.14 (6.9)
Diabetes self-care (DSMQ)	6.88 (1.7)	5.81 (1.7)
Attitudes towards online interventions (APOI)	39.71 (7.1)	40.09 (9.4)
	N (%)	N (%)
Gender	9 (43%) female	12 (57%) female
Highest educational level (ISCED-97 level)		
Level 2 (secondary education first stage)	4 (19)	4 (19)
Level 3 or 4 (secondary education second stage or post-secondary non-tertiary education)	12 (57)	6 (29)
Level 5 (first stage of tertiary education)	5 (24)	11 (52)
Prior psychotherapy	7 (33)	13 (62)
Diabetes type	16 (76 type 1)	16 (76 type 1)

Data are M (SD) or number (%).
AADQ, Acceptance and Action Diabetes Questionnaire; APOI, Attitudes towards Psychological Online Interventions Questionnaire; AQoL-8D, Assessment of Quality of Life 8-item Questionnaire; DSMQ, Diabetes Self-Management Questionnaire; FoP-Q-SF, Fear of Progression Questionnaire–Short Form; GAD-7, Generalized Anxiety Disorder 7-item Scale; ISCED-97, International Standard Classification of Education 1997; PAID, Problem Areas In Diabetes Scale; PHQ-9, Patient Health Questionnaire-9.

work-related aspects. Of them, n=6 participants (38%) attributed these experienced changes to the intervention. Thus, one-third of all treated participants experienced at least one negative change due to ACTonDiabetes.

Intervention adherence

Analyses on intervention adherence revealed that nine participants of the EG (43%) completed all seven modules within 8 weeks after randomisation. Excluding participants who never started the intervention, from randomisation to post-treatment 57% (n=10) dropped out before starting module 5 (figure 3). Eleven participants provided reasons for not starting or discontinuing: three participants indicated that participation was not useful to them, eight stated that they did not have enough time for further participation. Overall, 52% of all participants finished at least module 4 after 8 weeks.

Changes in psychometric outcomes

There was a significant difference between the groups regarding diabetes distress after the intervention (T2) favouring the EG (Cohen's d=0.65, 95% CI −1.27 to −0.02, p=0.042). The effect adjusted for the baseline value was (b=−0.68, 95% CI −1.36 to 0.02, p=0.048, adjusted R^2=0.17). Changes in the other assessed outcomes were non-significant between groups, however, all with a descriptive trend towards greater improvements in the EG (table 4).

DISCUSSION

This RCT evaluated the feasibility and potential effectiveness of an internet intervention to decrease elevated diabetes distress in people with type 1 or type 2 diabetes. To our knowledge, this is the first study that investigates an ACT-based internet intervention for this population. Participants reported elevated diabetes distress as well as depressive and anxiety symptoms, thus recruitment strategies reached people with an at least quantifiable level of psychological burden.

The participation rate in this study was at 71%, indicating that the applied procedure to transfer eligible individuals into the study is appropriate. We reached female and male participants equally; however, the majority of the participants had type 1 diabetes. This is somewhat surprising as different studies show that both groups report equal burden due to diabetes. The imbalance may be in part explained by the recruitment strategies. That is, the overall number of members in identifiable self-organised social media groups with diabetes type 1 was N=15 000, while identifiable self-organised groups for diabetes type 2 comprised only about 1000 members. Furthermore,

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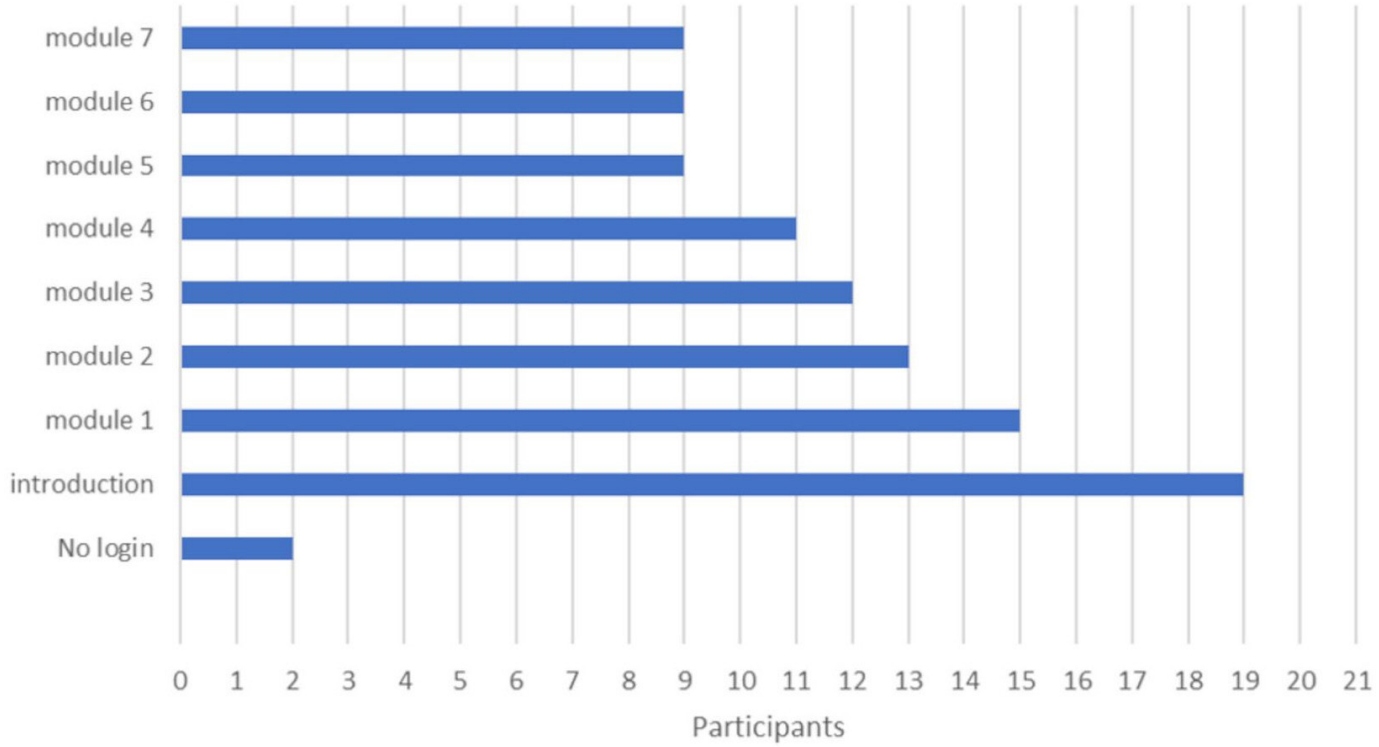

Figure 3 Intervention completion 8 weeks after randomisation.

many participants were recruited via specialised centres with an over-representation of people with type 1 diabetes compared with the primary care setting. Personal recommendation may have led to higher participation than advertisement only. Overall, the intervention seems to be particularly interesting for middle-aged persons of both sexes who treat their diabetes with insulin and are not currently undergoing psychotherapeutic treatment.

From randomisation to post-treatment, 30% of the participants dropped out, most of them discontinuing during the first half of the intervention. Only 43% of the participants finished all seven modules within 8 weeks after randomisation. However, 62% (n=13) of the participants completed the intervention within 21 weeks after randomisation, suggesting that a slower treatment performance was preferred by some people. Although the dropout is comparable with other trials in the field, offline or online[33 79] future studies (including the planned full-scale trial) would benefit from adding mechanisms to foster adherence. Low intervention completion could limit the effectiveness of the intervention in a confirmatory trial. Guidance, SMS coaching and reminders might be useful techniques to keep participants involved[80 81] and should be further extended. A greater variety in presentation forms, helping to clarify contents and facilitating comprehension, could be experienced as positive and help to increase participants' adherence.[82] Formative feedback on the intervention revealed that there should be less extensive and complex texts and better comprehensibility. Analyses of the processing time per module indicated that it took on average 24–39 min longer than expected to process through the intervention. However, 75% of participants indicated that the processing time was just right for them. This inconsistency might be explained by possible breaks during working on the modules. The finding of long processing times suggests that the contents should not be extended per module in the further developed version of ACTonDiabetes. Another point that was raised by the participants concerns the individualisation of contents. Higher degrees of individualisation could be realised by adding diabetes-specific aspects of living with diabetes to the case vignettes (eg, by condensing the narratives throughout the intervention). This could help to better fit the intervention contents to the target population. Additionally, more individualisation could be achieved by expanding the space for individual life stories within the intervention. This could comprise personal writing like the development of illness narratives.

More comprehensibility could be achieved by strengthening interdisciplinary exchange, that is, with regard to text comprehension researchers.[83] The use of written text as a medium for conveying contents should be limited in favour of other media and interactive materials like illustrations, videos and audio files. Another yet too little investigated and integrated factor is a positive experience and a gratification character when processing through internet interventions. Interventions could be further enriched by integrating token systems or serious games (eg, games with the primary purpose of knowledge transfer).[84] To optimise the ACTonDiabetes intervention based on these findings, the amount of written text should be reduced per module by replacing it with video and audio materials. Also, optimising persuasiveness of ACTonDiabetes might improve adherence.[85]

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Table 4 Linear regression analysis of changes from baseline to post-treatment

	Baseline (T1) M (SD)	Post-treatment (T2) M (SD)	Standardised coefficient ß	SE ß	95% CI	P value	Cohen's d
Diabetes distress (PAID)	45.1 (13.8)	23.9 (19.8)	−0.68	0.33	−1.36 to 0.002	0.048	−0.65
Depression symptoms (PHQ-9)	7.4 (5.3)	5.7 (4.4)	−0.36	0.25	−0.87 to 0.14	0.502	−0.66
Anxiety symptoms (GAD-7)	6.24 (4.17)	4.38 (3.53)	−0.44	0.27	−0.99 to 0.11	0.108	−0.57
Fear of progression (FoP-Q-SF)	34.33 (8.95)	31.39 (7.99)	−0.21	0.27	−0.76 to 0.33	0.428	−0.06
Diabetes acceptance (AADQ)	41.62 (7.15)	43.36 (4.82)	0.19	0.24	−0.30 to 0.69	0.418	+0.24
Diabetes self-care (DSMQ)	6.88 (1.66)	7.37 (1.29)	0.26	0.22	−0.20 to 0.71	0.243	+0.81
Quality of life (AQoL-8D)	68.99 (13.05)	71.56 (12.92)	0.32	0.22	−0.13 to 0.77	0.145	+0.53
Attitudes towards online interventions (APOI)	39.71 (7.13)	41.75 (11.26)	0.04	0.25	−1.73 to 0.30	0.86	+0.07
Treatment satisfaction (CSQ-8)	–	25.77 (5.54)	–	–	–	–	–

Between group differences at post-measurement adjusted for baseline differences. Intervention group was coded with 1 (independent variable), baseline values were used as covariate, positive values indicate higher values in the intervention group. Negative values indicate lower values in the intervention group. Data are M (SD), regression coefficients or Cohen's d.
AADQ, Acceptance and Action Diabetes Questionnaire; APOI, Attitudes towards Psychological Online Interventions Questionnaire; AQoL-8D, Assessment of Quality of Life 8-item Questionnaire; CSQ-8, Client Satisfaction Questionnaire; DSMQ, Diabetes Self-Management Questionnaire; FoP-Q-SF, Fear of Progression Questionnaire–Short Form; GAD-7, Generalized Anxiety Disorder 7-item Scale; PAID, Problem Areas In Diabetes Scale; PHQ-9, Patient Health Questionnaire-9.

The attitudes towards internet interventions were generally positive. More positive attitudes may be associated with increased effectiveness of internet interventions.[86] Thus, providing more detailed information about ACTonDiabetes prior to the beginning of the intervention, or the inclusion of an acceptance-facilitating intervention at the start, might evoke more positive attitudes towards the internet-based treatment, hence increasing adherence and treatment effectiveness.[61 87–89]

Satisfaction with the intervention was positive and comparable with results of psychological treatments in psychosomatic contexts.[63] Participants reported non-severe negative effects due to the intervention. This is consistent with the current literature suggesting that negative treatment effects should be expected and thus monitored carefully.[90–92] Nevertheless, almost one-third of the participants reported at least one negative change which was attributed to the intervention. This points to the importance of considering possible negative side effects of ACTonDiabetes in a larger trial. To prevent such experiences, regular assessments should be implemented.[93] However, none of the participants of the EG indicated to feel worse due to the intervention. Future trials should measure both symptom deterioration and perceived negative effects during the treatment phase.[93]

To draw conclusions on effectiveness of the intervention regarding diabetes distress, it requires a larger study. The same holds true for potential effects on other intended outcomes like depression, anxiety and fear of progression. Likewise, effects on self-management and diabetes acceptance need to be evaluated in a larger study. Due to feasibility as primary outcome of this study, the small sample size as well as indications of inhomogeneity between the groups regarding prior psychotherapy/counselling experiences and educational level, conclusions on effectiveness are not subject to this study.

Limitations of this study comprise the fact that all data are based on self-report. Future studies should at least rely on professional-assured diagnosis. Furthermore, the absence of HbA1c data is one of the main shortcomings of this study. Future studies should incorporate medical data like HbA1c values as the evaluation of potential changes in HbA1c might play a key role regarding the relevance of the intervention in diabetes care. Additionally, comorbid disorders could be assessed in future studies to achieve better insights into the physical conditions of participants.

Another limitation is that the study tested the EG against a waitlist CG with participants being a priori informed about the difference between the groups. Additionally, participants in the EG received the guided version of ACTonDiabetes while the CG received the unguided ACTonDiabetes intervention. Thus, effects of waiting for treatment and receiving ACTonDiabetes without guidance could have biased the data. For psychotherapy research in general, small effect sizes found in waitlist control groups suggest that testing a treatment against a waitlist might not be a very strict test.[94] Future trials should use enhanced treatment-as-usual groups

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or an attention placebo control group to avoid these limitations.

Finally, the current sample was not recruited in a naturalistic setting, thus it may not reflect the real-life uptake of patients in the healthcare system. In order to investigate this, a pragmatic trial would have to be conducted which systematically recruits participants from routine care setting. In addition to this, no exact data were obtained on the number of people who were invited to participate. A future trial should address this shortcoming to allow the evaluation of the proportion of individuals reached from the potential eligible population.

Although generalisability of results is arguably limited, an important strength of this trial is the provision of deeper insights into evidence on internet-based mental health support for people with diabetes. A major strength is that we tested whether the intervention is feasible prior to implementing it on a larger scale. The intervention will be further optimised on the basis of the present findings prior to proceeding to the definitive trial.

A confirmatory trial will be needed to support the present preliminary findings and draw firm conclusions about treatment effects of ACTonDiabetes.

This paper may be fruitful for researchers planning studies or developing internet interventions for people with diabetes or other chronic conditions and comorbid psychological burden. ACT-based interventions constitute a promising approach in this context. New interventions for diabetes distress in people with type 1 or type 2 diabetes are needed. ACT could be particularly effective for people with diabetes as it focuses on the acceptance of unchangeable circumstances more specifically than standard CBT. The present results support that ACT-based interventions may be beneficial for people with diabetes. Strategies to foster adherence as well as content modifications according to the present results will be implemented to address key barriers to continued use and increase treatment effectiveness regarding diabetes distress.

ACTonDiabetes will be investigated in a subsequent full-scale trial. Trial registration number: DRKS00016738.

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Contributors EB, NB and HB designed and planned the study. ACTonDiabetes builds on ACTonPain (Jiaxi Lin) and was developed by the Department of Clinical Psychology and Psychotherapy at Ulm University (lead developer EB). The supervision was realised in a hierarchical structure with HB supervising EB who supervised project staff throughout the study. EB operatively performed the study. EB analysed and interpreted the data. EB drafted the manuscript. PA and AS critically revised the manuscript. AS additionally audited the manuscript for important intellectual content. All authors approved the final version to be published and agree to be accountable for all aspects of the work.

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Patient consent for publication Not required.

Ethics approval All procedures involved in the study are consistent with the generally accepted standards of ethical practice as approved by the ethics committee of the University of Ulm (file number 283/17).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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7 Publication IV

The next generation: chatbots in clinical psychology and psychotherapy to foster mental health–a scoping review

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The Next Generation: Chatbots in Clinical Psychology and Psychotherapy to Foster Mental Health – A Scoping Review

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Keywords
Software agent · Chatbot · Clinical psychology · Psychotherapy · Conversational agent

Abstract
Background and Purpose: The present age of digitalization brings with it progress and new possibilities for health care in general and clinical psychology/psychotherapy in particular. Internet- and mobile-based interventions (IMIs) have often been evaluated. A fully automated version of IMIs are chatbots. Chatbots are automated computer programs that are able to hold, e.g., a script-based conversation with a human being. Chatbots could contribute to the extension of health care services. The aim of this review is to conceptualize the scope and to work out the current state of the art of chatbots fostering mental health. ***Methods:*** The present article is a scoping review on chatbots in clinical psychology and psychotherapy. Studies that utilized chatbots to foster mental health were included. ***Results:*** The technology of chatbots is still experimental in nature. Studies are most often pilot studies by nature. The field lacks high-quality evidence derived from randomized controlled studies. Results with regard to practicability, feasibility, and acceptance of chatbots to foster mental health are promising but not yet directly transferable to psychotherapeutic contexts. ***Discussion:*** The rapidly increasing research on chatbots in the field of clinical psychology and psychotherapy requires corrective measures. Issues like effectiveness, sustainability, and especially safety and subsequent tests of technology are elements that should be instituted as a corrective for future funding programs of chatbots in clinical psychology and psychotherapy.
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Die nächste Generation: Chatbots in der klinischen Psychologie und Psychotherapie zur Förderung mentaler Gesundheit – Ein Scoping-Review

Schlüsselwörter
Software-Agent · Chatbot · Klinische Psychologie · Psychotherapie · Gesprächsbot

Zusammenfassung
Hintergrund und Ziel: Das gegenwärtige Zeitalter der Digitalisierung bringt Fortschritte und neue Möglichkeiten in der Gesundheitsversorgung im Allgemeinen und im Besonderen in der klinischen Psychologie und Psychotherapie mit sich. Internet- und mobilbasierte Interventionen (IMIs) sind inzwischen vielfach evaluiert. Eine vollständig automatisierte Form von IMIs stellen Chatbots dar. Chatbots sind automatisierte Computerprogramme, die z.B. eine skriptbasierte Konversation mit einem Menschen führen. Chatbots könnten zukünftig dazu beitragen, gesundheitsbezogene Versorgungsangebote zu erweitern. Ziel dieser Übersichtsarbeit ist die Konzeptuali-

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sierung des Gegenstandsbereichs und die Erarbeitung der Evidenzlage bezüglich Chatbots zur Förderung mentaler Gesundheit. ***Methoden:*** Der vorliegende Beitrag stellt ein Scoping-Review zum Gegenstandsbereich von Chatbots in der klinischen Psychologie und Psychotherapie dar. Eingeschlossen wurden Studien, die die Verwendung von Chatbots mit dem Ziel der Förderung mentaler Gesundheit untersuchen. ***Ergebnisse:*** Die Technologie der Chatbots ist noch als experimentell zu bezeichnen. Studien haben vorwiegend Pilotstudiencharakter. Es fehlt an qualitativ hochwertigen randomisiert-kontrollierten Studien. Die Ergebnisse der bisherigen Forschung im Hinblick auf die Praktikabilität, Durchführbarkeit und Akzeptanz von Chatbots zur Förderung mentaler Gesundheit sind zwar vielversprechend, jedoch derzeit noch nicht unmittelbar auf den psychotherapeutischen Kontext übertragbar. ***Diskussion:*** Themen wie Wirksamkeit, Nachhaltigkeit und insbesondere Sicherheit sowie Technologiefolgeuntersuchungen sind Bestandteile, die vor dem Hintergrund der wachsenden Forschungsaktivitäten im Bereich Chatbots als Korrektiv ein fester Bestandteil kommender wissenschaftlicher Förderprogramme werden sollten. © 2019 S. Karger AG, Basel

Chatbots in Clinical Psychology and Psychotherapy to Promote Mental Health: A Scoping Review

We find ourselves in the age of digitization, an age in which our work, the economy, and science are using increasingly intelligent machines that make our everyday life easier, including our private lives [World Economic Forum, 2018]. The Federal Ministry of Education and Research has declared artificial intelligence (AI) as one of the key technologies of the future and the theme of science year 2019 [Bundesministerium für Bildung und Forschung, 2018]. AI systems are technical learning systems that can process problems and adapt to changing conditions. They are already being used for road traffic control and to support emergency workers [Bundesministerium für Bildung und Forschung, 2018]. New possibilities are also being created by AI in the clinical/medical context. User data can be linked with up-to-date research data, which could improve medical diagnoses and treatments [Salathé et al., 2018]. Digitization trends will also affect clinical psychology and psychotherapy, such as chatbots that could be used increasingly and gain importance as *next generation* of psychological interventions. In this context, chatbots are programs that hold conversations with users – in the first instance technically based on scripts (plots that steer the conversation), which should be created by psychotherapists [Dowling and Rickwood, 2013; Becker, 2018]. Such chatbots are currently closer to full-text search engines than to standalone AI systems [Yuan, 2018].

In Germany, only a small proportion of people who are diagnosed with a mental disorder have contact with the health care system with regard to their mental health problems within 1 year [Jacobi et al., 2014]. Those affected do not take advantage of the available services for various reasons [Andrade et al., 2014]. Among these are worry about stigmatization [Barney et al., 2006], limitations of time or location [Paganini et al., 2016], negative attitudes towards pharmacological and psychotherapeutic treatment options [Baumeister, 2012], negative experiences with professional caregivers [Rickwood et al., 2007], and lack of insight into their illness [Zobel and Meyer, 2018]. Psychological Internet interventions represent an innovative potential that has resulted from progress in digitization. Barak et al. [2009] define a web-based intervention as "a primarily self-guided intervention program that is executed by means of a prescriptive online program operated through a website and used by consumers seeking health- and mental-health-related assistance" [Barak et al., 2009; p. 5]. Psychological Internet interventions have frequently been evaluated and are viewed as a medium independent of time and place [Carlbring et al., 2018; Ebert et al., 2018]. They might be able to help reduce treatment barriers and expand the availability of care [Baumeister et al., 2018; Carlbring et al., 2018; Ebert et al., 2018]. Numerous studies have shown that these interventions, often using cognitive-behavioral techniques, are comparable in their effectiveness to classical face-to-face psychotherapy [Andersson et al., 2014; Carlbring et al., 2018]. Psychological problems such as anxiety and depression are already being effectively addressed in this way [Andersson et al., 2014, 2016; Carlbring et al., 2018]. When comparing the effectiveness of classical psychotherapy with Internet- and mobile-based interventions (IMIs), it should be considered that interindividual differences, for example with regard to openness to new experiences, could affect whether and how strongly people benefit from the different forms of presentation (online or classical) [Andersson et al., 2016; Carlbring et al., 2018].

Chatbots are an innovative variant of psychological IMI with the potential to effect lasting change in psychotherapeutic care, but also with substantial ethical, legal (data protection), and social implications. The key objectives of the present review are:

1. conceptualizing the scope of chatbots in clinical psychology and psychotherapy;
2. working through the evidence about chatbots in promoting mental health; and
3. presenting the opportunities, limits, risks, and challenges of chatbots in clinical psychology and psychotherapy.

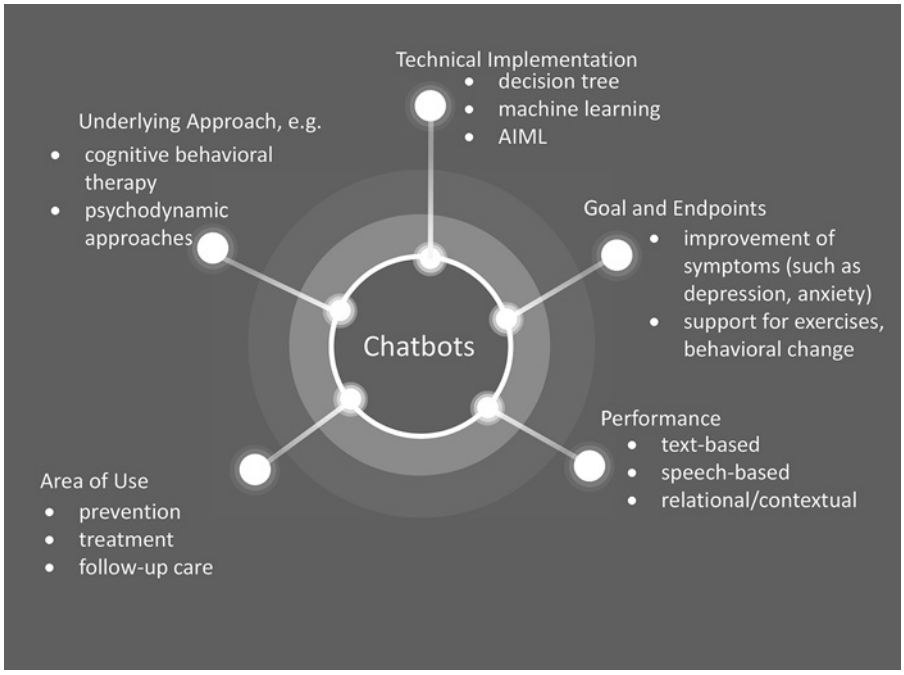

Fig. 1. Characteristics of chatbots in clinical psychology and psychotherapy. AIML, artificial markup language.

Conceptualizing the Scope

Chatbots are computer programs that hold a text- or speech-based dialogue with people through an interactive interface. Users thus have a conversation with a technical system [Abdul-Kader and Woods, 2015]. The program of the chatbot can imitate a therapeutic conversational style, enabling an interaction similar to a therapeutic conversation [Fitzpatrick et al., 2017]. The chatbot interacts with the user fully automatically [Abdul-Kader and Woods, 2015].

Chatbots are a special kind of human-machine interface that provides users with chat-based access to functions and data of the application itself (e.g., Internet interventions). They are currently used mainly for customer communication in online shopping [Storp, 2002], but also in teaching [Core et al., 2006] and the game industry [Gebhard et al., 2008]. Chatbots are already particularly important in the economic domain [World Economic Forum, 2018]. As demand for a certain application grows, new instances of a single chatbot can be launched with small technical efforts, so that the chatbot can hold many parallel conversations at the same time (high scalability). This enables people to use freed capacities for more complex aspects of their work [Juniper Research, 2018; World Economic Forum, 2018]. The rapid progress in new technologies is also bringing about changes and new opportunities in health care in general and clinical psychology/psychotherapy in particular [Juniper Research, 2018; World Economic Forum, 2018].

Research interest in chatbots for use in clinical psychology and psychotherapy is growing by leaps and bounds, as can be seen by the increasing number of (pilot) studies in this area [Dale, 2016; Brandtzaeg and Følstad, 2017], as well as the growing number of online services offered by health care providers (e.g., health apps with chat support).

Chatbots can be systematized with regard to (1) areas of application, (2) underlying clinical-psychological/psychotherapeutic approaches, (3) performance of the chatbot, (4) goals and endpoints, and (5) technical implementation (Fig. 1).

Areas of Application

Promising areas for the use of chatbots in the psychotherapeutic context could be support for the prevention, treatment, and follow-up/relapse prevention of psychological problems and mental disorders [Huang et al., 2015; D'Alfonso et al., 2017; Bird et al., 2018]. They could be used preventively in the future, for example for suicide prevention [Martínez-Miranda, 2017]. Current research shows that suicidal ideation and/or suicidal behavior among users of social media, for example, can be detected with automated procedures [De Choudhury et al., 2016]. Then chatbots could, for example, automatically inform users of nearby psychological/psychiatric services. In the treatment of psychological problems, they might offer tools that participants could work with on their own. After the completion of classical psychotherapy, chatbots might be offered in the future to stabilize intervention effects, facilitate the transfer of the therapeutic content into daily life, and reduce the likelihood of relapse [D'Alfonso et al., 2017].

Clinical-Psychological/Psychotherapeutic Approaches

The scripts used by chatbots to address clinical-psychological issues should be based on well-evaluated prin-

ciples of classical face-to-face psychotherapy (e.g., cognitive behavioral therapy). On the basis of such evidence-based scripts, within which the chatbot program follows options for action (e.g., using if-then rules), conversations can be held that are similar to therapeutic discussions [Dowling and Rickwood, 2013; D'Alfonso et al., 2017; Becker, 2018]. It is becoming clear from the research on IMIs that all approaches covered by the German Psychotherapy Guidelines, such as psychodynamic or behavioral therapy, can be suitable for translation into an online format [Paganini et al., 2016]. The approaches of interpersonal therapy, acceptance and commitment therapy, and mindfulness-based therapy have also been translated into online services and evaluated for use in either guided or unguided self-help interventions [Paganini et al., 2016].

Performance of the Chatbot

The effectiveness of the chatbot may vary depending on the modality in which the conversation occurs. There are *text-based* chatbots (often referred to in the literature as *conversational agents* or *chatbots*) and chatbots that use natural-language, *speech-based* interfaces in dialogue systems (such as Apple's Siri, Amazon's Alexa, Microsoft's Cortana, and Google's Allo) [Bertolucci and Watson, 2016]. From a technical point of view, speech-based chatbots are text-based chatbots that also have functions for speech recognition and speech synthesis (machine reading aloud).

The simpler chatbots are based mainly on recognizing certain key terms with which to steer a conversation. More powerful chatbots can analyze user input and communication patterns more comprehensively, thus responding in a more precise way and deriving contextual information, such as users' emotions [Bickmore et al., 2005a,b].

Relational chatbots, sometimes referred to as *contextual* chatbots, simulate human capabilities, including social, emotional, and relational dimensions of natural conversations [Bickmore, 2010]. Computer-generated characters, so-called avatars, are often used in the design of a chatbot identity; these mimic the key attributes of human conversations and are often studied under the label *embodied conversational agents* in the literature [Beun et al., 2003; Provoost et al., 2017]. The more mental attributes the chatbot has, the greater its similarity to humans (anthropomorphism) [Zanbaka et al., 2006]. Anthropomorphism refers to the extent to which the chatbot can imitate behavioral attributes of a therapist [Zanbaka et al., 2006].

In the psychotherapeutic context of promoting mental health, social attributes [Krämer et al., 2018] and the ability of the chatbot to express empathy appear to be important factors in fostering a viable basis for interaction between a person and a chatbot [Bickmore et al. 2005a; Morris et al., 2018; Brixey and Novick, 2019].

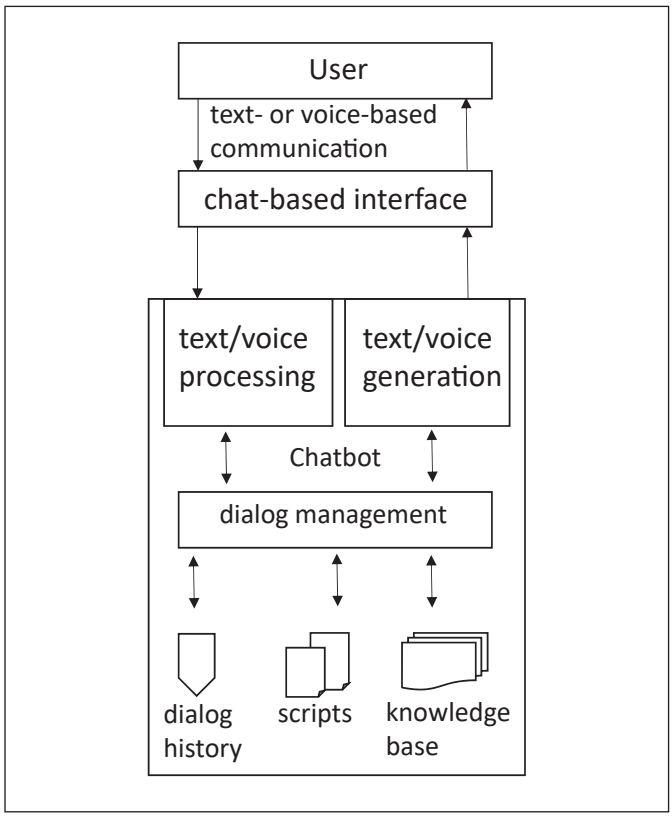

Fig. 2. Graphic representation of the technical implementation of chatbots.

Goals and Endpoints

Chatbots could take over time-consuming psychotherapeutic interventions that do not require more complex therapeutic competences [Fitzpatrick et al., 2017]. These are often investigated under the designation *microintervention.* Examples of microinterventions that do not need a great deal of therapist contact and can be initiated and guided by chatbots include psychoeducation, goal-setting conversations, and behavioral activation [Fitzpatrick et al., 2017; Stieger et al., 2018]. An example of a paradigm that is currently receiving much attention in this research context is therapeutic writing [Tielman et al., 2017; Bendig et al., 2018; Ho et al., 2018]. In the future, chatbots may have the potential to convey therapeutic content [Ly et al., 2017] and to mirror therapeutic processes [Fitzpatrick et al., 2017]. Combined with linguistic analyses such as sentiment analysis (a method for detecting moods), chatbots would be able to react to the mood of the users. This allows the selection of emotion-dependent response options and thematization of content adapted to the user's input [Ly et al., 2017] or the forwarding of relevant information about psychological variables to the practitioner. Regarding the possibilities that may emerge for psychotherapy, it is relevant to take up the current state of chatbot research in this context.

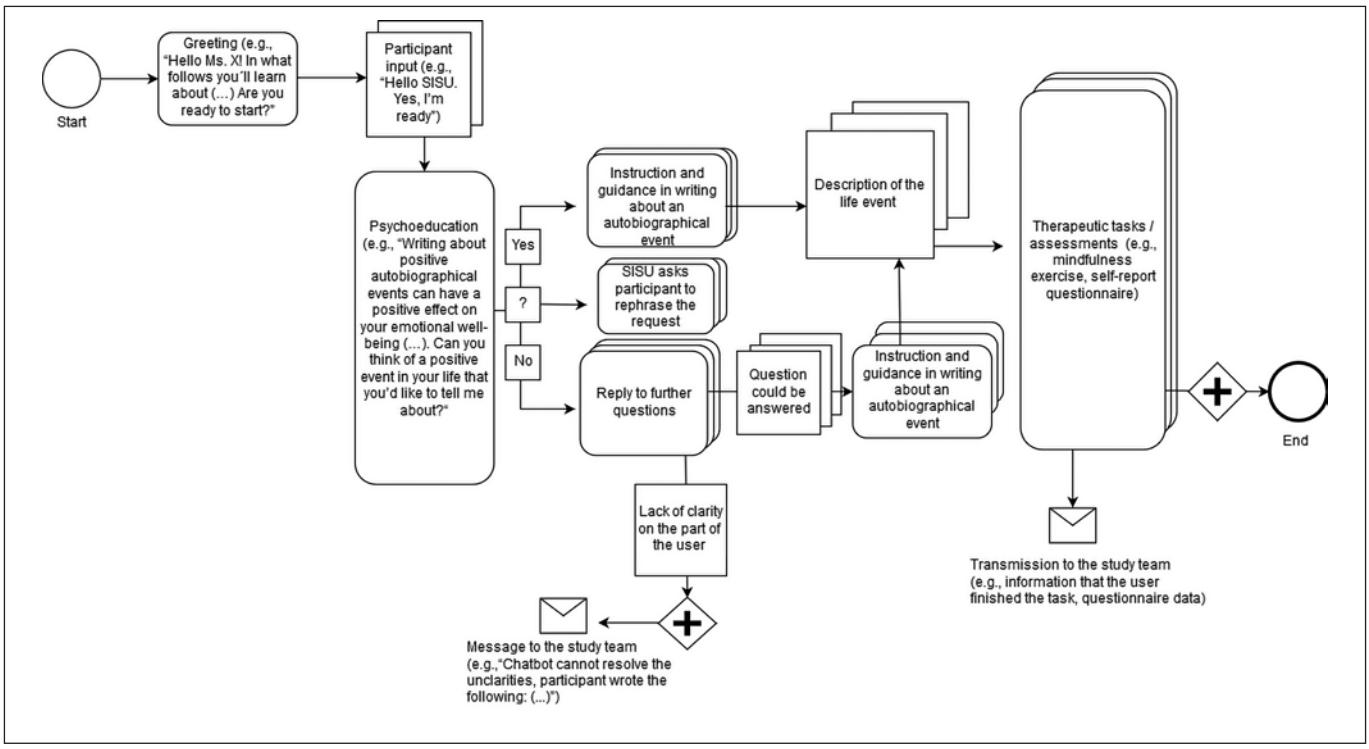

Fig. 3. Simplified, schematic representation of a dialogue with the chatbot SISU [Bendig, Erb, Meißner, 2018].

Technical Implementation

From a technical point of view, chatbots comprise various internal subcomponents [Gregori, 2017]. The component for recognizing information from the messages of the conversation partner is elementary. First and foremost, the intentions and relevant entities must be identified from the statements of the interlocutor. This is done using natural language processing (NLP), which is the machine processing of natural language using statistical algorithms. NLP translates the user's input into a language that the chatbot can understand (Fig. 2). The identified user intentions and entities, in turn, serve as the foundation for the appropriate response from the chatbot based on its components for dialogue management and response generation. Response generation is based, for example, on stored scripts, a predetermined dialogue, and/or an integrated knowledge base. The answer is made available to users via the chat-based interface, such as an Internet intervention or an app (Fig. 2).

Chatbots vary in their *complexity of interaction.* Simpler dialogue components are based exclusively on rule-based sequences (such as if-then rules). Conversations are modeled as a network of possible states. Inputs trigger the state transitions and associated responses of the bot, analogous to stimulus-response systems [Storp, 2002]. The chatbot internally follows a predefined decision tree [Chowdhury, 2003; Smola et al., 2008] (illustred in Fig. 3). The more complex chatbots also use knowledge bases or models of machine learning to construct their dialogues and AI to generate possible answers and to enhance the conversational proficiency of the bot (often called *mental capacities* in the research literature) [Lortie and Guitton, 2011; Ireland et al., 2016]. There are dedicated programming languages for programming chatbot dialogues. Artificial markup language (AIML; http://alicebot.wikidot.com/learn-aiml) has become particularly well established [Klopfenstein et al., 2017].

Classification of the Topic in the "Next-Generation" Clinical-Psychological/Psychotherapeutic Interventions

Through the advance of technology, online services are gaining in importance for classical psychotherapy [World Economic Forum, 2018]. Hybrid forms of online and offline psychotherapy are being investigated, the so-called blended care approaches [Baumeister et al., 2018]. Another area of research is stepped-care approaches, in which online services represent a low-threshold first step in a tiered supply model [Bower and Gilbody, 2005; Domhardt and Baumeister, 2018]. In the "next-generation" IMIs, chatbots could become increasingly important, especially as a natural interaction interface between users and innovative technology-driven forms of therapy. In the near future, chatbots will at first mainly conduct dialogues based on scripts created by psychotherapists [Dowling and Rickwood, 2013; Becker, 2018]. The dialogues can be of varying complexity depending on the

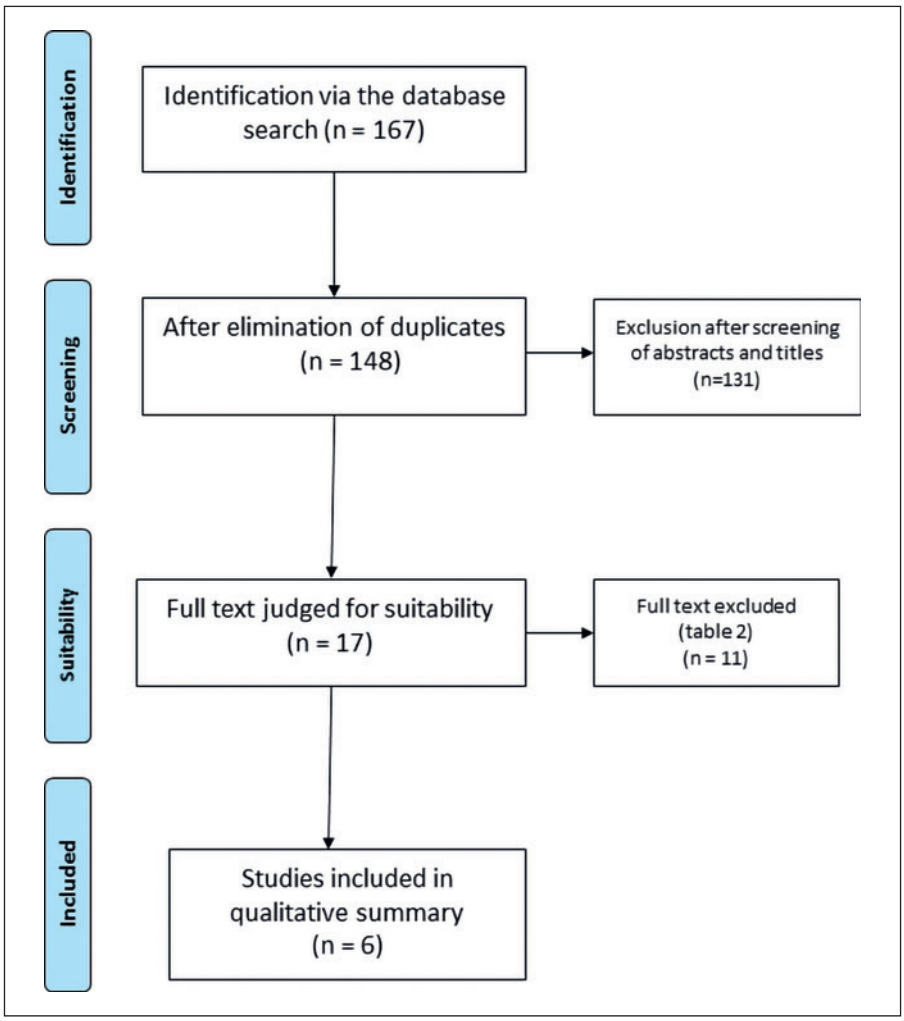

Fig. 4. Search process of the literature included in the review.

content and objective. ELIZA [Weizenbaum, 1966], the first chatbot, simulated a psychotherapeutic conversation using a trivial script, resulting in a dialogue with users by means of set queries based on the user's inputs [Gesprächspsychotherapie nach Rogers, 1957]. The SISU chatbot simulates a conversation modeled on the paradigm of therapeutic writing, with elements of acceptance and commitment therapy, which instruct participants to write about important life events [Bendig et al., 2018]. An example of such a dialogue is shown in Figure 3.

Next, we present the current state of research on chatbots that are based on a psychological/psychotherapeutic evidence-based script aimed at reducing the symptoms of psychological illness and improving mental well-being – that is, promoting mental health.

Method

The present article is a scoping review of chatbots in clinical psychology and psychotherapy. This method is used for quick identification of research findings in a specific field, as well as summarizing and disseminating these findings [Peterson et al., 2017]. Scoping reviews are particularly suitable for presentation of complex topics, as well as for generating research desiderata. The objective of the review was defined, the inclusion and exclusion criteria were set, the relevant studies were searched, and titles, abstracts, and full texts were screened (E.B. and L.S.-T.). The generalizability of the research results is not a systematic goal of the present study [Moher et al., 2015; Peterson et al., 2017].

Inclusion and Exclusion Criteria

Studies that utilized chatbots to promote mental health were included. Only chatbots based on evidence-based clinical-psychological/psychotherapeutic scripts were considered. Thus, the only studies that were included used chatbots based on principles that are judged positively in classical face-to-face psychotherapy (e.g., principles and techniques covered by the psychotherapy guidelines). Populations both with and without mental and/or chronic physical conditions were included. Only those studies were included that examined the psychological variables of depression, anxiety, stress, or psychological well-being as primary or secondary endpoints. Other inclusion criteria were adult age (age 18+) and complete automation of the investigated (micro)interventions. The latter criterion excluded so-called Wizard-of-Oz studies, in which a person, such as a member of the research team, pretends to be a chatbot. Primary research findings were included, as well as study protocols that were generated in the context of, for example, randomized controlled (pilot) studies, experimental designs, or pre-post studies.

Table 1. Characteristics of the 6 studies included in the review

Authors, year	Identifier/ acronym	Study location	Study design	Statistical analysis	Population	*N*	Age, mean ± SD (range)	Females, %	CG	Duration	Method	Psychological endpoint
Bird et al., 2018	Mylo	UK	2-arm RCT	ITT	Nonclinical	171	21.28 ±6.19	90.3	Active CG (ELIZA)	≥20 min	MOL [Carey, 2006]	Depression, anxiety, stress, DASS-21
Fitzpatrick et al., 2017	Woebot	USA	2-arm RCT	PP	Nonclinical	70	22.2 ±2.33 (18–28)	67.0	Active CG (info-material)	2 weeks	CBT	Anxiety (GAD-7), depression (PHQ-9), mood (PANAS)
Gardiner et al., 2017	Gabby	USA	2-arm pilot RCT	PP	Outpatients at the Boston Medical Center	61	35±8.4	100	Active CG (info-material)	1 month	MBSR	Perceived stress (PSS-4)
Ly et al., 2017	Shim	Sweden	2-arm pilot RCT	ITT	Nonclinical	28	26.2 ±7.2 (20–49)	46.4	Waiting list CG	2 weeks	CBT, positive psychology	Psychological well-being (FS), life satisfaction (SWLS), perceived stress (PSS-10)
Stieger et al., 2018	PEACH	Switzer-land	Study protocol 4-arm RCT	NA	NA	NA	NA	NA	2 waiting lists CG	10 weeks	Use of fin-dings of the impact-fac-tor research	Personality variables (BFI-2 and BFI-2-S)
Suganuma et al., 2018	Sabori	Japan	2-arm non-randomized pilot trial	PP	Nonclinical	454	38.04 ±10.75	70	Waiting list CG	1 month	CBT, BA	Psychological well-being (WHO-5-J), BADS, Kessler 10 (K10)

BA, behavioral activation; BADS, BA in depression; CBT, cognitive behavioral therapy; CG, control group; FS, Flourishing Scale; ITT, intention-to-treat; MBSR, mindfulness-based stress reduction; MOL, method of levels; NA, only study protocol available; nonclinical, participants who were neither given psychological treatment nor psychotropic drugs; PP, per protocol; PSS, Perceived Stress Scale; RCT, randomized controlled trial; SWLS, Subjective Well-Being Scale.

Search Strategy

To find suitable studies, an iterative process of keyword search and preliminary data analysis in March 2018 led to a final, systematic search in the databases PsycArticles, All EBM Reviews, Ovid MEDLINE®, Embase, PsycINFO, Cochrane databases, and PsyINDEX, using the search string: chatterbot OR chatbot OR social bot OR conversational agent OR softbot OR virtual agent OR software agent OR conversational agent OR automated agent AND (psych* OR counseling OR mental health OR psychotherapy OR therap* OR mental* OR clinical psychology). The hits were independently screened by 2 authors (E.B. and L.S.-T.); 148 duplicate-adjusted articles were found, which were then reduced in accordance with the search criteria in 2 rounds by title and abstract screening to 17 full texts (E.B. and L.S.-T.). Studies in which there was disagreement regarding inclusion/exclusion criteria were discussed (E.B. and L.S.-T.), resulting in 6 finally included articles. The search process is depicted in Figure 4.

Findings: General Characteristics of the Included Studies

Table 1 provides an overview of the study characteristics. All studies were published in the last 8 years, with half of them coming from the USA. The sample size varied between $N = 28$ and $N = 496$, with a mean of 156.8 (SD = 174.52). Participants were adults (mean age = 28.54 years, SD = 5.48), and 50% of the studies included students. They were either experiencing a problem that was causing distress [Bird et al., 2018], displaying symptoms of anxiety and depression [Fitzpatrick et al., 2017], or participants who had not been screened for psychological issues before study inclusion [Ly et al., 2017; Suganuma et al., 2018]. In the study by Gardiner et al. [2017], patients from outpatient clinics were included, while in the study by Suganuma et al. [2018], working people, students, and housewives were included (Table 1). Chatbots that are essentially based on cognitive-behavioral scripts have been the most frequently studied ($k = 5$). Newer approaches from the third wave of behavioral therapy (such as mindfulness-based stress reduction) were also used ($k = 1$). The most commonly studied endpoints were depression, anxiety, mental well-being, and stress. The majority of participants in all the studies were female (>50%) and from nonclinical populations, with the largest proportion being students. The studies are mostly so-called feasibility or pilot studies, with the objective to assess acceptance and make an initial assessment of effectiveness (practicability).

Evidence about Chatbots to Promote Mental Health

The MYLO chatbot (Manage Your Life Online, available at https://manageyourlifeonline.org) offers a self-help program for problem solving when a person is in distress [Gaffney et al., 2014]. The MYLO script is based on method-of-level therapy [Carey, 2006]. In a randomized controlled trial, participants were assigned either to the ELIZA [Weizenbaum, 1966] program, based on Rogerian client-centered therapy, or to the MYLO program [Bird et al., 2018]. Both chatbots impart problem-solving strategies and guide the user to focus on a specific problem. Through targeted questions, participants are encouraged to approach a circumscribed problem area from different perspectives. One objective of the study was to evaluate the effectiveness of MYLO in reducing problem-related distress compared to the active control group that used ELIZA. Self-reported distress improved significant-

Table 2. Characteristics of the 11 studies excluded in the screening process

Authors, year	Identifier/acronym	Study location	Purpose of the interaction with the chatbot	Exclusion
Bickmore et al., 2010a	–	USA	Transmission of discharge reports	Intervention, endpoint
Bickmore et al., 2010b	–	USA	Medication adherence	Intervention, endpoint
Bickmore et al., 2013	–	USA	Physical activity, nutrition	Endpoints
Burton et al., 2016	Help4mood	Romania, Spain, Scotland (UK)	Depression	Intervention
DeVault et al., 2014	SimSensei kiosk with Ellie, the therapist	USA	Conducting semistructured interviews for diagnosis of psychological problems	Intervention, design: hybrid; chatbot + online therapist
Fadhil, 2018	Roborto	Italy	Medication adherence	Endpoints
Hudlicka, 2013	Chris	USA	Mindfulness, meditation	Endpoints
Ireland et al., 2016	Harlie	UK	Monitoring Parkinson disease	Endpoints
Morris et al., 2018	Kokobot	USA	First steps in developing a bot that can express empathy	Design: no primary findings
Sebastian and Richards, 2017	–	Australia	Changing stigmatizing attitudes to anorexia nervosa	Endpoints
Tielmann et al., 2017	–	The Netherlands	Reconstruction of traumatic experiences	Intervention

The column "exclusion" lists the reasons for excluding the study from the present review.

ly in both groups ($F_{2, 338} = 51.10$, $p < 0.001$, $\eta^2 = 0.23$) [Bird et al., 2018]. MYLO was not superior to ELIZA in this regard, but participants rated MYLO subjectively as more helpful. This replicates the results of a smaller laboratory study on MYLO, which followed the same structure [Gaffney et al., 2014].

The WOEBOT chatbot offers a self-help program to reduce anxiety and depression [Fitzpatrick et al., 2017], with a script based on cognitive-behavioral principles. The aim of the study was to evaluate the feasibility, acceptability, and effectiveness of WOEBOT in a nonclinical sample ($N = 70$): 34 participants were randomized to the experimental group (EG), and 36 were assigned to an active control group (CG) (an eBook on depression). The authors reported a significant reduction in depressive symptoms (PHQ-8) [Kroenke et al., 2009] in EG ($F_{1, 48} = 6.03$, $p = 0.017$). With regard to anxiety symptoms, a significant decrease was observed in both groups, but the groups did not differ significantly from each other ($p = 0.58$) [Fitzpatrick et al., 2017]. In terms of feasibility and acceptance, chatbot users were overall significantly more satisfied than the participants in the active CG as well as with respect to the content [Fitzpatrick et al., 2017].

The SHIM chatbot is a self-help program to improve mental well-being [Ly et al., 2017]. The SHIM script is based on principles of cognitive-behavioral therapy as well as elements of positive psychology. The aim of the randomized controlled pilot study was to evaluate the effectiveness of SHIM and the adherence of the 28 participants: 14 in the EG compared to 14 in the waiting list CG (nonclinical sample). Intention-to-treat analyses revealed no significant differences between the groups regarding psychological well-being (Flourishing Scale [Diener et al., 2010]), Subjective Well-Being Scale [Diener et al., 1985]), and stress (Perceived Stress Scale [PSS-10] [Cohen et al., 1983]), while adherence to completion of the intervention was high ($n = 13$ in the EG, $n = 14$ in the waiting list CG), which speaks to the practicability of the chatbot. Completer analyses revealed significant effects for psychological well-being (Flourishing Scale) ($F_{1, 27} = 5.12$, $p = 0.032$) and perceived stress (PSS-10) ($F_{1, 27} = 4.30$, $p = 0.048$).

The SABORI chatbot was studied in a nonrandomized prospective pilot study [Suganuma et al., 2018]. SABORI offers a preventive self-help program for the promotion of mental health. The underlying script is based on principles of cognitive behavioral therapy and behavioral activation. Psychological well-being (WHO-5-Japanese [Psychiatric RU and Psychiatric CNZ, 2002]), psychological distress (Kessler 10, Japanese version [Kessler et al., 2002]), as well as behavioral activation (Behavioral Activation for Depression Scale [Kanter et al., 2009]) were compared for 191 participants in the EG versus 263 participants in the CG. Analyses of the data showed significant effects for all outcome variables (all $p < 0.05$), which suggests that the chatbot was practicable as a prevention program for the sample.

The GABBY chatbot was studied in a randomized controlled pilot study [Gardiner et al., 2017]. This self-help program is a comprehensive program for behavioral changes and stress management. The underlying stress reduction script is based on the principles of mindfulness-based stress reduction [Gardiner et al., 2013]. Unlike the EG ($n = 31$), the active CG ($n = 30$) received the contents of GABBY only as informational material (the contents of GABBY in written form + accompanying meditation exercises on CD/MP3). The findings showed no significant difference between the groups in terms of perceived stress ($p > 0.05$), but

there was a difference, for example, in stress-related alcohol consumption ($p = 0.03$). The results suggested the practicability of GABBY regarding the primary endpoints of feasibility (e.g., adherence, satisfaction, and proportion of participants belonging to an ethnic minority).

PEACH, a chatbot that is currently undergoing a randomized controlled trial [Stieger et al., 2018], is geared towards personality coaching. Based on research findings about mechanisms of action in psychotherapy, scripts were compiled for the microinterventions presented by PEACH. Among the things covered are the development of change motivation, psychoeducation, behavioral activation, self-reflection, and resource activation. Measures for acceptance and feasibility are explicitly considered in this study.

Some of the studies that did not fulfill the inclusion criteria of this review and were excluded from the full-text review ($n = 11$) nevertheless suggest further promising fields, which are yet to be developed in a broader context (health care in general) (Table 2).

Discussion

The present scoping review illustrates the growing attention being paid to psychological-psychotherapeutic (micro)interventions mediated via chatbot. The technology of chatbots can generally still be described as experimental. These are pilot studies, and all 6 studies were mainly concerned with evaluating the feasibility and acceptance of these chatbots. The findings suggest the practicability, feasibility, and acceptance of using chatbots to promote mental health. Participants seem to benefit from the content provided by the chatbot for psychological variables such as well-being, stress, and depression. In regard to evaluating effectiveness, it should be noted as a limitation that the samples are often very small and lack sufficient statistical power for a high-quality effectiveness assessment. The majority of the studies were published during the past 2 years, underlining the current relevance of the topic and predicting a substantial increase in research activity in this area over the coming years.

The first trials of chatbots for the treatment of mental health problems and mental disorders have already been done, for example the study by Gaffney et al. [2014], which used chatbots to help resolve problems caused by distress, as well as the study by Ly et al. [2017], in which chatbots were used to improve well-being and reduce perceived stress. Fitzpatrick et al. [2017], who used chatbots in a self-help program for students combating depression and anxiety disorders, were also able to support these findings with their study.

The descriptions of the technical background of the chatbots used, as well as more detailed descriptions of the content conveyed by the chatbots, are altogether too brief to assess their objective comprehensibility and to enable replication of the results. Since many startups are currently being created worldwide that use chatbots for clinical psychology and psychotherapy, commercial conflicts of interest are also an issue for the research teams or their clients (e.g., SHIM).

Opportunities, Challenges, and Limitations for Clinical Psychology and Psychotherapy

Evidence-based research in this field is still quite rare and qualitatively heterogeneous, which is why the actual influence of chatbots in psychotherapy cannot yet be reliably estimated. The rapid growth of technology has left ethical considerations and the development of necessary security procedures and framework conditions short of a desirable minimum.

An example is that many health-related chatbots are on the market that have not been empirically validated (e.g., TESS, LARK, WYSA, and FLORENCE). There are also many hybrid forms of chatbots and other therapeutic online tools. JOYABLE (https://joyable.com/) and TALK SPACE (https://www.talkspace.com/), for example, are commercial chatbots that are offered in combination with online sessions with a therapist.

In the current public perception, the topic of new technologies in the field of mental health is fraught with reservations and fears [DGPT, 2018; World Economic Forum, 2018]. It is important to keep informed about developments in this area to ensure that future technologies do not find their way into health care through the efforts of technologically and commercially driven interests. Rather, the effectiveness, but also the security and acceptance of new technologies, should be decisive for their implementation in our health care system. Serious considerations of the potential benefits and hazards of using chatbots are among the hitherto largely neglected topics. Questions regarding data protection and privacy attract particular attention here, given the very intimate data that users under stress may share too carelessly with dubious providers. Storage, safeguarding, and potential further processing, as well as further use, require urgent regulation to prevent misuse and to ensure the best-possible security for participants. Questions also arise about the susceptibility of participants to "therapeutic" advice from chatbots whose algorithms may be nontransparent. This pertains both to the danger of potential technical sources of error that may cause harmful chatbot comments and to the targeted use of the chatbots for purposes other than the well-being of the users (e.g., solicitation/in-app purchase options for other products). Finally, there is not only a need for more effective chatbots but also for chatbots with fewer undesired side effects. This refers especially to the potential of chatbots to respond appropriately in situations of crisis (e.g., suicidal communication).

Potential Opportunities and Advantages of Using Chatbots

Chatbots could be seen as an opportunity to further develop the possibilities offered by psychotherapy [Feijt et al., 2018]. An important aspect of the role of chatbots in clinical care is to address people in need of treatment who are not receiving any treatment at all because of various barriers [Stieger et al., 2018]. Chatbots could bridge the waiting time before approval of psychotherapy and provide low-threshold access to care [Grünzig et al., 2018]. Psychiatric problems or illnesses could be addressed by chatbot interventions in the future, whereby at least an improvement in symptoms could be achieved compared to no treatment at all [Andersson et al., 2016; Carlbring et al., 2018]. Chatbots can also offer new opportunities for accessibility and responsiveness: People with a physical illness and depressive symptoms, for example, could interact in the future with the chatbot when they are being discharged from the hospital to receive psychoeducation and additional assistance relating to the psychological aspects of their illness [Bickmore et al., 2010b].

Another important application for chatbots is as an adjunct to psychotherapy. Chatbots could increase treatment success by increasing adherence to cognitive-behavioral homework. It is conceivable that by adopting microinterventions that require little therapist contact (such as anamnesis or psychoeducation), the therapists will have time to see more patients or to give more intensive care [Feijt et al., 2018]. Chatbots could also be used to improve the communication of therapeutic content [Feijt et al., 2018].

To advance research in this area, piloted chatbots should be studied in clinical populations. The content implemented to date is expandable (Table 1). To actually be a useful supplement to clinical psychological/psychotherapeutic services, substantial research seems necessary on the conceptual side as well. This applies, among other things, to the development of a robust database of psychotherapeutic conversational interactions, which could allow chatbots, drawing upon such elaborated databases, to achieve more effective interventions than they do at the present time. In addition, issues such as acceptance, sustainability, and especially security, as well as subsequent tests of the technology are corrective elements that, amid the prevailing euphoria over digitalization, should become an integral part of future scientific funding programs.

Potential Challenges and Limitations of the Use of Chatbots

Concerning the use of chatbots to promote mental health, numerous ethical and legal (data protection) questions have to be answered. Studies on the anthropomorphization of technology (see section above Performance of the Chatbot) show that users quickly endow technical systems with human-like attributes [Cristea et al., 2013]. It will have to be clarified whether dangers may arise if users take a chatbot to be a real person, and the content expressed overwhelms the capabilities of the chatbot (for example, an unclear statement of suicidal thoughts).

In terms of the data protection law, it must be recognized that some of the conversational content is highly sensitive. In the development of new technological applications in general and chatbots in particular, it is important to systematically consider aspects of data security and confidentiality of communications from the outset. The context of mental health makes the requirements of data privacy and the security of the chatbot particularly essential. Quality criteria should be developed to identify evidence-based chatbots and to distinguish them from the multitude of unverified programs. New legislation that deals with this topic is needed to regulate the use of chatbots promoting mental health and to protect private content [Stiefel, 2018].

The German and European legal systems have a lack of quality criteria in regard to the implementation of IMIs in general and chatbots in particular. It is often difficult to differentiate between applications that are relevant to therapy and those that are not [Rubeis and Steger, 2019]. The certification of therapy-relevant applications as a medical product could resolve this problem in the future. Medical devices receive a CE (Conformité Européenne) label. This certificate could allow therapy-relevant chatbot applications to be distinguished from those that promise no clinical benefit or display low user security [Rubeis and Steger, 2019].

Future Prospects and Research Gaps

The findings of the present review suggest that chatbots may potentially be used in the future to promote mental health in relation to psychological issues. A review of IMIs from an ethical perspective by Rubeis and Steger [2019] affirms the potentially positive effects on users' well-being, the low risk, the potential for equitable care for mental disorders, and greater self-determination for those affected [Rubeis and Steger, 2019]. In light of the limitations up to now respecting the generalizability and applicability of chatbots in psychotherapy, the present findings should be interpreted with caution. The findings of yet-to-be-performed randomized controlled trials of chatbots in the mental health context may, in the future, be integrated into the picture of research on psychological Internet- and mobile-based interventions. IMIs that promote mental health, such as to combat depression, have already proven effective [Karyotaki et al., 2017; Königbauer et al., 2017]. Some of the studies that did not meet the inclusion criteria of the present review and were excluded from the full-text review (n = 11) suggest promising fields that are yet to be developed in a broader context (health care in general) [Bickmore et al., 2010a, 2010b, 2013; Hudlicka, 2013; Ireland et al., 2016; Sebastian and Richards, 2017]. This applies, for example, to

studies using chatbots to increase medication adherence [Bickmore et al., 2010b; Fadhil, 2018] and the study by DeVault et al. [2014], which used semistructured interviews to diagnose mental health problems (Table 2).

Further research is needed to improve the psychotherapeutic content of chatbots and to investigate their usefulness through clinical trials. The studies often originate from authors who mainly approach psychological issues (such as depression) from a background in information technology and begin to collaborate with clinical-psychological scientists after developing their chatbots (bottom-up). There is thus a paucity of theoretical work that initially evaluates what is needed in the clinical-psychological context (top-down). Using such analyses, assessments could be made about how certain psychological endpoints should be achieved and why.

There is a need for research into different forms of use (e.g., as an accompaniment to therapy vs. as a stand-alone intervention). Needs analyses could substantially enhance the research literature on the development of chatbots for use in therapy. What do therapists want? How can chatbots help to make therapists feel effectively supported by the application? It should also be examined whether chatbots can increase overall therapeutic success and whether, for example, they prove to be effective after the conclusion of psychotherapy to stabilize the treatment effects. It still seems to be an open question, just what the specific target groups require of the interface. Some studies deal with the question of which aspects of the design might be chosen for older people [Kowatsch et al., 2017] or for people with cognitive impairment [Baldauf et al., 2018]. It is important that the development of chatbots in clinical psychology and psychotherapy takes places within a protected and guideline-supported framework. Answering ethical questions about the information provided to people who live with a mental disorder is another priority task [Rubeis and Steger, 2019].

The review presents points of departure for future research in this field. Besides the need for replication of the studies in a randomized controlled design, the investigation of piloted (i.e., already proven potentially effective) chatbot interventions in clinical populations is another area still to be explored. Given that none of the previous studies are based on a true clinical sample, the transferability of the results to the psychotherapeutic context remains in question. Psychotherapeutic processes are much more complex than the conversational logic of current chatbots can convey.

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Author Contributions

The conceptualization and development of the manuscript was performed by E.B. B.E. and H.B. commented on the first draft. The comments were incorporated by E.B. The search and review of relevant literature were performed by E.B. and L.S.-T. Manuscript preparation and editing were performed by E.B., revision and finalization by E.B., B.E., and H.B.

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8 Publication V

Feasibility of a Software agent providing a brief Intervention for Self-help to Uplift psychological well-being (“SISU”). A single-group pretest-posttest trial investigating the potential of SISU to act as therapeutic agent

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Feasibility of a Software agent providing a brief Intervention for Self-help to Uplift psychological wellbeing ("SISU"). A single-group pretest-posttest trial investigating the potential of SISU to act as therapeutic agent

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ABSTRACT

Background: Software agents are computer-programs that conduct conversations with a human. The present study evaluates the feasibility of the software agent "SISU" aiming to uplift psychological wellbeing. Methods: Within a one-group pretest-posttest trial, $N = 30$ German-speaking participants were recruited. Assessments took place before (t1), during (t2) and after (t3) the intervention. The ability of SISU to guide participants through the intervention, acceptability, and negative effects were investigated. Data analyses are based on intention-to-treat principles. Linear mixed models will be used to investigate short-term changes over time in mood, depression, anxiety.

Intervention: The intervention consists of two sessions. Each session comprises writing tasks on autobiographical negative life events and an Acceptance- and Commitment Therapy-based exercise respectively. Participants interact with the software agent on two consecutive days for about 30 min each.

Results: All participants completed all sessions within two days. User experience was positive, with all subscales of the user experience questionnaire (UEQ) $M > 0.8$. Participants experienced their writings as highly self-relevant and personal. However, 57% of the participants reported at least one negative effect attributed to the intervention. Results on linear mixed models indicate an increase in anxiety over time ($\beta = 1.33$, $p = .001$). Qualitative User Feedback revealed that the best thing about SISU was its innovativeness (13%) and anonymity (13%). As worst thing about SISU participants indicated that the conversational style of SISU often felt unnatural (73%).

Conclusion: SISU successfully guided participants through the two-day intervention. Moreover, SISU has the potential to enter the inner world of participants. However, intervention contents have the potential to evoke negative effects in individuals. Expectable short-term symptom deterioration due to writing about negative autobiographical life events could not be prevented by acceptance and commitment therapy-based exercises. Hence, results suggest a revision of intervention contents as well as of the conversational style of SISU. The good adherence rate indicates the useful and acceptable format of SISU as a mental health chatbot. Overall, little is known about the effectiveness of software agents in the context of psychological wellbeing. Results of the present trial underline that the innovative technology bears the potential of SISU to act as therapeutic agent but should not be used with its current intervention content.

Trial-registration: The Trial is registered at the WHO International Clinical Trials Registry Platform via the German Clinical Studies Register (DRKS): DRKS00014933 (date of registration: 20.06.2018). Link: https://www.drks.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00014933.

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1. Introduction

Digitalization evokes societal changes in various fields (World Economic Forum, 2018). Fully automated and intelligent machines within the areas of work, economy and science become more and more integrated into people's daily lives. Innovative technologies are entering the context of mental health and could be part of a "next generation" of corresponding health care services.

Worldwide, mental disorders are a public health concern. However, the majority of individuals living with mental disorders do not receive any health care supply (Alonso et al., 2004; Kessler et al., 2005; Thornicroft, 2007). In Europe, only about 25% of people with mental disorders receive professional treatment (Wittchen and Jacobi, 2005). Either societal aspects keep them from receiving health care supply or people choose not to pursue supply offers due to various reasons (Andrade et al., 2014). Discussed are stigmatization (Barney et al., 2006), restrictions of time and location (Paganini et al., 2016), negative attitudes towards pharmacological and psychotherapeutic treatments (Baumeister, 2012), negative experiences with professionals (Rickwood et al., 2007) or too little conscientiousness for mental health (Zobel and Meyer, 2018).

Psychological Internet- and mobile-based interventions (IMIs) are frequently evaluated as medium to overcome some of the aforementioned barriers, with the potential of delivering psychological interventions on a large scale and a widespread roll-out (Carlbring et al., 2018; Ebert et al., 2018; Sander et al., 2016). IMIs are highly standardized, manualized computer-programs, which can be provided on an online-platform (Barak et al., 2009). They can help to reduce treatment barriers and expand supply offers (Carlbring et al., 2018; Ebert et al., 2018; Baumeister et al., 2018). Guided IMIs can provide low-threshold, flexible interventions that can be as effective as traditional face-to-face psychotherapy, e.g. in reducing depression and anxiety (Carlbring et al., 2018; Andersson et al., 2014). However, the scope of IMIs seems to be limited by a low uptake and intervention adherence of individuals (Baumel and Yom-Tov, 2018; Baumel et al., 2017). A high level of implemented persuasiveness could help to overcome these limitations (Baumeister et al., 2019).

A fully automated version of IMIs is software agents (Bendig et al., 2019). Software agents can automatically hold a text-based conversation in real-time via a chat-interface (e.g., smartphone application) (Abdul-Kader and Woods, 2015). Via software agents, components of persuasiveness (Baumeister et al., 2019) like personalising featured contents or adopting a social role to the software agent could easily be integrated (Araujo, 2018). Therefore, delivering IMIs by software agents could compensate for some of the disadvantages of conventional computer program-based IMIs (Baumeister et al., 2014). Thus, software agents gain importance especially as natural interaction port between people and innovative technology-driven or technology–enabled forms of psychological treatment (Bendig et al., 2019).

Software agents could deliver low-threshold, flexible and cost-effective interventions aiming at promoting psychological wellbeing in a large number of individuals. They could be used in the future as add on in the context of traditional face-to-face therapy, e.g. by delivering brief interventions which can be processed by clients independently from time- and location. Another application could be the use of software agents to deliver stand-alone interventions. Software agents in the context of clinical psychology and psychotherapy are on the rise. This is predictable from a growing body of research in that field (Brandtzaeg and Følstad, 2017; Dale, 2016) and increasing online offers of healthcare providers (e.g. health-apps with chat-support). Initially they will be primarily driven by technologies such as algorithmic decision trees and full-text search engines and not by advanced artificial intelligence (Yuan, 2018) - at least in the near future. Thus, within the context of psychotherapy, technological progress will initially mainly allow to implement brief, definable interventions which are able to converse with people on the basis of predefined, manualized scripts (Becker, 2018; Dowling and Rickwood, 2013).

Such a brief intervention could include a therapeutic writing paradigm. Writing with the aim of improving health has a long history (Pennebaker and Beall, 1986; McKinney, 1976). In the current literature, the labelling of corresponding writing approaches varies. Terminology includes e.g. expressive (Pennebaker and Beall, 1986), narrative or therapeutic writing (Bolton et al., 2004). Regardless of terminology, the writing approach in this study will refer to the written expression of thoughts and feelings in the context of upsetting or traumatic life events (Baum and Rude, 2013; Pennebaker, 1997; Spera et al., 1994). Meanwhile, writing approaches have been frequently investigated in the context of physical and mental wellbeing (Krpan et al., 2013; Baikie et al., 2012; Meston et al., 2013; Kállay, 2015). Previous research reports consistently short-term increases in emotional distress, negative mood and in physical symptoms immediately after writing prior to longer term physical and mental health benefits (Baikie and Wilhelm, 2005; McGuire et al., n.d.; Wetherell et al., 2005; Frisina et al., n.d.; Frattaroli, 2006; Bell-Pringle et al., 2004).

As instructions to write can be highly standardized and directive, writing interventions are easily translatable into an online offer (Baikie et al., 2012; Stockton et al., 2014; Goss and Anthony, 2004). Additionally, the paradigm could easily be implemented as a low-threshold, minimal time- and cost-effective intervention to uplift psychological and physical wellbeing (Goss and Anthony, 2004; Smyth and Helm, 2003).

However, software agents delivering brief interventions are few in numbers (Bendig et al., 2018). Furthermore, they have not yet been evaluated in the context of the implementation of a therapeutic writing intervention. Nevertheless, using the paradigm of therapeutic writing may clarify if participants are able to disclose themselves to a software agent. As the majority of psychological paradigms require at least some sort of identifying, labelling and disclosing emotional life experiences (Smyth and Helm, 2003; Smyth et al., 2008), this might be a key requirement of software agents delivering an psychological intervention. We developed a software agent gender neutrally called SISU (**S**oftware agent providing an **I**ntervention for **S**elf-help to **U**plift psychological well-being and finnish word ['sisu] for inner strength). This study investigates the potential of SISU to act as therapeutic agent. To answer this research question, we investigated 1) whether the application is suitable to deliver the paradigm of therapeutic writing as well as 2) the acceptability and 3) potential negative effects of SISU. Research questions were as follows:

1. Has SISU the potential to deliver the paradigm of therapeutic writing?
2. How is the acceptability of SISU?
3. Are there negative effects of SISU?

2. Materials and methods

2.1. Recruitment

Recruitment started on 21.06.2018 and the study was closed on 07.08.2018. We designed this trial with a planned enrolment of 30 individuals. Within the period of 6 weeks, $N = 30$ eligible participants provided informed consent. We recruited following an open recruitment strategy with offline and online recruitment strategies. Posters and Flyers were distributed at several universities, information on the study was provided in lectures and via e-mail to students who needed credits for their courses. Additionally, the study was advertised on facebook. As an incentive, participants could win six gift cards with a value of 30 € each. Participants were eligible to take part in this study if they were 18 years of age or older, were German native speakers, had a smartphone and provided informed consent.

2.2. Intervention

SISU is a script-based software agent and was developed at the Ulm University. It provides a two-day therapeutic writing intervention on autobiographical negative life events. The instructions delivered by the software agent as well as psychoeducation on experiential acceptance follow the principles of therapeutic writing enriched with Acceptance and Commitment Therapy-based principles (Hayes et al., 2011) as well as narrative psychology. The software agent supports participants in labelling and structuring information into a coherent narrative (Smyth et al., 2001). After each writing task, SISU delivers an ACT-metaphor (floating leaves on a moving stream, Hayes and Smith, 2005), supporting participants with distancing themselves from negative thoughts and feelings (Wengenroth, 2008). The latter is being implemented to account for the well-established finding, that therapeutic writing is often followed by an immediate increase of negative mood (Baikie et al., 2012; McGuire et al., n.d.; Wetherell et al., 2005; Frattaroli, 2006; Nyssen et al., 2016). Psychological benefits in terms of e.g. increasing wellbeing are usually followed in the longer run (Baikie and Wilhelm, 2005), thus not expectable shortly after writing. SISU imitates a human conversational style. Participants are guided by SISU to write each day at the same time for 10–20 min about a self-selected autobiographical negative life event (S1). On day 1 there is psychoeducation prior to the instructions for the writing task which is followed by the narratives of the participants. Participants are instructed to write about a meaningful negative life event on day 1 and on the same or another negative autobiographical life event on day 2. After each writing, SISU facilitates coping with the narrated life event in the present moment, gives brief psychoeducation on negative thoughts and feelings and provides possibilities for dealing with them. Afterwards, SISU applies strategies for cognitive defusion to help participants to distance themselves from the life event. Furthermore, SISU is able to automatically send prompts to participants (e.g. reminders via push-up messages to do their writing task on day 2). Additionally, SISU reacts to external triggers e.g. from the survey software (e.g. participant completed survey, SISU switches to the next state and e.g. thanks the user for participating). More details on intervention contents can be derived from Table A1, a schematic representation of the interaction with SISU can be seen in Fig. A1.

2.3. Technology and privacy

SISU is founded on a state machine-based conversation engine custom software system for computer-mediated communication with instant messaging applications that has been developed at Ulm University. It represents a modular middleware that can interface with existing instant messaging endpoints and act on any ongoing conversations and scripted events. This includes the interception and analysis of incoming messages, execution of internal handling processes, triggering of predefined rules or actions, and the dispatch of outgoing messages. Internally, SISU is backed by an execution engine with predefined, rule-based conversation scripts (i.e., conversation flow graph, associated rule sets and corresponding word lists). Here, SISU can also take contextual and session-related information for individualized conversation paths into account. In addition, SISU supports chat-external triggers (e.g., pre-scheduled timers) to resume conversations. SISU's only conversational input channel is arbitrary text sent by the user, which is then parsed, matched, and mapped into the ongoing conversational state machine. The state machines contain branches and alternative routes for individual conversational paths. Hence, the only means of interaction between the participants and SISU are the ongoing chat conversations.

The SISU application interfaces with the online messaging Wire Services SDK (https://wire.com/de/), a text-based instant messaging application with end-to-end encryption for its messages. SISU is embodied by a dedicated Wire user account that is under full control of the middleware system. Thus, SISU appears like any other conversation partner with the messenger of its users. Each new conversation partner spawns a separate session instance in the system so that SISU can conduct multiple conversations with different chat partners simultaneously.

Due to end-to-end encryption of any communication and the restricted and secured storage of conversation logs, SISU ensures the privacy for its users. In particular, conversations are not accessible to any third parties, including the providers of Wire.

2.4. Ethics and approval

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki. This trial was approved by the Ethics Committee of the Ulm University (No. 158/18, 04.06.2018) and registered in the German Clinical Trail Registry (DRKS DRKS00014933).

2.5. Implementation

Eligible participants who provided informed consent were asked to fill in the first online survey (t1). After this, participants were given instructions for downloading Wire and to connect with SISU. From that point, all processes were fully automated. Participants were invited by SISU to the second online-survey (t2) after completing the first session and they received the third (t3) online-survey after completing second session on day two. Outcomes, measurements and points of assessment are shown in Table A2. On each day, participants received instructions to write about an emotionally negative autobiographical life event. Subsequently participants processed through an ACT-metaphor exercise which was provided via audio. The exercise was followed by the second survey (t2). On the next day (24 h later), SISU reminded participants to continue the writing task. Participants could follow the reminder or reschedule the participation to a later time on that day. However, participants were again instructed to write about a personal negative life event and subsequently received the ACT-metaphor exercise via audio. After that, participants completed the third survey (t3) and were discharged from the study. If problems or uncertainties occurred during the study, participants were able to communicate with the study team via E-mail. Additionally, we assessed participants' probability of living with post-traumatic stress disorder symptoms PTSD-7 (Siegrist and Maercker, 2010) to detect potentially traumatised persons seeking support (PTSD-7-score ≥ 4). Persons which indicated elevated symptoms were provided automatic online feedback and a pamphlet with aids offered by the German health system. The flowchart of study procedures can be seen in Fig. 1.

2.6. Measurements of feasibility

Data were collected at baseline (t1) and after each interaction with SISU (t2, t3). We collected demographic data, feasibility data and user feedback on SISU in order to inform modifications to the prototype. Outcomes, measurements, and points of assessment are shown in Table A2.

2.6.1. Functionality: potential of SISU to deliver the paradigm of therapeutic writing

The post-writing questionnaire (Pennebaker and Beall, 1986; Herbert et al., 2019) was administered after each writing session for a manipulation-check. It measures whether participants are able to express their emotions with regards to a personally meaningful life event which is crucial to the paradigm. As literature suggests that the length of the narratives might be a further indicator of the personal significance of the events (Thompson, 2013), we assessed the amount of written words. To assess whether the ACT-based contents have the potential to keep immediate negative mood small after writing, we measure the mood on the positive and negative affect schedule (PANAS; Kroenke et al., 1996)

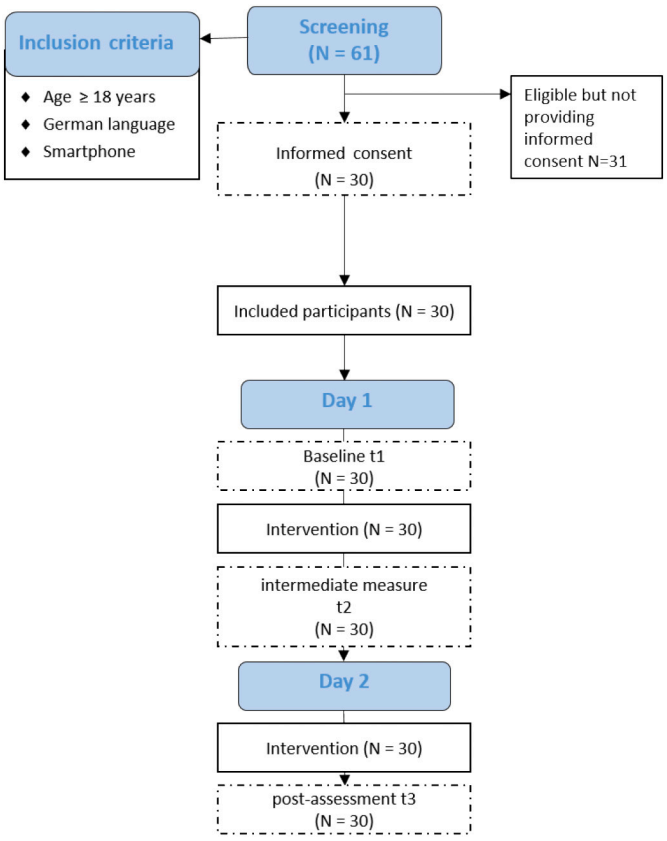

Fig. 1. Studyflow.

immediately after writing.

2.6.1.1. PANAS - Positive Affect Negative Affect Schedule

Participants filled in the German state version of the PANAS (Kroenke et al., 1996) after each writing. Answers indicate current effect of participants on two nearly orthogonal dimensions, positive and negative affect, with 10 adjectives describing each. Participants rate the intensity of the different moods on a 5-point-Likert scale (1 = "very slightly" or "not at all" to 5 = "extremely"). A mean score can be calculated for every dimension. Higher scores indicate greater positive or negative affect. The German version shows good internal consistencies between α = 0.84 and α = 0.86 (Kroenke et al., 1996).

2.6.1.2. Postwriting-Questionnaire. To assess if participants adhered to the instructions, participants were asked questions after each writing. Answers were rated on a 5-point-likert-scale (1="not at all", 3 = "few", 5 = "very much/extremely"). Participants indicated the degree to which they wrote in emotional and personal terms, the degree to which privacy was important to them to enable self-disclosure and the degree to which it was difficult to express one's feelings during writing. The questionnaire was adapted from the original version of Pennebaker and Beall (1986).

2.6.2. Acceptability

To collect data on acceptability, we assessed general attitudes and expectations of individuals towards chatbots delivering a psychological intervention (APOI; Schröder et al., 2015, t1, t3). Furthermore, intervention dropout as well as study attrition were investigated. To assess whether study assessment procedures are acceptable, we included likely outcomes as well as potential moderators/mediators of a future randomized-controlled trial (PANAS, PHQ-9, GAD-7, PTSD-7, ERQ, FAH-II). Furthermore, we investigated user experiences after the two-day intervention at t3 (UEQ; Laugwitz et al., 2008). These information on acceptability were complemented with qualitative user feedback on SISU collected at t3 on the best and the worst aspects of SISU as well as on improvement suggestions. The feedback was collected by means of three open questions ("What did you like best/least about your experience with SISU?", "How can SISU be further improved?") and evaluated following Fitzpatrick et al. (2017) using thematic maps.

2.6.2.1. APOI - Attitudes Psychological Online Interventions. The Attitudes towards Psychological Online Interventions Questionnaire (APOI) measures the position of a person regarding psychological Internet Interventions (Schröder et al., 2015). There are four subscales: Scepticism and perception of risks, confidence in effectiveness, threat due to technology and anonymity benefits. Participants rate 16 Items on a 5-point-Likert scale (1 = "I do not agree at all" to 5 = "I agree completely") and a sum score (range: 15–75 points) is generated. Internal consistency of the APOI total score is acceptable with α = 0.77 (Schröder et al., 2015).

2.6.2.2. UEQ - User Experience Questionnaire. The User Experience Questionnaire (UEQ) measures the experience of interacting with the chatbot (Laugwitz et al., 2008). The UEQ consists of 26 items grouped into six scales ("Attractiveness", "Perspicuity", "Efficiency", "Dependability", "Stimulation" and "Novelty"). Attractiveness refers to the look of the product, the degree to which it is perceived as enjoyable, friendly and pleasant (Schrepp, 2017). Efficiency refers to the degree to which the user interface looks nice and tasks can be performed fast and in a pragmatic way. Perspicuity refers to the degree to which the product is easy to understand, clear and simple. Dependability refers to the degree to which the interaction with the product is predictable and secure. Stimulation refers to the degree to which the product is perceived as interesting and exciting. Novelty refers to the degree to which the product is innovative, inventive and creatively designed (Schrepp, 2017). Each item of the UEQ consists of a pair of terms with opposite meanings and can be rated on a 7-point Likert scale (−3 = "fully agree with negative term" to 3 = "fully agree with positive term"). The standard interpretation of scale means is that values between −0.8 and 0.8 represent a neutral evaluation of the corresponding scale whilst values >0.8 represent a positive evaluation and values <0.8 represent a negative evaluation (Schrepp, 2017). Internal consistencies range between the scales from α = 0.65 to α = 0.89 (Laugwitz et al., 2008).

2.6.2.3. Open questions. For feedback on SISU, three open questions following Fitzpatrick et al. (2017) about the interaction with SISU were provided (t2). The answers are individually evaluated and thematically summarized (Figs. A2, A3).

2.6.2.4. ERQ – Emotion Regulation Questionnaire. The Emotion Regulation Questionnaire (ERQ; 72) is a 10-item questionnaire measuring positive and negative feelings as well as their regulation. Items refer to two different emotion regulation strategies: Reappraisal and suppression. Participants rate the items on a scale from 1 ("strongly disagree") to 7 ("strongly agree"). Means show the preference for each strategy indicating higher preference at higher mean scores. Internal consistencies are acceptable to good and differ from α = 0.75 to α = 0.82 (Gross and John, 2003).

2.6.2.5. FAH-II – Questionnaire for acceptance and action. The Questionnaire for acceptance and action (FAH-II; Hoyer and Gloster, 2013) consists of 7 items. On a 7-point-Likert scale that ranges from 0 = "never true" to 6 = "always true", participants rate processes of experiential avoidance and psychological inflexibility with higher scores indicating greater levels of psychological inflexibility. The questionnaire shows good to excellent psychometric properties in a German sample (α = 0.84 to 0.97) (Hoyer and Gloster, 2013).

2.6.3. Negative effects

We measured negative effects of SISU using the inventory (INEP; Ladwig et al., 2014) to assess potential risks. Additionally, we assessed if SISU has the risk of worsening depressive (PHQ-9; Kroenke et al., 2001), anxiety (GAD-7; Spitzer et al., 2006) or symptoms of posttraumatic stress (PTSD-7; Siegrist and Maercker, 2010).

2.6.3.1. PHQ-9 - Patient Health Questionnaire. The Patient Health Questionnaire (PHQ-9; Kroenke et al., 2001) records depressive symptoms regarding the 2 weeks prior to the measurement. Nine items are rated on a 4-point-Likert scale (0 = "not at all"to 3 = "almost every day"). There is an additional item, which asks if functionality is limited in daily life. The items are computed into a sum score. A meta-analysis concluded that it is a good screening tool for the detection of depression (Manea et al., 2012). Cronbach's α is high (α = 0.89; Kroenke et al., 2001).

2.6.3.2. GAD-7 - Generalized Anxiety Disorder Scale. The Generalized Anxiety Disorder 7-item Scale (GAD-7) measures anxiety symptoms regarding the 2 weeks prior to the measurement (Spitzer et al., 2006). There are seven Items to rate on a 4-point-Likert scale (0 = "never"to 3 = "almost every day"). A sum score is computed. Sum scores of fifteen points or higher indicate severe anxiety symptoms. Internal consistency is very good with Cronbach's α = 0.92 (Spitzer et al., 2006).

2.6.3.3. PTSD-7 post-traumatic stress. The PTSD-7 is a 7-item screening tool to examine symptoms of post-traumatic stress disorder (Siegrist and Maercker, 2010). A 4-point-Likert scale measures the frequency of PTSD-Symptoms ("not at all" to "5 times a week") during the last month. Symptoms exist if they occur at least 2 to 4 times a week. Sum scores are computed with a total of 0 to 7 symptoms and a cut-off with at least 4 symptoms marking a possible PTSD. The German version of the screening instrument has an excellent internal consistency of α = 0.90 (Siegrist and Maercker, 2010).

2.6.3.4. INEP – inventory to assess negative effects of psychotherapy. Self-reported negative effects of SISU are recorded with the 21-item inventory for the assessment of negative effects of psychotherapy (INEP; 63). Items 1 to 6 are rated on a bipolar 7-point scale ranging from 1 to 3 (=positive change), 0 (=no change) and −1 to −3 (=negative change). The remaining Items (7 to 21) are rated on a unipolar 4-point-scale (0 = "no agreement" to 3 = "total agreement"). Negative effects are assessed across six life areas: friends and family, intrapersonal changes, partnership, stigmatization, workplace and therapeutic misconduct. For each of the 21 items, participants rate whether the negative effects occur because of the intervention or due to other current life circumstances. The absolute number of negative effects per patient allows a statement about the side-effect load (Ladwig et al., 2014; Abeling et al., 2018; Nestoriuc and Rief, 2012; Grüneberger et al., 2017). For this purpose, all of the items answered in the negative range on the bipolar scales (−1 to −3) and all positively answered items of the unipolar scales (1 to 3) which were attributed to the intervention by the participants, were summed up. Excluded from this procedure are the three items of the misconduct scale (Item 18, 19, 21), since misconduct attributed to the chatbot is not a negative effect that can be attributed to a chatbot-based psychological intervention per se. The 21-item inventory has a good internal consistency of α = 0.86 (Ladwig et al., 2014).

2.7. Sample size and data analysis

Viechtbauer et al. (2015) stated that at least 29 participants are sufficient to detect problems with a probability of 0.10 and a 95% confidence interval. Therefore, screening at least 29 participants will ensure a high level of confidence (i.e. at least 95%) for the chosen minimum problem probability to investigate feasibility. Statistical analyses were conducted using SPSS 26 software. Data for evaluation was collected at baseline (t1) and after each interaction with SISU (t2, t3). For the characterisation of the sample and the assessment of negative effects (INEP), absolute and relative frequencies are calculated. For metric variables descriptive statistics with mean values (M), median (Md), range and the standard deviation (SD) were calculated. To evaluate if SISU has the potential to affect depression, anxiety and symptoms of posttraumatic stress as well as to investigate whether there are immediate intervention-related emotional responses, linear mixed models will be applied. Linear mixed models take into account that answers are nested within persons and the resulting dependency between variables. In this study, the repeated measurements (level 1) are nested within person (level 2) (Nezlek et al., 2006; Luke, 2004). All analyses are based on an intention-to-treat (ITT) principle.

3. Results

3.1. Baseline participant characteristics

Recruitment ended in August 2018 with $N = 61$ individuals expressing their interest to participate within one month. $N = 30$ individuals consented. Mean age of participants was $M = 23.17$ ($SD = 3.85$), 80% identified as female, all participants had fluent German language skills. 73% have had no prior psychotherapeutic experience, 20% had prior psychotherapy (>3 months ago), and two participants (6.7%) received psychotherapeutic treatment while participating in this study. Baseline participant characteristics are presented in Table 1. At baseline, the mean depression score (PHQ-9) was $M = 5.00$ ($SD = 3.54$) indicating that participants were on average not to mildly depressed. The mean anxiety score (GAD-7) was $M = 3.1$ ($SD = 2.69$) on average, indicating no to minimal levels of anxiety symptoms. Participants preferred on average the emotion regulation strategy (ERQ) of reappraisal ($M = 4.96$, $SD = 0.97$) over suppression ($M = 3.14$, $SD = 0.97$) ($t(29) = 5.13$, $p < .001$) and were on average psychological flexible ($M = 17.97$, $SD = 7.36$) (FAH-II; Hoyer and Gloster, 2013) (Table 2).

3.2. Functionality: potential of SISU to deliver the paradigm of therapeutic writing

Participants indicated on the 5-point-likert scale of the post-writing questionnaire, that they had expressed their emotions in their writings ($M = 4.03$, $SD = 0.41$, t2 and $M = 4.03$, $SD = 0.56$, t3). In addition, participants experienced their writings as highly self-relevant and personal ($M = 4.53$, $SD = 0.63$, t2 and $M = 4.50$, $SD = 0.57$, t3). Participants reported that privacy mattered to them for enabling self-disclosure ($M = 4.13$, $SD = 0.90$, t2 and $M = 4.07$, SD = 1.14, t3). Participants reported no difficulties with writing about an emotional negative life event ($M = 2.63$, $SD = 1.16$, t2 and $M = 2.47$, $SD = 0.97$, t3). Participants wrote on average $M = 357.13$ ($SD = 158.9$) words in the first and $M = 271.33$ (SD

Table 3
Sociodemographic sample characteristics.

Demographics	Total
Age (*M*, *SD*)	23.17 (3.85)
Gender (%)	80% female
Education (%)	High school or less 76.6
	Diploma 3.3
	University 20.0
Employment status	Full-time 23.3
	Part-time 43.3
	Student 26.7
	Unemployed 6.7
Prior psychotherapy experiences (%)	26.7
Marital status (%)	Single 50
	Solid partnership 43.3
	Married 3.3
	Divorced 3.3

Table 4
Clinical characteristics over time.

Measurement	T0 (*M*, *SD*)	T1 (*M*, *SD*)	T2 (*M*, *SD*)
Depression, PHQ-9	5.00 (3.54)		5.00 (3.75)
Anxiety, GAD-7	3.1 (2.69)		4.43 (3.52)
Mood, PANAS			
Positive affect	2.97 (0.65)	2.54 (0.82)	2.51 (0.78)
Negative affect	1.40 (0.37)	1.47 (0.45)	1.60 (0.58)
Emotion-regulation, ERQ			
Reappraisal	4.96 (0.97)		4.95 (1.17)
Suppression	3.14 (1.40)		3.25 (1.57)
Psychological flexibility, FAH-II	17.97 (7.36)		18.00 (7.99)
Posttraumatic stress, PTSD-7	9.03 (3.71)		9.1 (3.05)

= 112.61) words in the second writing session. Writing-related changes in positive and negative affect after each session were assessed by linear-mixed models. Immediate writing-related emotional responses comprised an increase of negative affect over time ($\beta = 0.09$, $p = .04$) and a decrease of positive affect over time ($\beta = 0.35$, $p = .002$).

3.3. Acceptability

All participants ($N = 30$) completed all measurements as well as all sessions of the brief intervention within two consecutive days.

Attitudes and expectations towards psychological chatbots were comparable to those towards psychological internet interventions in general $M = 49.83$ ($SD = 7.88$) at t1, $M = 48.17$ ($SD = 11.48$) at t3 (APOI; Schröder et al., 2015).

User experience (UEQ; Laugwitz et al., 2008) was rated as good on each of the six subscales (Perspicuity, Dependability, Stimulation, Novelty, Attractiveness, Efficiency), all $M > 0.8$ (Fig. 2). In comparison to general benchmarks provided by Schrepp (2017), Perspicuity ($M = 0.97$, $SD = 0.36$), Dependability ($M = 1.11$, $SD = 0.35$), Stimulation ($M = 0.94$, $SD = 0.37$), Attractiveness ($M = 0.96$, $SD = 0.22$) and Efficiency ($M = 0.89$, $SD = 0.52$) are in the average range of interactive products. Originality ($M = 1.43$, $SD = 0.34$), the degree to which the product is experienced as innovative and creatively designed exceeds the average benchmark thus achieving the attribute "good" in comparison to 452 product evaluations with a total of 20,190 participants in all evaluations ($M = 1.14$). Fig. 2 depicts and summarizes the scale means.

The evaluation of the qualitative feedback following Fitzpatrick et al. (2017) revealed two core topics respectively which were summarized as "Hardware" and "Software" of the Chatbot. Hardware-related feedback comprised technical execution, privacy aspects and the possibility of using SISU on any digital terminal device. As best hard skills, participants explicitly indicated innovativeness (13%), anonymity (13%) as well as the independence of the application from time and space (16%). "Software" comprised features concerning the programme of SISU. As best soft skills, participants indicated the therapeutic writing tasks (16%), the ACT-metaphor (20%) and the formulations/phrases of SISU (27%).

As worst Hardware-related aspects, participants mentioned that they had technical complications with SISU (e.g. no immediate answers from SISU) (33%) or insecurities with regards to confidentiality ("I'm not sure about what happens with my narratives now") (6%). As worst software-related aspects, participants mentioned that the conversational style of SISU felt unnatural (73%). Figs. A2 and A3 give an overview of the feedbacks ordered by thematic maps of the best/worst aspects of SISU. Improvement suggestions comprised more individualized feedback (e.g. more personal answers, addressing described issues) (37%), less repetitions (e.g. more language variation) (20%), more conversational contents after the writing tasks (e.g. chatting about a problem) (13%).

3.4. Negative effects

56.67% ($n = 17$) of the participants reported at least one negative effect attributed to the intervention (t3) (Table A3). On average, participants reported 1.88 negative effects (SD = 1.22) (Total value adjusted by the items for misconduct, item number = 18) (Table 3).

With regards intra- or interpersonal changes (Items 1 to 6), the frequencies of positive changes after the intervention (t3) ranged between 10.0 and 56.3%, with most of the positive changes attributed to the interaction with SISU rather than to other life circumstances (Table A3). Across Items 1 to 6 no negative effects attributed to the interaction with SISU occurred, except for Item 3, "I suffer more from past events since the interaction with SISU". Two participants (6.7%) indicated to suffer more from past events since the interaction with SISU and attributed this to intervention contents. The frequencies across the individual areas of life are shown in the Appendix Tables A3 and A4.

Changes in anxiety, depression and posttraumatic stress were assessed by linear-mixed models. Results show an increase in anxiety over time ($\beta = 1.33$, $p = .001$). Symptoms of depression and posttraumatic stress stayed unchanged ($p > .05$) (Table 2). One serious adverse event occurred, concerning the suicidal tendency of a participant. One person indicated suicidal thoughts/intentions for the first time (Table A4). An overview on feasibility variables can be found in Table 5.

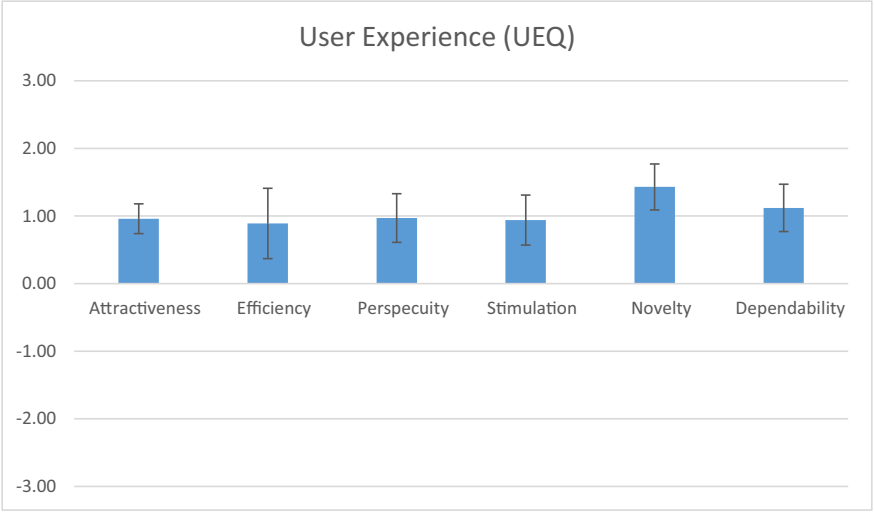

Fig. 2. Scale means of user experience.

Table 5
Feasibility-related outcomes.

Measurement	T0 *M* (*SD*)	T1 *M* (*SD*)	T2 *M* (*SD*)
Attitudes and expectations, APOI	49.83 (7.88)	–	48.17 (11.41)
Scepticism and perception of risks	9.80 (2.31)	–	10.27 (2.99)
Confidence in effectiveness	14.97 (2.04)	–	14.17 (3.65)
Threat due to technology	9.50 (2.62)	–	9.60 (3.23)
Anonymity benefits	12.17 (3.30)	–	11.87 (3.86)
User experience	–	–	1.04 (0.18)
Attractiveness	–	–	0.96 (0.22)
Efficiency	–	–	0.89 (0.52)
Perspicuity	–	–	0.97 (0.36)
Stimulation	–	–	0.94 (0.37)
Novelty	–	–	1.43 (0.34)
Dependability	–	–	1.11 (0.35)
Negative effects, INEP	–	–	1.88 (1.22)
Postwriting questionnaire			
How much did you reveal your emotions in your writing?		4.03 (0.41)	4.03 (0.56)
How personal was the text you wrote?		4.53 (0.63)	4.50 (0.57)
How important is it for you that you wrote this text anonymously?		4.13 (0.90)	4.07 (1.14)
How difficult was it for you to write something about this question?		2.63 (1.16)	2.47 (0.97)

4. Discussion

To the best of our knowledge, this is the first trial of a fully automated text-based conversational agent designed to deliver a brief self-help therapeutic writing intervention. The goal of our study was to investigate the feasibility of SISU for the implementation in a full-scale trial.

The study demonstrates, that the SISU-application can fully automated guide participants through a two-day intervention, including delivering study assessments. However, immediate emotional responses comprised an increase of negative ($\beta = 0.09$, $p = .04$) and a decrease of positive affect over time ($\beta = 0.35$, $p = .002$). Thus, ACT-based exercises could not prevent participants from immediate mood changes for the worse. These results are in line with frequent findings from therapeutic writing interventions (Baikie and Wilhelm, 2005; McGuire et al., n.d.; Wetherell et al., 2005; Frisina et al., n.d.; Frattaroli, 2006; Bell-Pringle et al., 2004). From the current trial we cannot say, if the short-term symptom deterioration is associated with medium to long-term effectiveness regarding psychological wellbeing. Future research needs to establish the effectiveness of SISU in long-term follow-ups and establish further safety measures for short-term symptom deterioration if the writing contents should be retained.

Results on the paradigm of therapeutic writing show that it is possible to enter the inner world of participants with SISU and thus without human involvement. Participants expressed their emotions with regard to self-relevant negative life events. To this, feeling safe/private was relevant for enabling disclosure. As the majority of psychological paradigms require at least some sort of affect management, identifying, labelling and disclosing emotions (Smyth and Helm, 2003; Smyth et al., 2008) might be a key requirement for the effectiveness of a software agent delivering a psychological intervention (Ritterband et al., 2009). The average length of participants' narratives was comparable to those in other studies online and offline (Baum and Rude, 2013; McGuire et al., n.d.; Stockton et al., 2014; Smyth et al., 2001).

High adherence in terms of no study and no intervention attrition as well as positive experiences of and with SISU suggest that the software agent provides a useful and acceptable format for participants. User experience (UEQ; Laugwitz et al., 2008) on each of the six subscales (Perspicuity, Dependability, Stimulation, Novelty, Attractiveness, Efficiency) was positive (all $M > 0.8$). Ratings on any subscale achieved at least an average level when compared to general benchmarks derived from 452 product evaluations and 20,190 participants (Schrepp, 2017). In comparison to these evaluations, SISU was experienced as outstanding innovative and creatively designed ($M = 1.43$, $SD = 0.34$). Thus the user experience of SISU could likely compete with interactive products which were evaluated in various contexts (web-based applications, business software) with the UEQ (Schrepp, 2017). This is important, as it is a current challenge in the e-mental-health sector to reduce attrition and improve uptake rates in internet interventions, which can likely be achieved by means of an attractive, persuasive intervention design (Baumeister et al., 2019).

Qualitative responses on acceptability complemented quantitative findings with regards to necessary changes to hardware- and software-related aspects of SISU. SISU should be further developed with regard to the experienced naturalness of the conversational style. SISU is driven by a predefined conversation flow graph as well as associated rule sets and corresponding word lists. On several branches, participants are asked to enter predefined answers (e.g. "End of my narrative") to trigger the next condition in the flow graph. This might feel unnatural in the conversational process. More individualized feedback, a heightened number of possible responses in the flow graph and associated rule sets as well as the avoidance of repetitions could help to improve the naturalness of the conversational style.

Regarding potential risks, 56.67% of the participants reported at least one negative effect attributed to the intervention (t3). One participant indicated to have suicidal thoughts or ideation for the first time. This emphasizes the absolute importance of corresponding systems for suicide risk detection. These ethical considerations have to inform the process of system design, construction, and use of chatbot-based interventions for mental health issues. One possible access could be via data-driven mechanisms to detect participants at suicide risk. Suicide risk detection systems can e.g. be based on combinations of questionnaires and text inputs of users (Tielman et al., 2019). People at risk could then be referred back to human contact persons (Tielman et al., 2019). Furthermore, participants reported on average $M = 1.88$ negative effects (SD = 1.22). Most frequently they reported negative changes with regards to the degree to which they suffer from past events since the interaction with SISU (6.7%). On the one hand, this result fits literature that shows, that psychological interventions, online and offline, can initially evoke negative effects and symptom deteriorations (Ladwig et al., 2014; Rozental et al., 2016). On the other hand, results could be explained by the fact that participants indicated on average to live with mild symptoms of depression and anxiety. Prior studies indicate, that therapeutic writing could be less effective in such vulnerable populations (Frisina et al., n.d.), which could again be associated with increased anxiety and depression after.

Negative effects could be directly related to the fact that a large part of the intervention focusses on personally meaningful negative life experiences. Bell-Pringle et al. (2004) state, that focusing on personally meaningful, unprocessed negative events may flood individuals with anxiety (Bell-Pringle et al., 2004). Encouraging participants in that manner to externalize their deepest thoughts and feelings with regards to a certain negative life event could cause harm (Connolly Baker and Mazza, 2004). The lack of collateral therapeutic support which e.g. provides external ideas on problem solving towards the narrated events might leave individuals behind with their current patterns (Lestideau and Lavallee, 2007). It can be derived from literature, that therapeutic

writing can be helpful for people and some researcher highlight the potential of the paradigm: Small benefits are consistently reported and the paradigm can be easily provided to a large number of individuals online at low-cost (Kállay, 2015; Frattaroli, 2006; Nyssen et al., 2016). However, innovation isn't all fun and games and there might be other approaches with comparable benefits and lower risks for the individual.

A growing body of literature emerges which suggests the integration of positive psychological interventions to promote wellbeing (Koydemir et al., 2020). Currently, there is rising evidence for the effectiveness of therapeutic writing interventions oriented towards more positive approaches (e.g. writing about positive experiences (Burton and King, 2004) or gratitude (Wong et al., 2018)). A more positive writing approach could be chosen as intervention delivered by SISU as it may come along with less negative effects than the pathological writing focus chosen in the present study.

There are limitations of this study which weaken the generalizability of the findings and motivate future investigations. First, this study was a feasibility trial not designed for the detection of significant effects in psychological outcome measures. The intervention needs to be investigated within the context of a robust large scale study design to reliably detect eventual effects between intervention and control groups.

Second, high adherence in this study might not be over interpreted, as the intervention comprised only two sessions in two consecutive days. Additionally, future studies should comprise more sessions, as more sessions have been found to have a larger effect on overall wellbeing (Frattaroli, 2006). Recent studies reported equally good user adherence rates when investigating chatbot-based interventions (Ly et al., 2017).

5. Conclusions

Overall, the study showed the potential of SISU to act as therapeutic agent delivering a brief psychological intervention, but not necessarily an intervention that delivers the paradigm of therapeutic writing. Although therapeutic writing can certainly be a powerful tool to improve psychological health (Baum and Rude, 2013; Baikie and Wilhelm, 2005; Craft et al., 2013), the paradigm of has been challenged several times with regards to its effectiveness and potential negative effects (Nyssen et al., 2016; Mogk et al., 2006). In the present study, the use of the paradigm mainly underlines that SISU has the potential to deliver an intervention that is associated with the need for emotion expression. Thus, SISU has the potential to enter the inner world of participants. This could be used to adapt the content of SISU towards a more positive approach. As writing about positive aspects and life events bears the potential to have similar positive effects on physical and psychological wellbeing, SISU could deliver an intervention which is more built upon the importance of positive emotions in the promotion and maintenance of wellbeing (Folkman and Moskowitz, 2000). The trial testing this hypothesis based on a further developed version of SISU alongside the results of this study is registered at the WHO International Clinical Trials Registry Platform via the German Clinical Studies Trial Register (DRKS): DRKS00016799.

Author contributions

Conceptualization and idea, E.B.; methodology, E.B., N.B.; software, B.E., D.M., E.B.; validation, H.B.; formal analysis, E.B.; investigation, E.B.; resources, H.B.; data curation, E.B.; writing – original draft preparation, E.B., writing – review and edition, all Co-Authors; supervision, H.B.; visualization, E.B.; project administration, E.B. All authors have read and agreed to the published version of the manuscript.

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Declaration of competing interest

E.B., B.E., D.M. and N.B. declare no conflict of interest. HB received consultancy fees, reimbursement of congress attendance and travel costs as well as payments for lectures from Psychotherapy and Psychiatry Associations as well as Psychotherapy Training Institutes in the context of *E*-Mental-Health topics. He has been the beneficiary of study support (third-party funding) from several public funding organizations.

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Appendix A

Table A1
Content and techniques of the intervention delivered by SISU.

Component	Content	Focused ACT technique
1 Introduction	Introduction, Psychoeducation on psychological wellbeing, therapeutic writing, ACT exercise	Psychoeducation
2 Writing tasks	Instructions for writing about a negative autobiographical life event	
3 Thoughts and feelings	Definition of negative thoughts and feelings and dealing with them	Contact with the present moment
4 Exercises	Leaves on a moving stream	Cognitive defusion

Notes. ACT = Acceptance and Commitment Therapy.

Table A2
Constructs, measurement instruments and points of assessment.

Construct	Instrument	Point of assessment		
		T1	T2	T3
Feasibility				
Demographics	Self-report	X		
Adherence	Intervention and study attrition			X
Attitudes and expectations	APOI	X		X
User experience	UEQ			X
Negative effects	INEP			X
Postwriting questionnaire	Manipulation check			X
User feedback (best/worst thing about SISU, improvement proposals)	Open questions			X
Trauma	PTSD-7	X		X
Mood	PANAS	X	X	X
Anxiety	GAD-7	X		X
Depression	PHQ-8	X		X
Emotion regulation	ERQ	X		X
Psychological Flexibility	FAH-II	X		X

Notes. t1 = Baseline; t2 = Intermediate; t3 = post measurement; PHQ-8 = Patient Health Questionnaire-8; GAD-7 = Generalized anxiety disorder 7-item scale; APOI = Attitudes towards psychological online interventions questionnaire; INEP = Inventory for the assessment of negative effects of psychotherapy.

Table A3
Negative effects: frequencies part I.

Life areas	Positive changes since intervention completion (*n*, %)	Attributed to intervention (*n*)	Attributed to other life circumstances since intervention completion (*n*)	Negative changes since intervention completion (*n*, %)	Attributed to intervention (*n*)	Attributed to other life circumstances since intervention completion (*n*)	No changes (*n*, %)	Attributed to intervention (*n*, %)	Attributed to other life circumstance since intervention completion (*n*)
1) Individual well-being	17 (56.6)	11	5	2 (6.7)	–	2	11 (36.7)	1	10
2) Trust others	5 (16.7)	5	–	2 (6.7)	–	2	23 (76.7)	3	20
3) Suffering from past events	13 (43.3)	11	2	2 (6.7)	2	–	15 (50.0)	1	14
4) Partnership	5 (16.3)	3	2	2 (6.7)	–	2	23 (76.7)	4	19
5) Family	3 (10.0)	2	1	2 (6.7)	–	2	25 (83.3)	4	21
6) Friends	5 (16.3)	5	–	2 (6.7)	–	2	23 (76.7)	1	22

Notes. 1) Since completion of the Interaction with the Chatbot I feel… 2) To trust others has been on my mind since Interaction with the Chatbot compared to the time before the interaction with the chatbot… 3) I suffer from past events since completion of the interaction with the Chatbot compared to the time before interaction with the Chatbot… 4) Since completion of the interaction with the chatbot I experience in my partnership in the comparison with the time before the interaction… 5) My relationship with my family after the Completion of the interaction with the chatbot in comparison with the time before the interaction with the Chatbot… 6) My relationship with my friends after the Completion of the interaction with the chatbot in comparison with the time before the interaction with the Chatbot.

Table A4
Negative effects: frequencies part II.

Areas and items	0 = not at all (*n*, %)	1 = a little bit (*n*, %)	2 = partly (*n*, %)	3 = entirely true (*n*, %)	Rated 1 = a little bit to 3 = entirely true and traced this back to the intervention, (*n*)	Rated 1 = a little bit to 3 = entirely true and traced this back other life circumstance, (*n*)
Stigmatisation						
7) Fear of colleagues/friends finding out about the therapy or telling them about it	18 (60.0)	7 (23.3)	3 (10.0)	2 (6.7)	10	2
Financial and legal disadvantages						
8) Problems with insurance (e.g. life insurance) or fear that problems could arise.	28 (96.7)	1 (3.3)	1 (3.3)	–	2	0
9) More financial worries	29 (96.7)	1 (3.3)	–	–	0	1
Therapeutic alliance						
10) I feel dependent on the Chatbot	26 (86.7)	3 (10.0)	1 (3.3)	–	3	0

(*continued on next page*)

Table A4 (*continued*)

Areas and items	0 = not at all (*n*, %)	1 = a little bit (*n*, %)	2 = partly (*n*, %)	3 = entirely true (*n*, %)	Rated 1 = a little bit to 3 = entirely true and traced this back to the intervention, (*n*)	Rated 1 = a little bit to 3 = entirely true and traced this back other life circumstance, (*n*)
16) I felt that statements of the chatbot were hurting	29 (96.7)	1 (3.3)	–	–	1	0
17) I had the feeling that the chatbot was making fun of me	26 (86.7)	3 (10.0)	1 (3.3)	–	4	0
11) It's harder for me to make important decisions alone	26 (86.7)	2 (6.7)	1 (3.3)	1 (3.3)	0	4
20) The chatbot made me do things which I didn't really want to	26 (86.7)	2 (6.7)	2 (6.7)	–	4	0
Partnership, family, friends						
12) My partner is/was jealous of my relationship with the Chatbot. (omit if no partnership)	20 (66.7)	1 (3.3)	1 (3.3)	–	1	1
Symptoms						
13) …I've had longer periods where I was feeling sick…	22 (73.3)	5 (16.7)	3 (10.0)	–	6	2
14) I've changed for the worse as a person	28 (93.3)	2 (6.7)	–	–	1	1
15) I had suicidal thoughts/intentions for the first time	29 (96.7)	1 (3.3)	–	–	1	0
Misconduct						
18) During the interaction there were unpleasant, direct attacks by the chatbot	29 (96.7)	1 (3.3)	–	–	1	0
19) I felt physically assaulted by the chatbot	29 (96.7)	1 (3.3)	–	–	0	1
21) It has come to my attention that the chatbot broke confidentiality	29 (96.7)	–	1 (3.3)	–	1	0

Notes. 12) n=8 participants indicated to have no partnership, 17) n=1participant indicated, that the chatbot answered basically the same after each writing session, n=1 participant indicated that the chatbot did not answer the question of how it knew that the participant was burdened, n=1 participant wrote that instructions of how to write were exaggerated, 20) N=1 participant indicated that he felt uncomfortable with writing the event to the chatbot as the negative event could possibly be traced back to him/her N=1 participant indicated that he/she felt uncomfortable to be encourage to write more although he/she did not want to write more, 21) N=1 participant felt like writing a story to a chatbot could possibly break confidentiality.

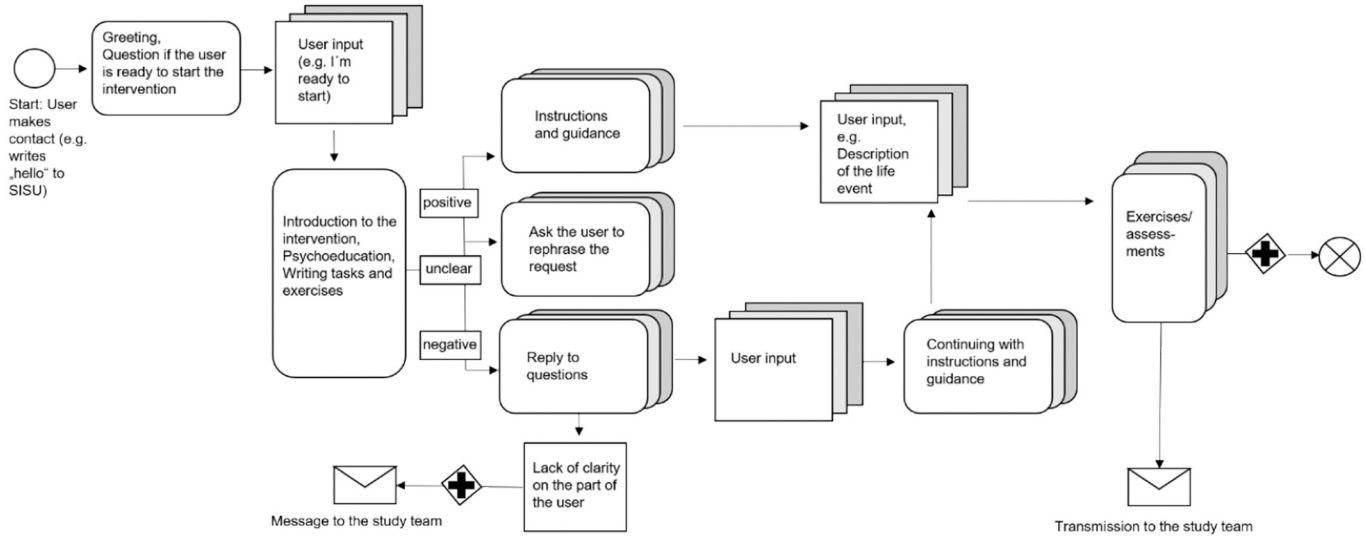

Fig. A1. Simplified, schematic representation of the interaction with SISU. (Adapted from Bendig et al. (2019)).

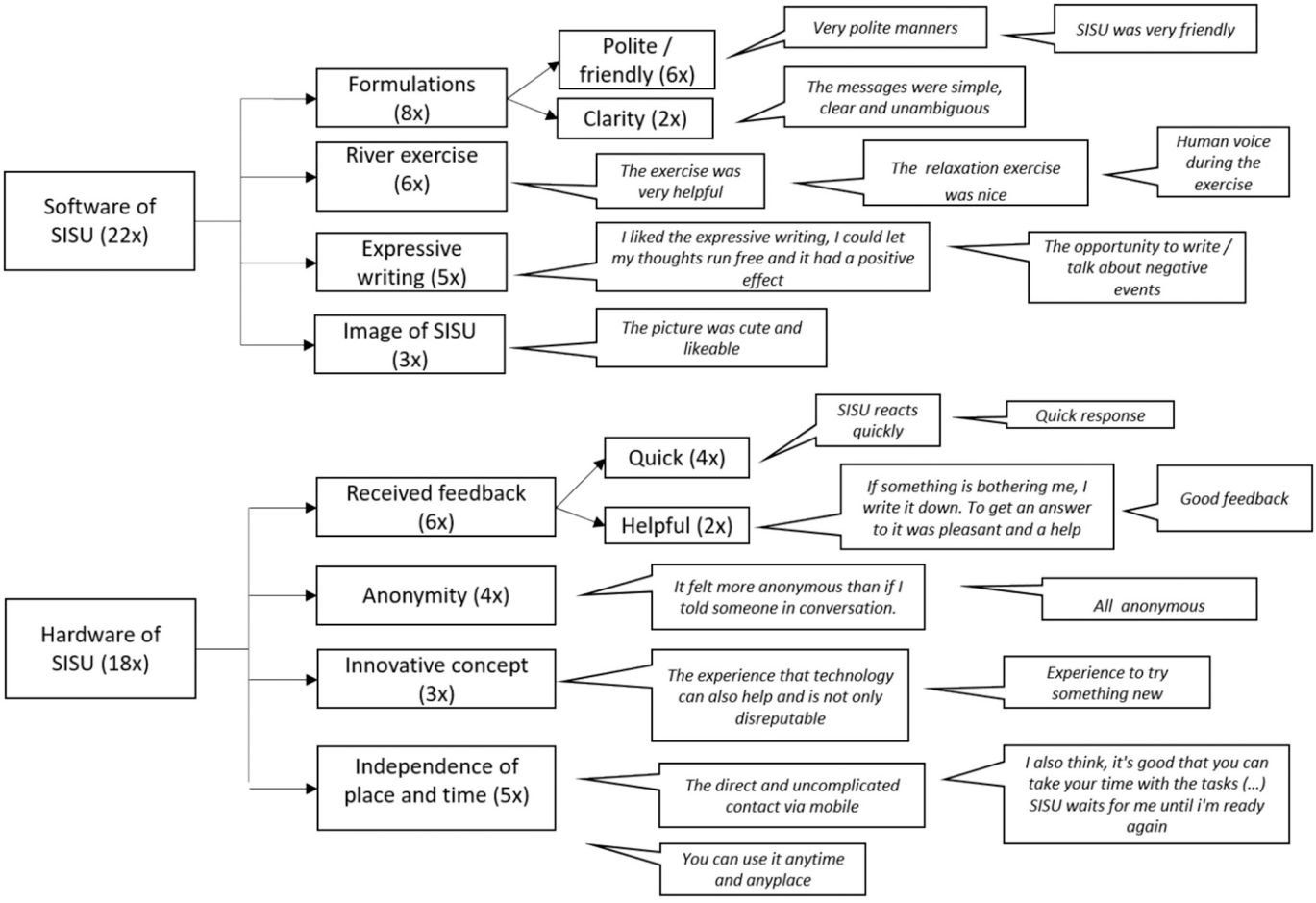

Fig. A2. Thematic map on the best aspects of SISU.

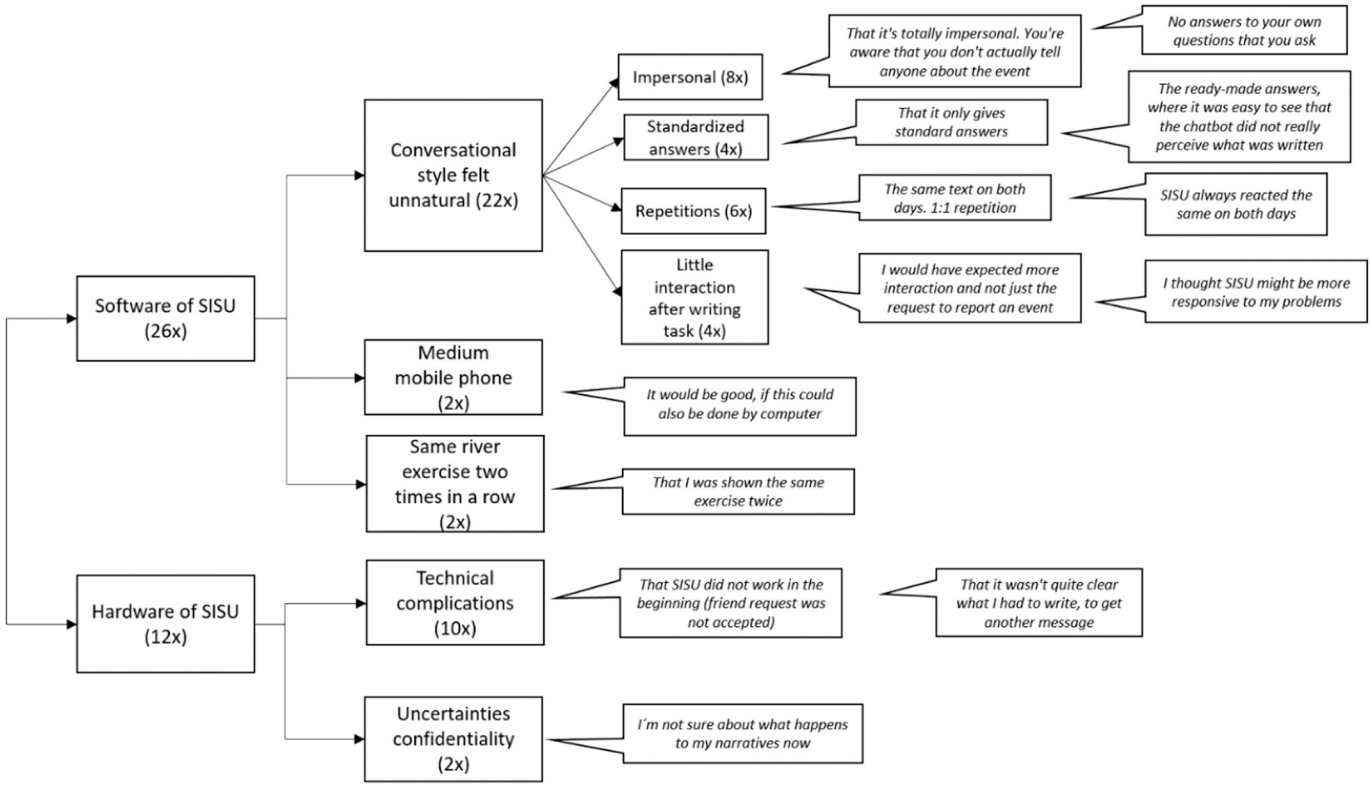

Fig. A3. Thematic map on the worst aspects of SISU.

Appendix B. Supplementary data

Excerpt of an exemplary interaction with SISU on day 1 (translated from German to English). Supplementary data to this article can be found online at https://doi.org/10.1016/j.invent.2021.100377.

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9 Publication VI

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/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 with a waitlist control group.

Methods and analysis Within a two-group randomised controlled trial, a total of 120 adult participants living with low well-being (Well-being Scale/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 3 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 (Flourishing Scale), psychological flexibility (Acceptance and Action Questionnaire-II), quality of life (Assessment of Quality of Life -8D), satisfaction with the intervention (Client Satisfaction Questionnaire-8) and side effects (Inventory for the assessment of negative effectsof psychotherapy). Examined mediators and moderators are sociodemographic variables, personality (Big Five Inventory-10), emotion regulation (Emotion Regulation Questionnaire), alexithymia (Toronto Alexithymia Scale-20), centrality of events (Centrality of Events Scale), treatment expectancies (Credibility Expectancy Questionnaire) and technology alliance (Inventory of Technology Alliance–Online Therapy). Data analysis will be based on intention-to-treat principles. SISU guides participants through a 3-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.

Trial registration The trial is registered at the WHO International Clinical Trials Registry Platform via the German Clinical Trials Register (DRKS): DRKS00016799 (date of registration: 25 April 2019). In case of important protocol modifications, trial registration will be updated. This is protocol version number 1.

Strengths and limitations of this study

- To our knowledge, this is the first full-scale randomised controlled trial 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.

INTRODUCTION

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

On one hand, there are societal barriers to receiving adequate mental healthcare 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 stigmatisation,[7 8] restrictions

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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 healthcare at a large scale, digital means are frequently discussed options.

Digitalisation 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 healthcare. 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 healthcare 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 programme, 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 programme.[21 31] However, fully unguided interventions could be a more cost-effective way of providing digital interventions (eg, [32]). Thereby, professional guidance does not only limit the cost-effectiveness, but also necessitates healthcare infrastructures that might not always be at place at a large (enough) scale. In addition to the possibility of an increased cost-effectiveness, unguided fully automated interventions like mHealth interventions have shown potential to effectively targeting mental health symptoms.[33]

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

A software agent or 'chatbot' is a computer program that can hold a fully automated text-based conversation in real time with people via a chat interface (eg, smartphone application) by using a natural language style.[37] The growing interest and body of research about software agents[38 39] is realised in various populations and contexts, such as problem-solving and stress.[40–42] In the context of clinical psychology and psychotherapy, research on software agents is sparse[43] but could create opportunities for the field regarding the provision of mental health services. Software agents could be used to convey therapeutic contents and brief interventions.[44 45] Establishing contact to a software agent might not be as stigmatising as using formal mental health services like starting a face-to-face therapy or asking a general practitioner for possibilities of mental healthcare.[46] Furthermore, they are flexible regarding location and time,[47] can be used anonymously[48 49] and provide personalisation through implicit customisation.[50] Therefore, software agents could help to overcome barriers and provide psychological and health behaviour change interventions on a large scale in the future.

Current mental health software agents are primarily based on cognitive–behavioural therapy.[43] However, other popular approaches with proven effectiveness in face-to-face settings could also readily be realised in a digital form, such as writing interventions[51] and acceptance and commitment-based approaches.[52]

Writing with the aim of improving health has a long history.[53] In the current literature, the labelling of this kind of intervention varies. Terminology includes expressive writing,[54 55] benefit-finding or positive writing,[56 57] and therapeutic writing (eg, [58]). Regardless of terminology, the writing intervention to be investigated in this study will refer to the process of freely and emotionally writing about a positive personal life event without paying attention to spelling or grammar. The call to write about personal life events, to tell a story, seems to go straight at the centre of subjective experiences,[59] which in turn is the main medium in traditional face-to-face therapy. In that, the term therapeutic writing will be used in this context to acknowledge that the intervention refers to some kind of therapeutic work.[60] It has been shown that writing interventions can be highly time-efficient and cost-efficient.[61] A recent meta-analysis shows that writing interventions can help to improve general psychological health (standardised mean difference (SMD)=–0.46, 95% CI –0.86 to –0.06).[62] Finally, a meta-analysis from Bolier *et al*[63] found an effect of Cohen's d=0.34 (95% CI 0.22 to 0.45) for positive interventions to uplift cognitive and/or affective appraisal of one's life as a whole and d=0.20 (95% CI 0.09 to 0.30) for optimal functioning including mastery, hope and purpose in life.

Acceptance and commitment therapy (ACT)[64] aims at acceptance, mindfulness and value-based living, and has been found to be effective in the prevention of stress and the increase of well-being.[27 65] The efficacy of ACT-based interventions in general and ACT-based IMIs in particular has been indicated in a number of studies and systematic reviews. Within a randomised controlled trial (RCT), Fledderus *et al*[29] investigated an ACT-based IMI

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for people living with depression. The authors found significant reductions in depression, anxiety, fatigue, experiential avoidance and improvements in positive mental health, compared with a waitlist control condition (effect sizes Cohen's d=0.51–1.00).[29] In their meta-analysis, Brown *et al*[66] examined 10 RCTs investigating the effectiveness of ACT in the treatment of depressive or anxiety symptoms and well-being in adult populations. ACT interventions were compared with passive control groups (N=3), active control groups (N=4) or both (N=3). The authors found small effect sizes regarding the improvement of depression (g=0.24, 95% CI: 0.04 to 0.45), while the heterogeneity of conditions and outcome measures on anxiety and well-being was too high to draw firm conclusions. Spijkerman *et al*[28] examined 15 RCTs in adults with various mental problems and healthy populations. Mindfulness interventions, of which the authors include ACT, were compared with passive control groups (N=10), active control groups (N=5) or both (N=2). The authors found small to medium effect sizes concerning the improvement of depression (g=0.29, 95% CI: 0.13 to 0.46), anxiety (g=0.22, 95% CI: 0.05 to 0.39) and well-being (g=0.23, 95% CI: 0.09 to 0.38).[28]

We developed a gender neutral software agent called SISU (Software agent providing an Intervention for Self-help to Uplift psychological well-being and Finnish word ('sisu') for inner strength) with the aim to provide an easily deployable software agent that improves people's well-being. Therefore, SISU combines therapeutic writing and acceptance-based and commitment-based principles. Results of a feasibility trial on SISU[67] showed that SISU is feasible in terms of user acceptance and the potential of the software agent to deliver a brief writing intervention. Thus, SISU is feasible to be implemented within a confirmatory clinical trial. Hence, the present study is designed to investigate the clinical effectiveness and acceptance of the software agent SISU thereby focusing on the following specific research aims:

1. To estimate the effects of SISU on psychological well-being compared with the waitlist control group (WL) at post-treatment at day 3 (t3) (primary outcome).
2. To estimate the effects of SISU regarding the secondary outcomes flourishing, quality of life and psychological flexibility compared with the WL at t3.
3. To explore, which factors are associated with, moderate or mediate the effects of SISU.
4. To investigate if the intervention is associated with measured side effects.
5. To investigate the level of acceptance (satisfaction, adherence) with the intervention.

METHODS

Study design

This is a two-arm, parallel RCT with the intervention group SISU (IG) and a 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 4 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 4 weeks' follow-up (t4).

The present study is conducted and will be reported in accordance with the Consolidated Standards of Reporting Trials 2010 guidelines for RCTs[68] and the guidelines for executing and reporting IMI research.[69] The study protocol follows recommendations of the Standard Protocol Items: Recommendations for Interventional Trials 2013 Checklist for clinical trial protocols.[70]

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 online 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 (eg, 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.[71] 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 (Well-being Scale (WHO-5) ≤52) and (e) possess sufficient German language skills.

Study procedures

If eligibility criteria are fulfilled, applicants will receive an online information letter including detailed information about study procedure and informed consent. They will be informed that they can withdraw from the intervention and/or study at any time without any negative consequences. After signing the informed consent, participants will be randomised to the IG or WL condition. Following, they will receive their individual ID and get an invitation for the baseline questionnaire (t1) at unipark.de via email. Afterwards, participants will learn about their group membership. The IG will get in contact with SISU and the intervention using the end-to-end encrypted online messaging app 'Wire' after finishing baseline (t1). SISU guides participants through a writing intervention on 3 consecutive days using a standardised conversation script. Each writing intervention is automatically followed

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by an assessment. Participants who are part of the WL will receive access to SISU 4 weeks after randomisation. If participants complete questionnaires for t3 and t4, they will each time get the chance to win a €10 gift card from Amazon as a monetary incentive to promote retention and follow-up completion. All participants with a low WHO-5 score (<28) in the screening receive an automatised email with further information about offers of the healthcare system.

Randomisation and blinding

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

Intervention

The software agent (SISU) provides a brief 3-day intervention. The writing instruction provided by SISU is based on the paradigm of therapeutic writing as well as ACT.[72] The version of SISU used for this study was improved through participant feedback collected in the feasibility trial.[67] Revisions included the enrichment of the instruction for writing about positive life events with elements of ACT (more mindfulness exercises, authenticity of the dialogue through reduction of repetitions, interactions on reported life events) and elements for the reconstruction of narrative identity.

SISU mimics a human conversational style. Participants are guided to write each day at the same time for 10–20 min about a self-chosen autobiographical, positive life event. On day 1 there is psychoeducation in the beginning. Then, instructions for the writing tasks are followed by the narratives of the participants. Participants are instructed to write about a meaningful, outstanding positive life event on day 1 and about an outstanding positive event from adulthood on day 2. On day 3 participants are guided to write about their best possible future. After the writing task, SISU encourages participants to experience the positive emotions due to the reported event in the present moment. Mindfulness exercises are provided by an audio file right after the writing intervention, while ACT metaphors are integrated into the conversational content. Participants are encouraged to practise on a daily basis. To increase adherence, SISU reminds participants at 24-hour intervals. More details on intervention contents can be derived from table 1. For an illustration of content and chronological structure, see figure 1.

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

The (ultra)brief intervention rational of 3 days was chosen because we wanted to provide participants with a brief possibility to do something for their mental well-being, despite their busy everyday lives. Indeed, evidence suggests that brief writing interventions of, for example, only 1 week can increase emotional well-being even 6 months after the intervention,[73] particularly in case of interventions focusing on improving mental health rather than treating mental disorders.

Waitlist control group

Participants of the WL get access to the writing intervention provided by SISU 4 weeks after randomisation. The intervention has the same content for both groups.

Administrative and technical support

In case participants forget their individual ID or have other technical issues, they can make use of the study

Table 1 Content and techniques of the writing tasks as delivered by SISU

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

ACT, acceptance and commitment therapy.

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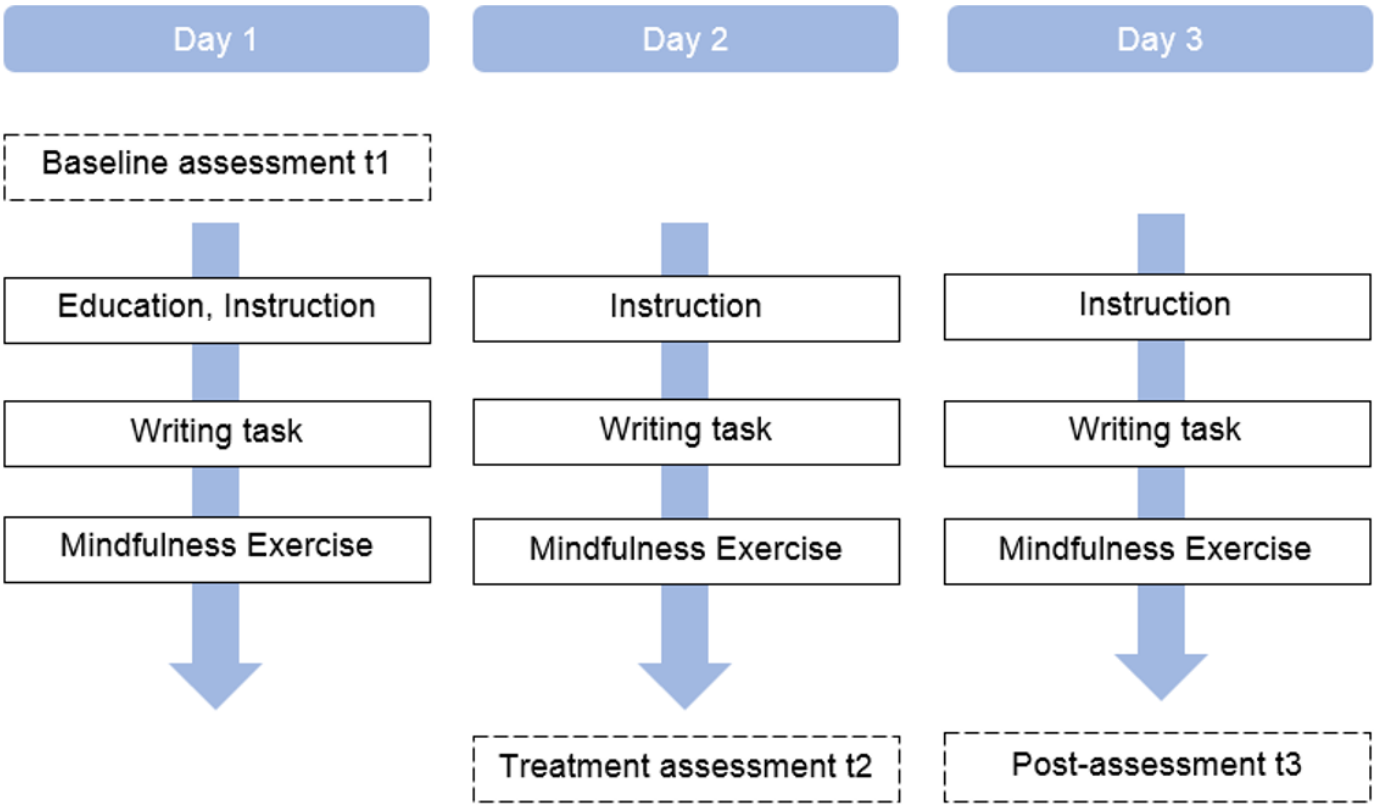

Figure 1 Content and chronological structure of the study.

team via email for technical support at every point during the training.

Outcome assessment

Screening for eligibility takes place at t0. Data for relevant outcomes will be collected prior to the intervention on day 1 (t1), on day 2 (t2) and day 3 (t3; intervention completed) and 4 weeks after randomisation (t4; follow-up). Demographic data and personality traits are measured once (t1). A flow chart of the study can be seen in figure 2. The outcomes, their measurement instrument and points of assessment are shown in table 2.

Screening, T0

The short WHO-5 is administered to assess the subjective psychological well-being of participants in the last 2 weeks.[74] 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.[74] Scores ≤52 indicate a low and scores ≤28 indicate a very low psychological well-being. Topp *et al*[74] 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.[74] 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 WHO-5[74] already described in the section for screening.

Secondary outcomes and covariates

Emotional well-being

The German version of the Flourishing Scale[75] is a measure of psychosocial well-being and personal growth and development (ie, flourishing). Each of the eight 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.[75]

Psychological flexibility

The German version of the Acceptance and Action Questionnaire-II[76] is a general measure for psychological inflexibility and consists of seven items. On a 7-point Likert scale that ranges from 0='never true' to 6='always true', the questionnaire assesses a person's

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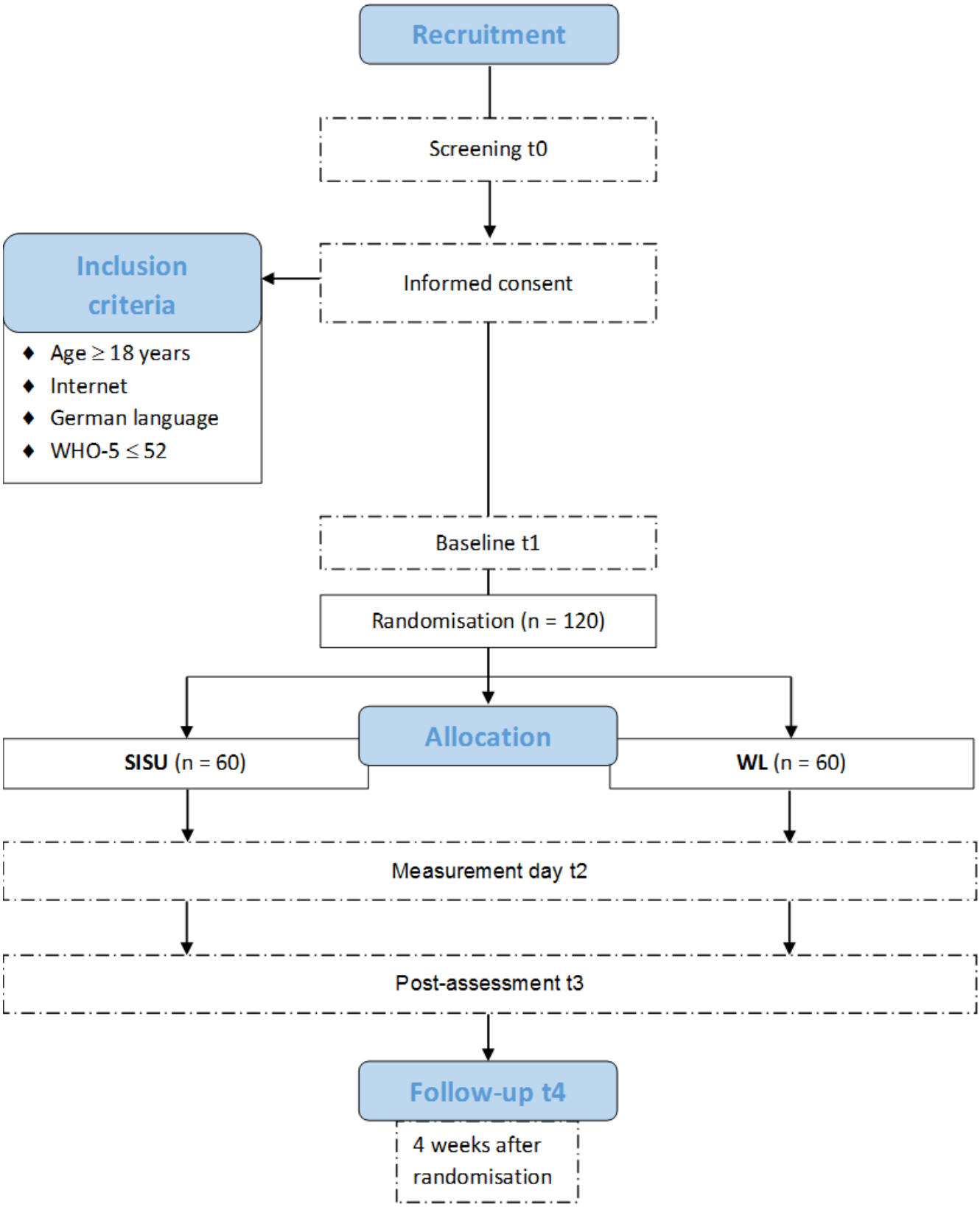

Figure 2 Flow chart of the planned study procedure. WHO-5, Well-being Scale; WL, waitlist control group.

willingness to experience unwanted thoughts and feelings and a person's ability to act despite the presence of undesirable thoughts and feelings. In this study items were reverse coded to assess psychological flexibility. Sum scores (range: 0–42) are computed with higher scores indicating higher psychological flexibility. The questionnaire shows good to excellent psychometric properties in a German sample.[76]

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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	✔	✔	✔	✔	✔
Secondary endpoints						
Emotional well-being	Flourishing Scale	–	✔	✔	✔	✔
Psychological flexibility	Acceptance and Action Questionnaire-II	–	✔	✔	✔	✔
Quality of life	Assessment of Quality of Life	–	✔	–	✔	✔
Satisfaction with the intervention	Client Satisfaction Questionnaire	–	–	–	✔*	–
Side effects	Inventory for the assessment of negative effects of psychotherapy	–	–	–	✔*	✔†
Manipulation-check writing	Post-Writing Questionnaire	–	–	✔*‡	✔*	–
Questions on content	Open questions for the interaction with SISU	–	–	–	✔*	–
Willingness to use software agents in the future	Open questions	–	–	–	✔*	–
Moderators/mediators						
Centrality of events	Centrality of Events Scale	–	–	✔*‡	✔*	–
Personality	Big Five Inventory	–	✔	–	–	–
Treatment expectancy	Credibility Expectancy Questionnaire	–	✔	–	–	–
Alexithymia	Toronto Alexithymia Scale	–	✔	✔	✔	✔
Emotion regulation	Emotion Regulation Questionnaire	–	✔	✔	✔	✔
Technology alliance	Inventory of Technology Alliance–Online Therapy	–	–	✔*	✔*	–

Note: t1=baseline; t2=during treatment (2 days post-randomisation); t3=post-treatment (3 days post-randomisation); t4=follow-up (4 weeks after randomisation).
*Questionnaires only used by IG.
†Adapted version for WL.
‡Additionally assessed retrospective for the first contact with SISU at t2.
IG, intervention group; WL, waitlist control group.

Quality of life

With the help of the inventory Assessment of Quality of Life (AQoL-8D), participants' quality of life is recorded.[77] Each of 35 items loads on one of eight dimensions of quality of life and is rated on 4-point to 6-point Likert scales. For analysis there is an algorithm which can be used for quality of life in general as well as for particular subdimensions. In total, scores between 0 and 1 are possible. Standard values are available. Reliability of AQoL-8D is very good with Cronbach's α of 0.96.[77]

Side effects

Subjective adverse events of the intervention are recorded with the 15-item inventory for the assessment of negative effects of psychotherapy.[78] Items are rated on a 4-point Likert scale (0='no agreement' to 3='total agreement') or a bipolar 7-point scale. Adverse effects in social life, intrapersonal factors or work-related situations are taken in consideration. The original inventory with 32 items has an internal consistency of α=0.95.[79]

Satisfaction with the intervention

To assess the global satisfaction with the intervention, a revised version of the German version of the Client Satisfaction Questionnaire (CSQ-8[80]) was used. Participants rate their satisfaction on a 4-point Likert scale for each of the eight items. A sum score is computed. Higher scores indicate higher satisfaction. Internal consistency of the CSQ-8 is very good with α=0.90.[81] A study on reliability and validity of assessing user satisfaction with internet-based interventions indicates good overall psychometric quality of the measure.[82]

Post-Writing Questionnaire

To assess therapeutic writing after every writing session, the participants answer four questions about their feelings and thoughts during and after the writing experience. Answers are rated on a 5-point Likert scale (1='not at all', 3='few', 5='very much/extremely'). The questionnaire was adapted from the English version of Pennebaker and Beall.[55]

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Open questions

For the final survey (t3), four open questions inspired by the open questions from Fitzpatrick *et al*[83] about the interaction with SISU are provided. The answers are individually evaluated and thematically summarised.

Questions for the future of software agents

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

Moderators/mediators

Centrality of events

The Centrality of Events Scale[84] 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) an element of the personal identity. Participants rate the seven 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.[84]

Personality

To assess the big five personality traits of participants, the short version of the Big Five Inventory[85] 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.[85]

Alexithymia

The German version of the Toronto Alexithymia Scale[86] 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 three factors[87]: '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 an α=0.80.[87]

Emotion regulation

The Emotion Regulation Questionnaire[88] is a 10-item questionnaire measuring positive and negative feelings as well as their regulation. Items refer to two different emotion regulation strategies: reappraisal and suppression. Participants rate the items on a scale from 1='strongly disagree' to 7='strongly agree'. Means show the preference for each strategy indicating higher preference at higher mean scores. Internal consistencies are acceptable to good and differ from α=0.75 to α=0.82.[88]

Treatment expectancy

Treatment expectancy is measured with the Credibility/Expectancy Questionnaire[89] with six items. Participants rate four items on a 9-point and two items on a 10-point Likert scale with varying descriptions. The scale can be separated into two factors: credibility and expectancy. Cronbach's α for credibility differs from 0.79 to 0.90, for expectancy from 0.81 to 0.86 and for the total scale from 0.84 to 0.85, indicating acceptable to high internal consistency.[89]

Technology alliance

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

Data privacy and ethics

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

The participation in this study should not be associated with any specific risks. However, temporary changes in mood could arise directly after the writing task.[57] Furthermore, therapeutic writing can lead to emotional–cognitive (change) processes[60] with which the participants could have difficulties in dealing with. Therefore, participants will have the opportunity to contact the study team at every point during the trial. Additionally to the interventions, participants with a very low WHO-5 score (<28) in the screening will be sent an automatised email with further information about offers of the healthcare system.

Sample size

A meta-analysis by Bolier *et al*[63] found an effect size of d=0.34 for positive psychological interventions aiming at uplifting well-being. Riddle *et al*[62] reported an effect size of d=0.46 for writing interventions to enhance well-being. However, for internet-based mindfulness interventions,

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Spijkerman *et al*[28] found a somewhat smaller effect of g=0.23.

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

Statistical analysis

Patterns of missing data will be investigated, and analyses will be adjusted accordingly (multiple imputation). Regarding the imputation method and predictor selection, we will follow the recommendations of Buuren and Groothuis-Oudshoorn.[90] It will be assumed that missing values are missing at random. Analyses will be conducted on a two-sided level of significance (α=0.05). Participant characteristics will be described descriptively.

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

The primary outcome will be analysed using linear regression models at t3 as dependent variable and the baseline value as covariate, adjusting for sex and age. The necessity of multilevel models will be explored by interclass correlations (ICCs). On substantial ICC (>0.10), multilevel models will be specified to account for the dependency in the data.[91] To analyse between-group effect sizes, SMDs with 95% CIs will be calculated for post-treatment (t3) and follow-up (t4). Secondary outcomes will be analysed accordingly.

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

For the planned exploratory moderator analyses, regression models will be employed. Initially, each potential moderator described under 'covariates' will be analysed in a separate regression model. The primary outcome psychological well-being at t3 will be the dependent variable. Predictors will comprise group, the moderator variable and the interaction of group and moderator. In a next step, a comprising model of all identified moderators will be tested.

Mediation analyses will be conducted according to the principles of time-lagged mediation.[92] Psychological well-being at t3 will be the outcome variable. Group will be chosen as independent variable, whereas the variables defined in the section 'Moderators/mediators' will constitute the respective mediating variables. No interim analyses will be applied to the data.

Patient and public involvement

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

DISCUSSION

To the best of our knowledge, this study will be the first to investigate an intervention on therapeutic writing combined with mindfulness-based exercises provided via a software agent. It is a two-parallel arm controlled trial with the aim of evaluating SISU, a software agent as an innovative form of providing a scalable mental health interventions[43] to uplift people's well-being.

The proposed study can be characterised by several strengths. First, our software agent SISU was successfully tested within a feasibility trial of Bendig *et al* submitted[67] and provides elements of established approaches.[57 72] 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 IMIs in the context of self-help interventions to uplift psychological well-being. Still, we will systematically record via questionnaire (Inventory for the assessment of negative effects of psychotherapy) if and which negative effects of SISU might appear. This will contribute to the still understudied area of research on risks and side effect[93] and therefore help make future IMIs safer.

Second, besides the relevance and necessity of our intervention, the methodical quality of our study is another strength. This is especially relevant in the relatively young field of research on therapeutic software agents, where highly qualitative studies are still sparse. First, we will use a randomised controlled design and we will apply ITT analysis to avoid a possibly overestimated effect of the intervention. Second, the writing intervention is highly standardised due to the completely automated instructions and feedback given by SISU. Third, we will collect data on many variables and time points to enable moderator and mediator analysis on an explanatory level. The knowledge of how and for whom interventions work best is an important prerequisite improving their content and target groups.[94]

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 (eg, [95]), this is the very first study to evaluate

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

Usually, moderate to high dropout rates are a problem within online interventions, which needs to be addressed in the planning of a study.[96] In our feasibility trial, 39% of the participants dropped out during study progress (assessment dropout), which could be (partly) explained by organisational effort providing informed consent and unfulfilled expectations concerning the intervention or the interaction with SISU. Nonetheless, the dropout rate of 14% during the intervention with SISU (intervention dropout) is comparably low, which could be traced back to the responsiveness/guidance by SISU. Those have been shown to improve intervention adherence.[97] For the present trial we maintained these successfully tested techniques.

Another possible limitation is the use of a WL. This can be associated with overestimation of effects compared with psychological placebo or no intervention.[98] If SISU shows its effectiveness compared with a WL, a next step should be to compare it with an active control group like, for example, participants receiving a pamphlet with instructions for doing mindfulness exercises at home. Furthermore, a potential methodological confound concerns blinding. Participants are not blinded towards the primary outcome and could possibly answer in a socially desirable way. However, as participants are unlikely to know the study team personally, test manager effects might be low. Another methodological problem could arise from assessment reactivity. Frequent assessments can trigger self-reflection which can lead to an incremental effect regardless of the intervention.[99] However, this is a general problem which can be particularly noticeable in control groups and in groups which receive low-threshold intervention offers.

Last but not least, the planned analyses are based on classic inferential statistics to test the significance of group differences. A sample size calculation (G*Power) was performed to plan the sample size accordingly. However, recent evidence emphasises that it might be fruitful not to test for differences from zero. Instead, Bayesian methods could be used. They allow discovering uncertainties of the effects of treatments instead of solemnly focusing on dichotomising evidence into significant and not significant.[100] If this trial points towards the usefulness/effectiveness of SISU, future trials could substantiate results using Bayesian methods.

Ethics and dissemination

This trial has been approved by the ethics committee of the Ulm University (No. 448/18, 18.02.2019) and registered in the German Clinical Trials Register (DRKS-ID: DRKS00016799) on 25 April 2019. Written informed consent for participation in the study will be obtained from all participants prior to their involvement. Participants will receive written information on study conditions, data security, publication of anonymised results, voluntariness of participation and the right to leave the study at all times. They will also be informed that in case of study withdrawal, they will be able to decide whether they want their data to be included in the analysis or to be deleted. Additionally, participants will be asked for permission for the research team to share relevant data with people from regulatory authorities, where necessary. This trial will only involve the collection and storage of self-report data, not of biological specimens. Data collection will be pseudonymised and data will only be accessed by authorised study personnel obliged to secrecy. After data collection is completed, personalised information will be deleted and all data will be completely anonymised. All participant information will be stored securely in locked file cabinets and/or password protected in a secured cloud storage with restricted access. All reports, data collection and administrated forms will be identified by a coded ID number only to maintain participant confidentiality. All records that contain names or other personal identifiers, such as informed consent forms (online supplemental file 1), will be stored separately from study records identified by ID number. Listings that link participant ID numbers to other identifying information will be stored in separate password-protected files with limited access. According to German law, data will only be shared with parties outside the project team in anonymised form. Trial results will be submitted for publication in a peer-reviewed journal and presented at conferences.

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

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Competing interests HB reports to have received consultancy fees and fees for lectures/workshops from chambers of psychotherapists and training institutes for psychotherapists in the e-mental health context. A-MK has received fees for lectures/workshops from chambers of psychotherapists and health insurance companies. DE reports to have received consultancy fees/served in the scientific advisory board from several companies such as Minddistrict, Lantern, Schoen Kliniken and German health insurance companies. He is a stakeholder of the Institute for Health Training online (GET.ON), which aims to implement scientific findings related to digital health interventions into routine care. All other authors declare not to have competing interests.

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10 Epilogue

10.1 Summary of Main Findings

The six publications included in this dissertation are based on two systematic overviews, three studies and one study protocol. The research covers different foci regarding the feasibility of innovative internet interventions for mental health of adults with a chronic somatic disease. The different focal points allow for a staged approach to identify and address research gaps and thus approach the goal of this dissertation. Main findings of the publications are shown in Figure 2.

A large body of research literature shows that internet interventions can be effective in preventing and treating mental disorders in the general population without a chronic somatic disease (Andersson & Titov, 2014). Meta-analyses show that there must not be a significant difference in effectiveness between internet interventions and traditional face-to-face interventions in the treatment of mental disorders (Carlbring et al., 2018). The extent to which findings of systematic reviews and meta-analyses in the general population can be generalised to people with a comorbid chronic somatic disease still needs to be examined.

The first stage of this dissertation focused on the state-of-the-art of internet interventions for people with a chronic somatic disease (publication I). The review indicates that internet interventions can support people with a chronic somatic disease effectively with reducing risk behaviours (e.g. small effect sizes for smoking, physical inactivity) and support the (co-)treatment of the chronic medical condition (e.g. foster medication adherence). In the course of answering research question one, the first publication conceptualises internet interventions in the field and systematises the state-of-the art of internet interventions for people with a chronic somatic disease. A framework is created within which open research questions, existing approaches, opportunities and potential pitfalls of current research are identified and mapped. In summary, the answer to research question one is that the evidence base and quality of studies concerning certain chronic somatic diseases is scarce. Specifically, evidence on CAD and diabetes is limited and often too heterogenous to calculate effect sizes or draw firm conclusions regarding their use in the population (Bendig et al., 2018).

At stage two, the focus was to investigate internet interventions in these specific populations. Publications two and three, therefore, focused on investigating the feasibility of a guided cognitive behaviour therapy-based (CBT) internet intervention for people with CAD (Bendig, Bauereiß, Buntrock, et al., 2021) and a guided acceptance and commitment-based (ACT) internet intervention for people with diabetes (Bendig, Bauereiß, Schmitt, et al., 2021). It was shown in publication two (WIDeCAD) that it was not possible to recruit a sufficient number of participants within 25-month despite intensive efforts. The few participants who started the intervention showed low adherence to the intervention (88% dropout) and low satisfaction with contents. The answer to research question two is that the internet-based depression treatment for people with CAD is not feasible to be investigated in a full-scale trial in its present format. Given intensive recruitment efforts and compared to successful trials with similar recruitment strategies (ACTonCancer, German Clinical Trials Register (DRKS), DRKS00013195; W-Decide, German Clinical Trials Register (DRKS), DRKS00012536; iSoma, Hennemann et al., 2022), this may indicate a target group-specific difference that requires further investigation. The results of the WIDeCAD-trial provide starting points for further studies to shed more light on potential target group-specific characteristics.

In the third publication on ACTonDiabetes, it was shown that the acceptability of the ACT-based intervention was good and that the intervention was potentially suitable to reduce diabetes distress (d = 0.65, 95%CI -1.27 to -0.02, p = .042) (Bendig, Bauereiß, Schmitt, et al., 2021). The answer to research question three is that ACTonDiabetes can be evaluated in a full-scale trial with content revisions alongside participants´ formative feedback. For a definitive trial, increasing mechanisms to foster intervention adherence is desirable to raise the average treatment dosage per person as the intervention dropout was high (62% completed all treatment modules). According to these results, the study protocol of a definitive trial on ACTonDiabetes was designed, and the trial is currently being conducted (Bendig et al., submitted).

As mentioned, guidance as a mechanism could be even more relevant to foster adherence in the target population than in people without chronic somatic disease (Baumeister et al., 2014). Also mentioned above, increased guidance may hamper the cost-effectiveness of an intervention due to

the need for increased human resources to achieve this (Baumeister et al., 2014). At this stage, the question of new ideas to provide internet interventions arose to address this shortcoming.

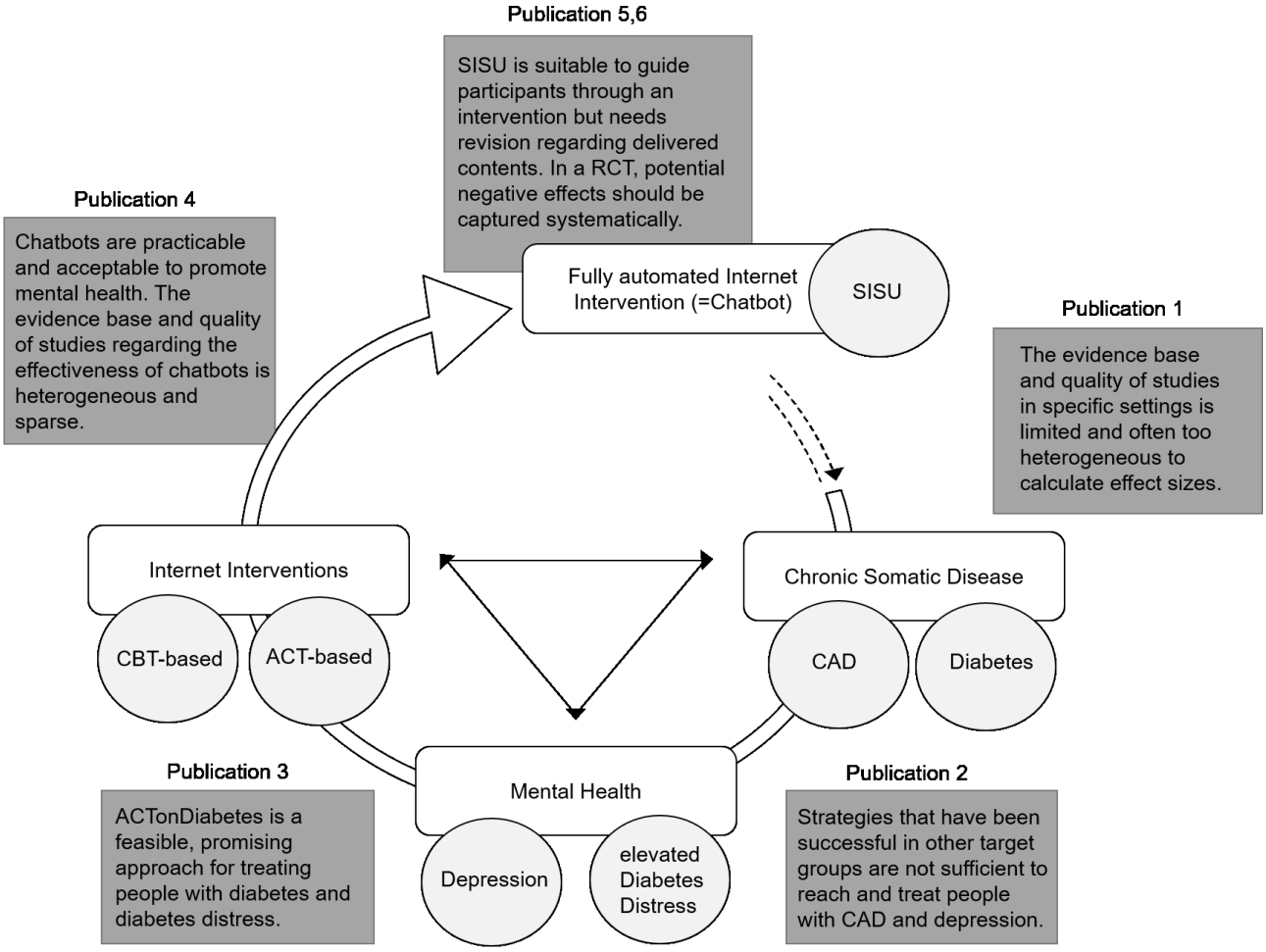
Subsequently, in the third stage of the dissertation, chatbots came into focus. The fourth publication aimed at defining the concept of fully automated internet interventions, so-called chatbots, and systematise evidence on chatbots for clinical psychological purposes (research question 4) (Bendig et al., 2019). Results of the systematic overview indicate that the evidence base is heterogeneous and high-quality studies are still rare in this area (which is particularly alarming when you look at how many are available in return). However, the growing interest in chatbot-delivered psychological interventions will result in more evidence in the future. The next research question addresses this issue.

The fifth research question was whether the custom-delivered chatbot "SISU“ has the potential to guide participants through a brief intervention. The results show that the chatbot-based intervention could guide participants through the intervention (Bendig, Erb, Meißner, Bauereiß, et al., 2021). It also showed the potential to enter the emotional world of participants by, e.g. supporting them with expressing emotions. User experience, as well as intervention adherence, was good (100% processed through the intervention). Negative effects were evaluated by using linear-mixed models. Results indicated that participants´ immediate responses to the intervention modules comprised an increase of anxiety over time ($\beta = 1.33$, $p = .001$). Short-term negative effects were expectable as intervention contents invite participants to enter emotionally adverse life events. The conversational contents of SISU were meant to buffer against these negative effects by using ACT principles. Results indicate that corresponding contents could not prevent participants from experiencing negative emotions shortly after the intervention. As a result, intervention contents need to be revised prior to the investigation of SISU in a full-scale trial. Altogether, the answer to research question five is that the chatbot can act as a therapeutic agent, but contents need to be revised prior to further investigations. Subsequently, the acceptability and effectiveness of the chatbot-delivered intervention should be evaluated within a full-scale randomised controlled trial (RCT) (Bendig, Meißner, Erb, Weger, et al., 2021).

The sixth research question was how SISU could be optimised and investigated in terms of acceptability and effectiveness in increasing psychological well-being (Bendig, Meißner, Erb, Weger, et al., 2021). Therefore, contents, as delivered by the chatbot, were revised according to the findings of the previous publication five. Revisions mainly comprised contents that invited participants to re-access adverse life events. Studies show that it is also possible to therapeutically use positive emotional life events to increase psychological well-being with effect sizes comparable to adverse life events (Baikie et al., 2012; Bolier et al., 2013; Burton & King, 2009). At the same time, fewer side effects are to be expected if positive psychological content is used (Bolier et al., 2013). Consequently, a positive psychological therapeutic writing approach was used in this study (publication VI). Therefore, the answer to this dissertation's last resesarch question is that the chatbot-delivered intervention should rather focus on strategies to broaden and build resources and positive emotions (Baikie et al., 2012; Bolier et al., 2013; Burton & King, 2009). Additionally, the RCT design should enable the evaluation of the effectiveness of the chatbot-delivered intervention and necessarily also carefully investigate possible negative effects due to the intervention and its acceptability. Therefore, a randomised controlled trial was designed to investigate the chatbot SISU's effectiveness and acceptability. The primary outcome was psychological well-being post-treatment in the intervention group compared to a treatment-as-usual control group (Bendig, Meißner, Erb, Weger, et al., 2021).

Figure 2

Overview of Main Findings



Note. Abbreviations CAD = coronary artery disease, CBT = Cognitive Behaviour Therapy, ACT = Acceptance and Commitment Therapy, SISU = Software-Agent providing a brief Intervention for Self-help to Uplift psychological well-being.

10.2 Comparison with Previous Research

This dissertation aimed to contribute evidence in innovative treatment concepts for mental health in people with a chronic somatic disease. Results of the six studies will be compared with related work and placed in the broader context of current literature.

Findings of publication one are comparable to findings of other studies concerning the heterogeneity in quantity and quality of studies across different chronic somatic conditions and investigated (primary) outcomes (Charova et al., 2015; Mehta et al., 2019; Van Beugen et al., 2014).

Besides changing behavioural factors, studies consistently indicate that internet interventions are also promising for treating mental disorders like depression in people with chronic somatic disease (Mehta et al., 2019). However, evidence from the general population may not be transferable one-to-one to populations with chronic somatic disease (Charova et al., 2015; Karyotaki et al., 2017; Mehta et al., 2019). The number of high-quality studies on internet interventions for mental health in populations with chronic somatic disease is very small in comparison to the research corpus that exists from the general population (Carlbring et al., 2018). Internet interventions addressing behavioural aspects (e.g. improving self-management) seem to have been more prominent in the field than internet interventions addressing genuine psychological issues in specific medical conditions thus far (Carlbring et al., 2018; Kloek et al., 2017).

In contrast to behavioural aspects, addressing mental health could differ concerning plausibility for people with a chronic somatic disease. The importance of changing behavioural factors might seem more plausible as (risk) behaviour (more) directly affect physical symptoms (Abbafati et al., 2020). Examples of such behaviours are physical inactivity, alcohol consumption or smoking (Abbafati et al., 2020; Van Gool et al., 2003). Psychological variables like the influence of thoughts and feelings are perhaps less evident in their association to physical health / could contradict an existing somatic understanding of health and disease in people with a chronic somatic disease (Prince et al., 2007). This could also be a reason why internet interventions aiming at shaping behavioural factors seem to be better accepted by both practitioners and treated persons (Schröder et al., 2017). Acceptance facilitating measures could help to raise awareness of the importance of psychological aspects and to reduce possible reservations in stakeholders (Baumeister, Nowoczin, et al., 2014; Baumeister, Seifferth, et al., 2015; Ebert et al., 2015). While these research questions are of interest for all chronic somatic diseases, in many places it is worthwhile to take a closer at certain population groups based on specific research questions.

For instance, research repeatedly raises the question of whether and to what extent interventions need to be tailored to specific needs and target groups (Donker et al., 2015; Johansson et al., 2012). This question is not trivial against the background of the need for cost-effective

interventions accessible to a wide range of people (Donker et al., 2015). Tailoring content may usually be costly as several variables and user characteristics need to be considered (e.g. co-morbidities, individual preferences) (Donker et al., 2015). Recent research addresses this issue in two ways. First, there is increasing evidence that transdiagnostic interventions can effectively reduce depressive symptoms or anxiety, which could be especially helpful in people with a co-morbid disease (Păsărelu et al., 2017). Under certain conditions, and especially in chronic somatic diseases, a more disorder-specific tailored intervention could be more helpful, e.g., for depressive symptoms (Păsărelu et al., 2017). In addition, there may be not only disease-related differences between populations but also inter-individual differences within populations with a specific disease. So second, researchers increasingly investigate interventions that use causal modelling to adapt intervention contents to individual needs (Nahum-Shani et al., 2018). One example are so-called just-in-time adaptive interventions that capture individual needs and adapt to such real-time needs by providing the right type and dose of content just-in-time (Nahum-Shani et al., 2018).

Such approaches could be suitable especially for people with CAD. From the results of the WIDeCAD trial and from related work it can be concluded that new proposals are needed to reach and treat people with CAD (Bendig, Bauereiß, Buntrock, et al., 2021). In that, results of the WIDeCAD trial are comparable to current research in the field of people with CAD in several ways. Other research groups report similar findings for psychological online and face-to-face interventions for people with CAD (Messerli-Bürgy et al., 2012). Many studies in the field report recruitment difficulties / are underpowered (Norlund et al., 2018; Ramamurthy et al., 2013; Schneider et al., 2020). The majority of those trials also reports low intervention adherence (Norlund et al., 2018; Wallin et al., 2018). Both low uptake of and low adherence to psychological treatment for CAD are often reported in online and offline (traditional face-to-face) settings (Ramamurthy et al., 2013). This leads to the assumption that reaching and treating people with CAD and depression is an endeavour that still has many unanswered questions (Johansson et al., 2021).

A starting point for further investigation could be whether there are specific needs and patient expectations in the population (Bente et al., 2021). Clues to this are provided by many studies that

could not yet prove the benefits of interventions (Johansson et al., 2021). Research suggests that cohort-specific assumptions about health and disease could be active, the label "depression“ could not fit the understanding of the somatic disease (Aalto et al., 2005; Grace et al., 2005). In that it could be discussed whether the understanding of health and illness has an impact on the willingness of people with a heart disease to classify psychological support as relevant for themselves or make use of it.

A second point for further investigation concerns low treatment uptake and adherence in the target group. Studies that are an exception in this context (Johansson, Westas et al., 2019) are closely linked to the medical care of patients and contain a comparatively high dosage of (nurse given or telephone provided) guidance. The connection of psychological interventions with medical care could play a significant role in this group, bridging the gap between cardiac care and the treatment of depression, i.e., combining expertise from both areas (Westas et al., 2020). Since there may often not be sufficient capacity for trained staff to bridge the gap between medical and psychosocial treatment, other ideas and approaches would be helpful (Donker et al., 2015). Chatbots could be trained in both areas and take over these task in the future (Titov et al., 2013). For example, it becomes conceivable that patients will receive a chatbot-guided intervention in addition to their routine appointment that highlights the significance of psychological variables. This low-threshold acces can then be used to implement psychological interventions. However, this is still a matter of future non-inferiority studies which should evaluate to what extent chatbots have similar guidance effects as traditional eCoaches.

To further elaborate on yet unanswered questions and potential requirements for depression treatment in CAD, a deeper understanding of (sub-)populations, peoples’ needs, perceptions of illness and underlying motivations for internet interventions is required. These questions could be explored in qualitative research designs that enable digging into individual experiences or via the use of smart sensing to learn about differences e.g. regarding different stages of a disease (Pryss, 2019). Corresponding research designs and methods that collect data beyond self-report could be

key to generate new ideas regarding paths and approaches that could be taken to reach and treat the target group.

Although CBT-based approaches in internet interventions are well researched in hundreds of randomised controlled trials (Carlbring et al., 2018), it might be fruitful to investigate whether and how other approaches can be chosen in people with CAD. Other approaches than traditional CBT, like acceptance and commitment therapy (ACT), could better meet the patients´ needs (Hayes & Hofmann, 2017) as it could circumvent active cohort-specific reservations associated with a deficit-oriented approach to mental health. ACT principles stress strengthening resources rather than removing symptoms (Hayes, 2004). Somatic symptoms are likely to accompany people throughout their lives, so accepting unchangeable aspects of a disease might be an important milestone on the road to mental health (Hayes & Hofmann, 2017).

Furthermore, the changeability of symptoms could be limited due to the somatic condition and, to some extent, regarding symptoms of depression (Khandaker et al., 2020). Accumulating research suggests that biological processes can influence depression in people with CAD (Kiecolt-Glaser et al., 2015). The view of depression as a variable risk marker that fluctuates together with mechanisms leading to poor cardiovascular health (Shao et al., 2020). Inflammation could play an essential role in the link between depression and cardiovascular disease (Khandaker et al., 2020; Kiecolt-Glaser et al., 2015; Shao et al., 2020). This connection between inflammatory processes and depression is also discussed in other chronic somatic diseases (Hysing et al., 2019). ACT has proven its value for lowering depressive symptoms in this population (Lin et al., 2017). Thus it could be fruitful to investigate interventions following this approach for people with CAD in future studies (Johansson et al., 2021).

Besides the question of whether a particular therapeutic approach (e.g. CBT or ACT) is suitable for addressing mental health in people with a chronic somatic disease in general, one can also ask if the above-described concept of tailoring to different chronic somatic diseases is indicated. Should depression treatments be tailored to peoples' somatic conditions, or are transdiagnostic contents sufficiently suitable? Results of the CAD trial (publication II) against the background of

related work reveal ideas on this issue. For example, there is a social gradient in the incidence of cardiovascular disease globally, which are reflected in participants´ sociodemographic characteristics reported in publication two. The lifetime prevalence of cardiovascular disease is higher in people with lower socioeconomic status (Greene & Murdock, 2013; Rosengren et al., 2019). A lower socioeconomic status could come with the perception of limited decision-making and control possibilities regarding the own health-related situation (Greene & Murdock, 2013; Janowski et al., 2013). A recent qualitative study indicates that people with CAD seem to benefit from increasing health-related control beliefs (Westas et al., 2020). Thus, content which fosters control beliefs might be relevant for people with CAD and low socioeconomic status.

Another aspect that should be considered when it comes to psychological treatment in people with a chronic somatic disease in general, and, e.g. CAD in particular, concerns the duration and stage of disease (Lin et al., 2013; Olver & Hopwood, 2013). Contents should be adaptable to intra- and interindividual variations and temporal dynamics of specific characteristics of the disease (e.g. stage, duration, medical prognosis) and the disease management process (Lin et al., 2013; Olver & Hopwood, 2013). Even the best treatments will not work for everyone and relevant intraindividual changes may occur during a chronic somatic disease like experiencing physical complications or developing psychological symptoms (Holmes et al., 2018; Verhaak et al., 2005). Also, in this context, technologies are discussed that allow the adaptation of contents just in time to inter- and intraindividual needs (Nahum-Shani et al., 2018). In this regard, researchers are investigating, for example, intelligent internet interventions that can track emotional changes and react to them with appropriate content (Pryss, 2019). It becomes possible to automatically find that a person fears, e.g. an upcoming surgery and provide, e.g. a brief intervention to reduce pre-operative anxiety and thus improve treatment outcomes (Rief et al., 2017).

The results of the ACTonDiabetes study are comparable in many respects to current research in the field of people with diabetes. First, other studies indicate that psychological internet interventions could effectively address psychological aspects of the disease (Ebert et al., 2017; Nobis et al., 2015). Reportings in publication three of this dissertation fit these results (Bendig,

Bauereiß, Schmitt, et al., 2021). ACT seems to be a feasible approach for people with type 1 or type 2 diabetes (Bendig, Bauereiß, Schmitt, et al., 2021). From a theoretical point of view, as outlined in the prologue of this dissertation, diabetes distress comprises negative emotional reactions towards symptoms associated with diabetes (Skinner et al., 2020). The idea of ACT supports change in individuals towards being no longer stressed by a symptom but instead learning to accept it and live a goal and value-oriented life with the symptom (Hayes, 2004). Thus, it makes sense to use ACT as a therapeutic approach to reduce elevated diabetes distress. However, non-inferiority evidence on ACT against CBT in the field of diabetes is pending (Johansson et al., 2021). Publication three shows that the ACT approach could help address elevated diabetes distress (Bendig, Bauereiß, Schmitt, et al., 2021).

The first three publications can be summarised in the context of related work in order to make statements about similarities and differences in digitised psychological interventions for people with chronic somatic diseases (Bendig et al., 2018; Bendig, Bauereiß, Buntrock, et al., 2021; Bendig, Bauereiß, Schmitt, et al., 2021). Both, similarities and differences, must be taken into account to provide effective treatment. For example, it may be essential to enable the adaptation of contents to disorder-specific inter- and intraindividual needs (e.g. fear of hypoglycaemia in diabetes) (Pryss, 2019). Additionally, guidance could be especially beneficial for people with CAD (Westas et al., 2020). More guidance needs more resources which are costly and could thus hamper the cost-effectiveness of interventions (Baumeister, Haschke, et al., 2015). Therefore, future studies should carefully examine how much guidance is valuable and necessary to ensure adherence and to counteract under- or oversupply of guidance in specific target groups. For example, studies two and three have shown that the same amount of guidance was just right for diabetes (Bendig, Bauereiß, Schmitt, et al., 2021), whereas it might have been not enough for people with CAD (Bendig, Bauereiß, Buntrock, et al., 2021). Furthermore, participants in the WIDeCAD (publication II) or ACTonDiabetes trial (publication III) often indicated that they had difficulties integrating the programme into their daily lives (Bendig, Bauereiß, Buntrock, et al., 2021; Bendig, Bauereiß, Schmitt, et al., 2021). This is where the threads come together. Reflections on results of studies one to three

lead at one point or another to the assumption that novel technologies are needed to enable more flexibility, more guidance and the adaptation of contents to individual preferences and needs.

Another contribution of the dissertation is that included studies expand the knowledge in the field of more innovative technologies. The fourth publication summarises current research in chatbots as a delivery format for clinical psychological and psychotherapeutic contents (Bendig et al., 2019). Chatbots appear to be feasible for being used in this field, and people seem to accept this delivery format (Bendig et al., 2019). This finding can be integrated into other research that indicates that patients accept chatbots for disease-related issues like self-management support (Griffin et al., 2020). Chatbots seem to be also accepted for answering medical questions and giving advice to people regarding their somatic disease-related condition (Laranjo et al., 2018) and mental health (Abd-Alrazaq et al., 2021; Vaidyam et al., 2019). Results reported in publication five on SISU indicate that the chatbot-based application could also be acceptable for increasing psychological well-being (Bendig, Erb, Meißner, Bauereiß, et al., 2021). Additionally, publication five contributes to evidence as it shows that chatbots can guide users through a psychological intervention and enable self-disclosure (Bendig, Erb, Meißner, Bauereiß, et al., 2021). This finding fits current literature (Croes & Antheunis, 2021; Weis & Herbert, 2022) and is relevant for research in the field as it potentially enables a high level of guidance on low cost and also higher levels of flexibility (Pryss, 2019) and (emotional) interaction (Weis & Herbert, 2022) than in traditional web-based internet interventions.

How and to what extent chatbot-delivered and chatbot-guided interventions can be used for the population of people with a chronic somatic disease in the future needs to be further researched. Nevertheless, precautions are necessary to provide a safe and sound product (Abd-Alrazaq et al., 2020). Possible side effects are a relevant issue that needs to be considered as participants process through content without human assistance (Abd-Alrazaq et al., 2020). Research in this respect is still in its infancy, and no solid conclusions regarding effectiveness and safety can be drawn from recent research (Abd-Alrazaq et al., 2020; Bowie-DaBreo et al., 2020; Vaidyam et al., 2019). Notwithstanding, the amount of available chatbot-based psychological interventions are on the rise, and the need in the population to access remote care in times of the Covid-19 pandemic is perhaps

more significant than ever before (Inkster et al., 2020). Hence it is of importance to ensure that they withstand clinical and data security and privacy guidelines (Martinengo et al., 2019). Especially deficit-oriented approaches should necessarily include safety mechanisms in case of the emergence of symptom deterioration or suicidal tendencies (Sander et al., 2020). These considerations must lead to professional policy decisions on quality criteria and concrete recommendations for action, such as removing mental health software that does not withstand quality criteria from app stores (Inkster et al., 2020). To meet scientists' call to make high-quality internet interventions quickly available, especially to those who are most vulnerable, internet interventions that follow a resource-oriented approach seem to be particularly suitable for people with chronic somatic disease (Inkster et al., 2020). This demand includes internet interventions that promote positive emotions and psychological well-being (Bolier et al., 2013; Inkster et al., 2018). Several research groups are currently taking up the mandate of evaluating the quality of such interventions, and this is also where the sixth and last publication of this dissertation can be placed.

10.3 Strength and Limitations

This dissertation has several strengths. Altogether, this thesis extends the existing literature by reviewing internet interventions for adults with chronic somatic disease (publication I) and reviewing and extending the literature on the next generation of internet interventions, so-called chatbots (publications IV, V, VI). Studies in this dissertation extend existing research by focusing on specific chronic somatic diseases, diabetes and CAD (publications II, III) and then bringing them together in this dissertation as a whole to provide recommendations for the field.

The comprehensive illumination of innovative treatment concepts for people with chronic somatic diseases from different perspectives can be seen as a strength of the dissertation. Two different medical conditions were included, internet-based intervention concepts for two different therapeutic approaches were examined, and chatbots as representatives of novel internet approaches were investigated. Essential insights into the feasibility of internet psychological interventions were gained, and a new intervention concept was developed.

Beyond that, a methodological strength is that the randomised controlled trials (WIDeCAD and ACTonDiabetes) were designed, pre-registered, conducted and reported in line with good research practices for RCTs as stated by the CONsolidated Standards Of Reporting Trials for feasibility studies (Eldridge et al., 2016) (studies two and three).

A conceptional strength of the ACTonDiabetes and WIDeCAD trial is the use of internet interventions already evaluated in other contexts, which is often recommended, especially for vulnerable populations like people with a chronic somatic disease (Balcombe & De Leo, 2021; Shivayogi, 2013). Furthermore, in all three empirical studies (WIDeCAD, ACTonDiabetes and SISU), the interventions were developed with public involvement in interdisciplinary teams of experts, patients and researchers as recommended by clinical trial quality guidelines (Eldridge et al., 2016; Schulz et al., 2010).

A methodological strength of publication six is that the novel technology behind the intervention (SISU) was tested prior to the use within a feasibility design and reported in publication five. This approach is highly desirable from an ethical point of view as it helps to ensure that potentially burdened people do not receive an unsophisticated/immature application (Balcombe & De Leo, 2021).

Another strength is that ACT served as a basis for publication three, which has never been done before in an online format for people with diabetes. Also, the studies surrounding the chatbot SISU extend the research field by testing novel technologies for clinical-psychological questions. Since interdisciplinary collaboration of developers (e.g. engineers, computer scientists) and psychologists in this field is crucial to create ideal conditions for a good internet intervention (Schueller et al., 2013), the development of SISU in a team of computer scientists and psychologists can be seen as another strength of this work.

A practical strength of the dissertation is that results from the three empirical trials will support researchers in designing and implementing adequately powered studies for people with CAD or diabetes in the future.

The scope and diversity of the studies included (see Figure 2) can be seen as a strength, as described. At the same time, the broad focus is accompanied by a reduced depth of investigation of selected constructs. The reduced depth in this respect can be seen as a limitation of the dissertation. However, the broadly chosen research question is a prerequisite for the high-quality, in-depth investigation of the described areas in future research (see study protocol ACTonDiabetes, study protocol SISU) (Bendig et al., 2022; Bendig, Meißner, Erb, Weger, et al., 2021).

Beyond this, there are methodological limitations of the included reviews (publications I, IV). Systematic reviews and meta-analyses were reviewed in publication one (Bendig et al., 2018). One limitation is that the logic of the review does not strictly follow pre-established eligibility criteria and a strictly pre-defined research question. The study was also not a priory specified in firm detail and published in a protocol. The objectiveness of results does thus not fulfil the highest quality standards (Page et al., 2021). Due to Type I and Type II error which can arise in this way, the results of this review do not allow for generalisable statements on the effectiveness of internet interventions in the population of people with a chronic somatic disease (Bourhis, 2017; Page et al., 2021). However, the aim of the systematic meta-review (publication I) was to identify landmarks regarding the broad scope of internet interventions for lifestyle change and (co-)treatment of chronic somatic disease. Nevertheless, it would have been beneficial to the quality of this review (publication I) to add a second reviewer and to include more databases than Pubmed and the Cochrane database to identify relevant studies (Page et al., 2021).

Limitations of the review on chatbots (publication IV) comprise the narrative nature of scoping reviews (Moher et al., 2015; Peterson et al., 2017). Although the inclusion of individual studies was systematised (e.g. two independent rater, searches in various databases), the generalisability of the results is limited due to several methodological limitations (Page et al., 2021). There was no a priori specified, and pre-published protocol and eligibility criteria were not very strict (Peterson et al., 2017). Correspondingly, the research questions in publication four were not clearly delineated but rather broad. Thus, the review does not fulfil the highest quality standards regarding the objectiveness of results (Page et al., 2021). The number of type I and II errors in scoping reviews might be high

(Bourhis, 2017; Munn et al., 2018). Due to these methodological limitations, it is not possible to make statements on the effectiveness of chatbot-delivered interventions in the context of clinical psychology and psychotherapy (Bendig et al., 2019). Systematic reviews and meta-analyses are needed in the future to collate evidence on their effectiveness (Chandler et al., 2021; Moher et al., 2015). However, the review's aim in this dissertation (publication IV) was to reflect and map the landscape to achieve a more inclusive picture of available research (Bendig et al., 2019). The method was used to enable fast identification of research findings in this specific field and to summarise and disseminate these findings (Peterson et al., 2017). This approach can help to further develop new fields of research (Moher et al., 2015). Narrowly defined parameters would have undermined this goal due to a restrictive effect (Moher et al., 2015).

The reviews in this dissertation have a raison d'être, as the regular scientific examination of relevant literature is elementary to the further development of a field of research. In the next step, systematic reviews and meta-analyses for specific chronic somatic diseases are needed to draw firm conclusions on effectiveness for narrowly defined research questions. In this field of research, this might be essential to enable faster implementation of new technologies in actual practice. The systematic review and meta-analysis in Cochrane Heart builds on these grounds and investigates the effectiveness of depression treatments in people with CAD (Tully et al., 2021)

All three empirical trials WIDeCAD (publication II), ACTonDiabetes (publication III) and SISU (publication V), yield limitations that are to be discussed alongside the research questions of this dissertation.

The generalisability of the results of feasibility studies can be considered in three ways (Eldridge et al., 2016). First, in terms of the generalisability of the results to the associated definitive trial. Second, regarding the generalisability of the results to other feasibility and definitive trials. Third, concerning areas of feasibility that remain unclear after the trial (Eldridge et al., 2016).

There is remaining uncertainty regarding the feasibility of the WIDeCAD trial (Bendig, Bauereiß, Buntrock, et al., 2021). First, although a categorical classification as "not feasible" for the investigation in a definitive trial can be made based on the results, a high degree of differentiation of

this state is not possible. For a better understanding on the participant level, the *reach* of WIDeCAD should have been determined. Therefore, besides the absolute number of individuals willing to participate, the proportion and representativeness of persons who would have been eligible for inclusion but did not participate should have been recorded (=participation rate) (Eldridge et al., 2016). The collection of this data would have indicated the perceived need/attractiveness of WIDeCAD in the target population.

Second, to better understand the settings and stakeholders approached in this trial, the *adoption* of WIDeCAD should have been determined. Besides the acquisition of the absolute number of stakeholders who were willing to recruit for WIDeCAD, it would have made sense to record the actual number of people approached. Furthermore, information could have been collected to assess the representativeness of the respective recruitment facilities for the care of people with CAD and depressive symptoms. For example, it would have been helpful to see how many patients meeting the inclusion criteria have been seen in, e.g. stationary settings vs ambulatory settings in total. Furthermore, participants' sociodemographic characteristics in different recruitment sites could have been recorded and explored.

Information on reach and adoption could have allowed for a differentiated consideration of application areas (e.g. stationary or ambulatory settings) and would have shed light on sub-populations. This information would help answer for whom and in what settings WIDeCAD could work and for whom or what settings not. In a nutshell, a deeper understanding of (sub-)populations and underlying motivations for the engagement in internet interventions is required.

Beyond this, research question two could also have been investigated in a mixed-methods design. Quantitative findings could have been enriched with qualitative ones regarding the acceptability of the intervention and study procedures and participants´ experiences of dealing with psychological issues to develop more effective recruitment and retention strategies (Eldridge et al., 2016).

A limitation of the ACTonDiabetes trial is the small sample size against which statistical tests regarding diabetes distress were performed and reported. However, the explorative nature of

analyses was made clear in the rationale of the corresponding publication three to avoid misinterpretations of findings. The result of these exploratory analyses is a medium effect (d = 0.65) which now needs to be replicated in a trial designed for this purpose. Additionally, the great engagement of study staff regarding recruitment may have been a source of contamination, i.e. the recruitment strategy could have worked better in the feasibility trial as it would in a large-scale trial. For a definitive trial, recruitment difficulties could arise as high guidance levels to bridge the gap between expression of interest of participants and study inclusion are not feasible on a larger scale. Therefore, a definitive trial in the area should be tethered (e.g. to specific institutions) to enable a close-meshed inclusion of patients. Both sources of potential bias have been considered in the study protocol for the definitive trial on ACTonDiabetes (Bendig et al., 2022).

A limitation of the feasibility trial on SISU is that there is remaining uncertainty regarding the feasibility of interventional contents to be investigated in a definitive trial (Bendig, Erb, Meißner, Bauereiß, et al., 2021). In the feasibility trial on SISU, it was found that writing about negative events triggered negative emotions in participants. Short-term negative emotions were expected to some extent (Herbert et al., 2019), so ACT principles to buffer against these negative emotions were implemented in the original intervention. However, negative emotions could not be cushioned by ACT principles (e.g. mindfulness/acceptance). This result led to a modification of the intervention for the definitive trial using a positive psychological writing approach (Bendig, Meißner, Erb, Weger, et al., 2021). However, this specific form of intervention was not tested for acceptance and side effects in the feasibility trial. The assumption that the chosen intervention approach, which includes writing about positive events, is associated with less negative emotions has already been suggested by several studies (Burton & King, 2009; Guastella & Dadds, 2006; Nazarian & Smyth, 2013). However, it cannot be ruled out that short-term negative emotions may occur as writing may trigger feelings that the participants cannot cope with. Consequently, the integration of nested feasibility measures in the definitive trial should be considered to allow continued monitoring of the feasiblity, particularly in terms of acceptability and potential side effects. Within the definitive trial on SISU, these issues will be captured (Bendig, Meißner, Erb, Weger, et al., 2021).

Albeit the feasibility trial on SISU certainly helped to overcome sources of potential bias in the definitive trial (publication VI), there are still sources of potential bias left in the effectiveness trial on SISU (Bendig, Meißner, Erb, Weger, et al., 2021). One source of potential bias that the feasibility trial could not eliminate is that there is intensive monitoring involved in the SISU study. Participants have to respond to questions on their mood and well-being frequently. However, in order to record mood fluctuations over time as instantaneously as possible (=ecological momentary assessment), several measurement points are indispensable. The downside of this is potential assessment reactivity as participants might become aware of and rethink their psychological well-being, which could influence behaviour and affect the treatment effect in the definitive trial. Several studies also suggest an effect of mood tracking, which found that real-time data collection of positive and negative affect reduced depressive symptoms (Kramer et al., 2014; Yim et al., 2020). While an overestimation of the treatment effect can probably be prevented because the wait-list control group receives the same assessment, the delta between treatment and control group can become smaller and blur with a possible treatment effect.

A limitation of all three empirical trials (publication II, III, V) is, that the trial design did not include measures of long-term effects (Bendig, Bauereiß, Buntrock, et al., 2021; Bendig, Bauereiß, Schmitt, et al., 2021; Bendig, Erb, Meißner, Bauereiß, et al., 2021). It remains to be seen what the long-term impact of the interventions will be. Additionally, intervention groups of all three empirical trials, WIDeCAD (publication II), ACTonDiabetes (publication III) and SISU (publication V), were compared to wait-list control groups. It is known that wait-list control groups can yield effects in the expected direction caused by the expectation of the intervention (Hesser et al., 2011). The opposite can also occur, e.g. when people who are on the wait-list are disappointed by it or because every intervention works better than no intervention (Hesser et al., 2011). As all three empirical studies were not designed to evaluate effectiveness, potential type II errors and not detecting differences due to low sample size are not major limitations.

Additionally, it can be seen that adherence rates regarding assessments are higher in wait-list control groups when compared to treatment as usual (TAU) control groups (Hesser et al., 2011).

Participants in TAU control groups could e.g. feel like there is nothing in it for them if they fulfil assessments but can not get the treatment (Watts et al., 2015). Thus, results regarding adherence in these studies are not generalisable if other control groups are to be chosen for definitive trials. However, potential expectation effects in the wait-list control group of the feasibility trial on ACTonDiabetes will be ruled out in the definitive trial on ACTonDiabetes using a TAU control group. The downside of this is that the results on adherence from the feasibility trial are not generalisable to the definitive trial. First, additional mechanisms to foster adherence, like gratifications, will be applied there. Second, participants of the TAU control group will receive psychoeducative info material on diabetes distress (=TAU+) to further foster adherence. The latter additionally enables a relatively strict test of effectiveness as the intervention group will be compared to an active control group.

Further limitations of publications two and three include the lack of diagnostic certainty regarding depression or elevated diabetes distress and medical conditions. Evaluations were based on self-reports. In this respect, the methodological quality of evaluations is restricted. Effectiveness studies should use physician-confirmed diagnoses of the chronic somatic disease, and mental health status should be captured by a clinician via standardised diagnostic interviews or supplemented by, e.g. smart sensing technologies to achieve a broader clinical picture (Moshe, Terhorst, Opoku Asare, et al., 2021). Results would enable statements about whether treatment for depression or elevated diabetes distress is effective for the respective population.

The findings of the feasibility trials on ACTonDiabetes, WIDeCAD and SISU have limited external validity, i.e. are not generalisable to situations outside research settings like routine clinical practice. This requires full-scale pragmatic trials (Zwarenstein et al., 2008). However, it is crucial to consider aspects of generalisability at this stage to design pragmatic trials so that the results can be transferred to real-world care as far as possible. For example, the results of the ACTonDiabetes study stimulated considerations of the full-scale pragmatic trial concerning recruitment strategies.

10.4 Implications

Implications can be drawn from findings for practice, theory and subsequent research. Theoretical implications can be derived from the two reviews on internet interventions for chronic somatic diseases (publication I) and chatbots in clinical psychology (publication II). The illustration of the current state-of-the-art of internet interventions for people with a chronic somatic disease helps to identify research desiderata to further work on. Research desiderata in this regard can be found for the most common conditions cardiovascular disease, chronic respiratory disease, cancer and diabetes and are probably even more remarkable for less common chronic somatic conditions that were not explicitly included in this review.

Another theoretical implication can be drawn from the review on chatbots (publication IV). Numerous applications are available, and the field is growing rapidly, but evidence on effectiveness is sparse. So the acquisition of a better understanding of the current evidence and role of chatbots is another theoretical challenge in the field. This requires further feasibility studies, randomised controlled trials and, in a further step, systematic reviews and meta-analyses to determine the effectiveness of chatbots for clinical psychological research questions.

Methodological implications include information for the methodological optimisation of feasibility studies in internet interventions for people with chronic somatic diseases. This concerns the selection of target groups, recruitment measures, and diagnostics. The results on the applicability of utilised research methods may serve as a learning area for analysing similar research questions.

Besides these methodological implications, practical implications can be derived.

It is vital to different stakeholders like researchers, funders, or patients to implement resource-efficient projects. Testing whether a planned study design and intervention work before its extensive investigation on a large scale can help ensure this for all involved parties. Results of the smaller-scale trials in this dissertation point to necessary adjustments regarding internet interventions for people with chronic somatic disease and study designs to investigate treatment effectiveness and negative effects. Further, results could be used to identify improvement potentials regarding the implementation of resource-efficient projects. For example, in the ACTonDiabetes trial, diabetes

distress was demonstrated to be potentially well-addressable by the intervention. This might support the conduct of high-quality studies that yield robust results on effectiveness, provide the best possible interventions to patients, and help decision-makers in the field decide effectively and most reasonably which and how related projects can be funded. For example, publications two and three showed that ACTonDiabetes in its form with minor adaptations is well suited for a full-scale trial, while WIDeCAD in its current form should probably not be carried out because the risk of a failed trial would be relatively high.

The provision of internet interventions via chatbot could be an especially suitable mode of delivery for people with a chronic somatic disease in the future. They enable a high level of flexibility regarding the integration of interventions into everyday life and guidance with at the same time high scalability and low cost. Subsequent research could investigate if there is a need for a differentiated view on guidance in specific medical conditions like CAD. Dismantling studies to identify active ingredients would be a starting point for further research in this regard. For example, chatbot-based guidance could be compared to human guidance, and it could be examined whether potential subgroups profit differentially from different types and amounts of guidance. In the next step, it could be an aim to derive recommendations for the type and amount of guidance in individual fields. Additionally, results on SISU imply that research should also investigate chatbots with a resource-oriented approach in clinical samples enabling the investigation of SISU in a more robust trial design.

Taken together, these implications offer some fruitful starting points for further research in terms of theoretical, practical and methodological considerations in the field. Starting from these implications, which are firmly anchored in the results of the studies, future perspectives can be identified.

10.5 Future Perspectives

The spectrum of future perspectives in relation to the topic of this dissertation is broad, and innovative internet interventions are a fast-growing, technology-driven field. Some questions and ideas that have emerged in this thesis will be further discussed.

The results of the WIDeCAD study compared to the ACTonDiabetes study, reported in this dissertation and against the background of related work, give hints that there may be target group-specific differences that should be considered in mental health care. One factor that may not primarily linked to specific target groups could be the labelling of interventions. Whilst the WIDeCAD study and the analogue trial for people with cancer "W-Decide“ (German Clinical Trials Register (DRKS), DRKS00012536) advertised as "depression treatment“ yielded recruitment difficulties, the more resource-oriented labels of ACTonDiabetes as well as of the analogue trial in a population of people with cancer "ACTonCancer“ yielded no such recruitment issues (German Clinical Trials Register (DRKS), DRKS00013195). Provided that the therapeutic approaches compared are equivalent in terms of effectiveness (e.g. CBT and ACT), labelling could be taken into account to increase recruitment success. Qualitative studies could be conducted to determine if different intervention labelling affects intervention uptake.

Another idea would be to use sociodemographic characteristics when recruiting via website to adapt the labelling to individual characteristics or interests. For example, people with CAD who are older on average at the onset of the disease (Mendis et al., 2011) than, e.g. people with diabetes type 1 (Harjutsalo et al., 2010) may respond differently to different information presentations, e.g. prefer earnest vs more fancy approach. The website could capture such characteristics as age and adapt labelling correspondingly. However, studies will probably not enable absolutist recommendations for specific target groups in the sense that "this labelling is fundamentally better for the target group than the other“. Inter-individual differences between conditions and intra-individual changes regarding stages of disease might not be considered satisfactorily in this way.

Just-in-time adaptive interventions (=JITAI) could resolve this discussion as the technology enables high levels of adaptation to several inter-individual differences and needs at low cost. JITAIs could easily include sociodemographic aspects and then adapt the type and representation of contents accordingly. For example, it could be possible to adapt the appearance of an intervention to the socio-economic characteristics of participants in terms of their age, educational level or specific needs. In this way, ACTonCancer is being further developed into a JITAI for people with

breast cancer in the framework of the large-scale third party funded BetterCare project (Wöckel et al., 2021). By linking patients' diagnostic information to specific intervention contents, the intervention can adapt contents to, e.g. currently elevated distress levels of patients and deliver support strategies for immediate stress reduction. Not only will the adaptivity of content continue to develop, but also the diagnostic process will become smarter.

Taken together, a chatbot could then accompany participants through JITAIS, for example, and the type and scope of counselling could also be adapted not only to different target groups but also to the personal needs of the individuals receiving the information needed for this via Smart Diagnostics. Furthermore, different counselling formats could be combined if participants prefer traditional face-to-face interactions. Blended care approaches bring both worlds together by linking online and offline sessions. However, all these ideas are still pie in the sky. Studies are needed from phase I to phase III of clinical trials to support the field with evidence. In addition to feasibility trials and full-scale randomised controlled trials, micro-randomised trials should be considered to push the field forward (Klasnja et al., 2015). This methodology allows for the high-quality study of individual parts of intervention and could be more resource and time-efficient than conventional techniques (Klasnja et al., 2015). Additionally, close cooperation between disciplines (medical staff, psychologists, computer scientists) is needed to develop high-quality interventions. Project funding at this interface can be applied to promote pragmatic trials in this direction.

To complete the circle of this dissertation, it can be stated that new technologies could become part of mental/medical health care of chronic somatic diseases in the future. The future perspectives described contain many unresolved problems like many technologies being partly under- or un-evaluated, and evidence so far exists almost exclusively in limited research contexts. This outlook thus points to essential and exciting perspectives for future research.

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Declaration on Honour

I hereby certify that I have written this thesis independently and have not used any sources or aids other than those indicated, and that I have marked the passages taken over verbatim or in content as such and have observed the currently valid statutes of the Ulm University to ensure good scientific practice (§ 8 Abs. 1 Nr. 5 Rahmenpromotionsordnung).

I agree that the dissertation may also be used for the purpose of checking compliance with generally applicable scientific standards, in particular also by using electronic data processing programmes (§ 8 Abs. 1 Nr. 8 Rahmenpromotionsordnung).

Ulm, 2022, March 21 ……

(Signature)