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Online Support for Newly Diagnosed Cancer Patients: Development, Feasibility and Efficacy of the Intervention “STREss-Aktiv-Mindern” (STREAM)

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Astrid Grossert-Leugger Basel, Januar 2020

Frage nicht, was die Welt braucht.

Frage dich selbst, was dich lebendig macht, und gehe und tue das,

denn was die Welt braucht, das sind Leute, die lebendig geworden sind.

Howard Thurman (1899 - 1981)

Amerikanischer Philosoph, Theologe, Autor und Bürgerrechtskämpfer

Table of Content

Glossary of abbreviations and acronyms

ACT	Acceptance and commitment therapy
ANCOVA	Analysis of covariance
CBT	Cognitive-behavior therapy
DT	Distress thermometer
DBT	Dialectic behavioral therapy
EKBB	Ethikkommission beider Basel (in English: Ethics Committee of Basel)
EKNZ	Ethikkommission Nord und Zentralschweiz (in English: Northwest and Central Swiss Ethics Committee)
FA	Facebook advertisement
FACIT-F	Functional Assessment of Chronic Illness Therapy–Fatigue
GAW	Google AdWords
HADS	Hospital Anxiety and Depression Scale
HIN	Health Info Net
ITT	Intention to treat

PP	Per protocol
MBSR	Mindfulness-based stress reduction
NCCN	National Comprehensive Cancer Network
QoL	Quality of life
SNF	Swiss National Science Foundation
SSL	Secure Socket Layer
STREAM	**STRE**ss **A**ktiv **M**indern (in English: active stress reduction).
SUS	System usability scale
WHO	World Health Organization

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Abstract

Cancer is associated with high individual and societal burden worldwide, caused not only by mortality but also by morbidity and physical impairment of the patients. In addition, cancer frequently causes major psychological distress. Although distress screening programs aim to ensure appropriate psycho-oncological support, cancer patients often do not use these services. Therefore, the majority of newly diagnosed cancer patients lack psychological support.

The development and testing of the first web-based stress management intervention (STREAM: STREss-Aktiv-Mindern) for newly diagnosed cancer patients forms the main part of this thesis. The rationale for this *early* intervention was three-fold: First, distress in patients with cancer peaks shortly after the diagnosis [Fang et al., 2012], irrespective of the cancer type. Second, the period immediately after the diagnosis tends to be busy with diagnostic and therapeutic appointments. Therefore, self-management of time, location, and autonomy facilitated by web-based interventions might be of particular value to these patients [Andersson, 2016]. Third, successful early psychosocial interventions have shown a substantial potential to affect the course of the disease beyond psychosocial outcomes.

Although various web-based psychological tools have been available for at least a decade, such instruments have retained their evolutionary character. Healthcare professionals often fear to lose the therapeutic relationship with the patient which is known to play a role in the therapeutic effectiveness (e.g. [Orlinsky et al., 1994]). In line with the growing literature on web-based interventions for many mental and physical diseases, we aimed to include those patients who are currently not reached by conventional support options by providing web-based support that does not exclude the helpful therapeutic relationship.

Our findings showed that a web-based, minimal-contact stress management program is an attractive as well as time- and cost-effective way to provide psycho-

oncological support to newly diagnosed cancer patients. Use of our tool resulted in significant and clinically relevant improvement of the patient’s quality of life (QoL) and distress reduction.

1. Preface

The diagnosis of cancer inevitably changes the life of affected patients, both physically and emotionally. In Switzerland, around 40,000 people are diagnosed with cancer each year [Bundesamt für Statistik, 2016]. According to estimated incidences of cancer worldwide, more than 29 million new cases are expected in 2040 [Global Cancer Observatory, 2019]. The increasing cancer burden is due to several factors, including population growth and aging as well as the changing prevalence of certain causes of cancer linked to social and economic developments.

A cancer diagnosis can turn a person’s life upside down from one day to the next, and nothing is the same as it used to be. While medical care for such patients is usually ensured, mental support may be insufficient. Mental needs may be manifested by feelings of being lost, disorientated, depressed, anxious, or even ashamed. These feelings can result in the patients’ withdrawal from social life and entrapment in circles of thoughts. Fears, both the realistic ones as well as exaggerated ones, may paralyze the patients and prevent them from taking personal action. In the course of time, this often leads to a poorer QoL for the patients.

Cancer patients should receive tailored support during the early stages of their disease since this tends to be a highly vulnerable phase for affected individuals. This thesis is an integral part of an interdisciplinary research project conducted at the University of Basel to study the impact of non-drug interventions on treatment outcome in cancer patients. The project entitled “Non-drug interventions to enhance efficacy of drug treatment in cancer patients” was supported by the Swiss National Science Foundation (SNF) professorship funds awarded to Viviane Hess (Grant No. SNF

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This thesis is based on three publications accepted and published by peer-reviewed scientific journals (see Section 4 for the published papers and appendix for the published study protocol of the STREAM-1 trial). Our studies aimed to investigate whether newly diagnosed cancer patients are in need of support to handle their difficult situation. Moreover, we tested the usability, feasibility, and efficacy of the web-based program STREAM, an intervention tool for newly diagnosed cancer patients. The German acronym was formed from ***STRE***_ss_ ***A***_ktiv_ ***M***_indern_ (in English: active stress reduction).

2. Background

2.1 Impact of cancer on distress and quality of life

2.1.1 Distress

The number of cancer patients is increasing steadily in Switzerland [Arndt et al., 2016; Herrmann et al., 2013] and worldwide [Ferlay et al., 2019; Global Cancer Observatory, 2019]. Multimodal treatment regimens may prolong tumor-free survival times and extend the patient's life expectancy. A diagnosis of cancer elicits high levels of distress in the majority of patients, and every second cancer patient suffers from clinically relevant psychosocial distress [Mehnert et al., 2014; Mehnert et al., 2018]. The National Comprehensive Cancer Network (NCCN) guidelines define distress as a multifactorial, unpleasant experience of a psychological (i.e. cognitive, behavioral, emotional), social, spiritual, and/or physical nature that may interfere with the ability to cope effectively with cancer, its physical symptoms, and its treatment. Distress extends along a continuum, ranging from normal feelings of vulnerability, sadness, and fears to problems that can become disabling, such as depression, anxiety, panic, social isolation, and existential and spiritual crises [National Comprehensive Cancer Network, 2019]. Psychosocial distress encompasses emotional lability, rearranging of roles and responsibilities, change in appearance, change of plans, fear of recurrence, depression, and anxiety resulting in poorer QoL [Penedo et al., 2013; Rehse & Pukrop, 2003; Wu & Harden, 2015]. This might lead to a vicious cycle in that high levels of distress might reduce compliance with treatment and thus increase the side effects [Chambers et al., 2012; Park & Gaffey, 2007]. In turn, this will lead to a poorer QoL and diminished treatment tolerability [Duijts et al., 2011; Luebbert et al., 2001]. In the worst case, psychological distress may negatively affect the course of disease [Kim et al., 2017; Stagl et al., 2015]. Existing guidelines highlight the importance of understanding the patients' need of supportive care in relation to their individual perspectives [Adler &

Page, 2008; National Comprehensive Cancer Network, 2019]. This standard is widely accepted and is implemented in international guidelines. Moreover, it represents a criterion for fulfilling cancer center accreditation [Bultz et al., 2014; Pirl et al., 2014].

2.1.2 Quality of life

QoL has a different meaning for each individual. While one person derives the greatest satisfaction from spending time with his/her family and friends, another person thrives on traveling around the world. The World Health Organization (WHO) defined QoL as *"an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships, and their relationship to salient features of their environment"* [World Health Organization, 1993]. Today's medical opportunities help to save increasing numbers of cancer patients due to continuous advances in the clinical diagnostics and treatments. This advance has led to improved cure rates and longer survival times and goes along with having to deal with long-term side effects because of the toxicity of treatments. In recent years, the focus of cancer treatment has been increasingly shifted towards aspects of QoL, in addition to survival time. Recent reviews report evidence for a positive relationship between QoL and overall survival in cancer patients [Gotay et al., 2008; Quinten et al., 2009]. In contrast, anxiety present in half of the cancer population is inevitably associated with diminished QoL [Stark et al., 2002].

Besides prolonging survival time and managing treatment side effects, the individual perception of QoL has gained increasing importance in the past years. A recent article [Stickel & Goerling, 2018] provides an overview of the concept of QoL, emphasizing both its individuality and changeability with respect to cancer patients. The authors subsume the dependence of time and context and cite Aristoteles (384-322 BC)

"*…and often the same person changes his mind: when he becomes ill, it is health, and as long as he is healthy it is money."* This shift in the subjective assessment of QoL is reflected in today's clinical practice and must be taken into consideration when working with patients suffering from cancer. Moreover, surgery often leads to changes in physical perception and body image concerns [Avis et al., 2005; Fingeret et al., 2012]. Fatigue as a common early and chronic side effect of radiation therapy is reported in up to 80% of patients during radiation therapy and by 30% of patients at follow-up visits [Jereczek-Fossa et al., 2002]. Patients undergoing chemotherapy or combined radiotherapy-chemotherapy often suffer from fatigue on top of side effects such as nausea, vomiting, impacts on cognition, and pain [Carlson et al., 2004]. Fatigue is by far the most common symptom affecting QoL of cancer patients. Cancer-related fatigue is a *"draining, ongoing exhaustion that limits one's ability to enjoy life and engage in activities"* [National Comprehensive Cancer Network, 2003]. Moreover, fatigue may have implications for therapeutic decisions to interrupt the therapy or to decrease the dose. This in turn could influence the efficacy of the therapy.

2.2 Adjustment to cancer

A cancer diagnosis leads to a long process of individual adaptation. Adjustment to a disease such as cancer "*consists of the psychological processes by means of which the individual manages or copes with various demands or pressures*" (p18. [Lazarus, 1969]). Cognitive models of adjustment and coping assume that the interpretation of an (individual) stressful event determines the (individual) response to it [Folkman & Greer, 2000; Lazarus & Folkman, 1984]. Receiving the diagnosis of cancer is a stressful event associated with concerns about the threats and course of disease as well as everyday problems of organizing daily life, often accompanied with confusion of thoughts and feelings. Certain patients might view their cancer diagnosis as a challenge and will feel empowered to master the consequences. In contrast, other patients might feel extremely threatened and restricted in their scope of action and access to resources. In extreme cases, affected patients will contemplate their immediate death. Thus, the range of reactions to the diagnosis of cancer is broad. Mehnert et al. reported a 4-week prevalence rate of 31.8% for any mental disorder, with the most common comorbid disorders being adjustment disorder (11%), anxiety disorder (11%), and mood disorder (11%) [Mehnert et al., 2014]. Symptoms such as fear of recurrence or demoralization, which many cancer patients are facing are often recognized [Herschbach, 2015].

The model of Lazarus and Folkman [Lazarus & Folkman, 1984] describes two main appraisals of importance after an event. First, the model elucidates whether the event is perceived as stressful. The second question addresses the resources available to face the stressful event: "*Do I have the resources to face it*?" If patients answer the first question with "*yes*" and the second with "*no*", they will presumably declare to be stressed, or they will achieve high scores on the validated distress thermometer (DT; [Mehnert et al., 2006] [National Comprehensive Cancer Network, 2019]). The model has been extended to include meaning-based coping (Folkman, 1997; Folkman & Greer, 2000). Thus, the first and second evaluation processes (primary and secondary appraisals) have been supplemented by the individual search for meaning, by reflecting or modifying life goals and attempting to give the current (disease) situation a personal meaning.

Social-cognitive transition (SCT; [Brennan, 2001] is an extension of the model of Lazarus and Folkman. Its conceptualization offers an inclusion of the experience of the social world and refers to the psychological adaption processes including personal growth as a reaction to a life event [Parkes, 1971]. It is an attempt to account for the huge diversity of experiences that people with cancer report, ranging from positive personal growth to psychological “disorders”. Although the clinical derivation of the model is conclusive, an exact measurement of these variables is still lacking. Measures of self-efficacy, control, and coping as well as individual perception of QoL might be used as congruent concepts [Brennan, 2001].

2.3 Psycho-oncological support

In German-speaking countries, psycho-oncological care is mainly provided by psycho-oncology departments at the university hospitals (inpatient/outpatient) or cancer-counseling centers, e.g. the national cancer league (Krebsliga) in Switzerland or cancer aid (Krebshilfe) in Germany. In addition, psychologic/psychiatric private practices may provide outpatient services.

Additionally, numerous rehabilitation clinics make an important contribution to psycho-oncological care [Mehnert & Hartung, 2015]. To identify patients with marked distress and a need for psycho-oncological support, standard screening tools such as the DT are widely used [Donovan et al., 2014; Mehnert et al., 2006; Mitchell, 2007]. These screening methods have the potential to remove barriers and facilitate access to psychosocial services. Nevertheless, the majority of newly diagnosed cancer patients lack psychosocial support due to constraints on both the providers’ and the patients’ sides [Carlson, 2013; Carlson et al., 2004; Waller et al., 2013]. Consequently, measures and a better understanding of patients' need of supportive care are needed.

2.4 Psycho-oncological interventions

Psychotherapeutic manuals to address stress management in general are well known (e.g. [Kaluza, 2004; Strobel, 2018]). There are two specific manuals addressing stress management in cancer patients [Antoni, 2003a, 2003b, 2003c; Moorey & Greer, 2015]. Both manuals use the cognitive-behavior therapy (CBT) approach. Antoni developed a group intervention for women with breast cancer with the aim to increase personal awareness by psycho-education and the provision of coping strategies such as anxiety reduction and cognitive restructuration skills [Antoni, 2003a]. Morrey and Greer developed cognitive, behavioral, emotional, and interpersonal techniques to help people adjust to cancer in the challenging clinical environment of oncology and palliative care [Moorey & Greer, 2015]. A key aspect in the field of psycho-oncology is the concept of acceptance, which is "*the willingness to accept the cancer and its effects as they are at the present moment and not to actively try to influence them*" (p 79 [Geuenich, 2012]). Geuenich developed strategies to develop acceptance-enhancing skills. For her, acceptance of a cancer disease is the willingness to perceive the disease itself and its effects as existing [Geuenich, 2012]. The method is based on dialectic behavioral therapy (DBT, [Linehan, 2016]) and acceptance and commitment therapy (ACT; [Hayes et al., 1999]), both focusing on the concept of acceptance. DBT [Linehan, 2016] is based on CBT and places equal value on change and acceptance. This is of importance for the field of psycho-oncology because this theory supports the psychotherapeutic technique of confrontation with unpleasant feelings. People can only succeed if they perceive and accept their feelings and their triggers. Further, the term "double awareness" is used in the palliative context to describe a person's capacity to engage in the world while preparing for their impending death. The acceptance and commitment movement [Hayes et al., 1999] enriches the psycho-oncological field with skills to work with awareness and acceptance and supports cancer patients to cope with their fatal illness.

Psychosocial support for cancer patients is effective in alleviating distress and improving QoL including fatigue, the most common complaint of cancer patients [Carlson et al., 2004; Duijts et al., 2011; Fors et al., 2011]. Randomized controlled studies have shown that psychosocial interventions have significant positive effects in cancer patients. Cognitive behavioral techniques support patients to develop appropriate coping strategies and reduce anxiety, depression, and distress levels thus improving QoL [David et al., 2013; Naumann et al., 2012; Osborn et al., 2006; Rehse & Pukrop, 2003]. For example, Duijts et al. concluded in their review that behavioral techniques significantly reduce cancer-related fatigue (d = -0.16), depression (d = -0.336), and distress (d = -0.16) [Duijts et al., 2011]. Luebbert et al. found significant effects of relaxation techniques on emotional adjustment, depression (d = 0.54), and anxiety (d = 0.45) [Luebbert et al., 2001]. Zainal et al. demonstrated the effectiveness of mindfulness-based stress reduction (MBSR) in breast-cancer patients (stress reduction: d = 0.71, reduction of depression d = 0.58) [Zainal et al., 2013]. Moreover, psycho-oncological interventions may reduce side effects of cancer treatment [Antoni et al., 2009; Duijts et al., 2011; Kwekkeboom et al., 2012; Söllner & Keller, 2007; Wells et al., 2003]. For example, relaxation techniques have a small but significant effect on treatment-related symptoms such as pain (d = 0.43) and nausea (d = 0.45) [Luebbert et al., 2001].

2.5 Online psycho-oncological interventions

The use of the internet[1], which has become an integral part of all aspects of our lives, has the potential to provide more patients with psychosocial support. At least 70% of cancer patients use the internet as a source of information shortly after having been diagnosed [van de Poll-Franse & van Eenbergen, 2008]. Recent approaches of integrating the internet into the patient's care concepts include the setup of patient forums and information sites as well as therapeutic games [Andersson, 2016; Kato et al., 2008]. Web-based interventions are usually implemented as self-guided or therapist-guided internet or cell phone-based programs, following a predefined structure with a given number of modules or exercises to be completed. Blended interventions are integrated combinations of face-to-face therapy together with an online program [Barak et al., 2009]. Internet programs based on cognitive behavioral techniques with patient guidance by regular online contact with a healthcare professional have emerged as being particularly effective. For a range of psychological disorders, including anxiety disorders and depression in non-cancer patients [Buntrock et al., 2016; Kessler et al., 2009], therapist-guided online interventions seem similarly effective as face-to-face interventions [Andersson et al., 2014]. Online interventions offer advantages such as anonymity, which can be accompanied by increased openness or disinhibition [Suler, 2000] and may extend the user spectrum to patients with a low threshold for support uptake. Moreover, the written exchange and asynchronous communication allow for a well-founded, reflective expression and flexibility in scheduling. In addition, the contents of the program can be accessed repeatedly. However, there are a number of limitations

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[1] Note: In 2018, the American Medical Association (https://www.ama-assn.org/) proposed to use the lowercase for the term “internet“ due to its frequent use.

of this form of support. Online interventions are not suitable in an acute psychosocial crisis with suicidal tendencies or disorders that require immediate therapeutic action. Barriers to use online intervention are lack of basic computer skills or lack of access to an online device, as well as missing possibilities for written exchange. [Knaevelsrud et al., 2004]. A detailed overview of advantages and disadvantages of online therapy can be found in a recent publication [Schuster et al., 2018].

The success of web-based guided self-help tools in psychological disorders [Andersson, 2016; Andersson et al., 2014] has boosted our interest in online interventions in oncology. Such psychosocial tools are of particular merit to cancer patients living in rural areas or places far away from large cancer centers [Carlson et al., 2004]. Numerous piloted and on-going trials in cancer patients seek to define suitable indications, formats, and settings [Beatty et al., 2016]. The few larger randomized, controlled trials published so far [Carpenter et al., 2014; Hummel et al., 2017; van den Berg et al., 2015] show encouraging results with improvement in a number of relevant psychosocial domains, including coping with cancer [Carpenter et al., 2014], sexual functioning [Hummel et al., 2017], and distress [van den Berg et al., 2015] in breast cancer survivors.

2.5.1 User-friendliness of web-based interventions

User-friendliness often determines whether a website or internet program is used by the intended population [Gorlick et al., 2014]. The few existing guidelines (e.g. [Leykin et al., 2012] stress the importance of conducting formalized usability testing of web-based healthcare interventions in the target population to assess whether the end-user can work with the webpage during specific tasks. Usability is defined as "*the extent to which a product can be used by specified users to achieve specified goals with effectiveness, efficiency, and satisfaction in a specified context of use*" (ISO 9241-11 [International Standardization Organization, 1998]). In formalized usability testing, the observed usability problems are grouped to identify flaws within the system, ultimately leading to design improvements that remove these barriers [International Standardization Organization, 1998; Tullis & Albert, 2013]. Appropriately designed online tools can augment dissemination of psychosocial care by making participation convenient, confidential, and less stigmatizing [Leykin et al., 2012; Owen et al., 2004]. Nevertheless, high dropout rates [Baltanas et al., 2013; David et al., 2013] and low levels of commitment have been reported for some web-based interventions [Gorlick et al., 2014].

2.6 Objectives

Although distress-screening programs aim to ensure appropriate psycho-oncological support, cancer patients often do not use such services. We aimed to understand the acceptance and reasons of acceptance of psycho-oncological support.

The investigation of the first web-based stress management intervention STREAM for newly diagnosed cancer patients forms the main part of this thesis. The rationale for this early intervention was three-fold: First, distress in patients with cancer peaks shortly after the diagnosis [Fang et al., 2012], irrespective of the cancer type. Second, the period immediately after the diagnosis tends to be busy with diagnostic and therapeutic appointments. Therefore, self-management of time, location, and autonomy made possible by web-based interventions might be of particular value to these patients [Andersson, 2016]. Third, successful early psychosocial interventions have shown a substantial potential to affect the course of the disease beyond psychosocial outcomes [Temel et al., 2010]. We conducted a preparative usability testing with the aim to adjust the final website to the specific use by our target population. Usability testing of the tool was followed by the prospective randomized wait-list controlled trial to assess the following:

- Feasibility including patient’s characteristics, patient’s adherence, dropout rate, therapeutic alliance as well as the time required for psycho-oncological support.
- Efficacy of the intervention with respect to improved QoL and mood and lowered distress in newly diagnosed cancer patients.

3. Methods

3.1 Research projects

As outlined above, this thesis is based on two projects linked by contents in the same target population. My focus was the development of STREAM and its testing in the randomized, controlled trial entitled “Web-based stress management for newly diagnosed cancer patients (STREAM-1): a randomized, wait-list controlled intervention study” with the subproject “Usability testing of a newly developed stress management website for cancer patients” which was part of the development procedure. Furthermore, during my clinical work as psycho-oncologist at the Department of Medical Oncology at the University Hospital Basel, I contributed to the project “Understanding why cancer patients accept or turn down psycho-oncological support: A prospective observational study including patients’ and clinicians’ perspectives on communication about distress*”*.

The following section summarizes the methodology of each project. These projects influenced each other by transferring the findings from clinic to science, and vice versa. Because of the focus of the various studies, the sequence of their description is as follows: acceptance psycho-oncological support, usability testing of STREAM, as well as feasibility and efficacy testing of STREAM.

3.1.1 Acceptance of psycho-oncological support

For support options to be effective, the specific needs and limitations of the intended population have to be known. We analyzed the willingness of cancer patients to accept psycho-oncological support as part of the project entitled “Understanding why cancer patients accept or turn down psycho-oncological support: A prospective observational study including patients’ and clinicians’ perspectives on communication about distress” [Zwahlen et al., 2017]. This study was approved by the local ethics committee (EKNZ 220/13) and was funded by the Swiss Cancer League (Grant No.

KLS 3186–02-2013). The study took place at the oncology outpatient clinic of the University Hospital Basel, Switzerland.

We conducted a prospective, observational study in a Swiss oncology outpatient clinic and assessed distress, intention to use psycho-oncological support, and use of the psycho-oncology service by using the DT, a semi-structured interview, and hospital records. Our population included cancer outpatients who presented at the outpatient clinic for the first time. Patients were eligible when fulfilling the following inclusion criteria: aged ≥18 years, fluent in German, not being physically or cognitively impaired in a way that impeded study participation, and having at least one further consultation planned with an oncologist. We analyzed the data with a mixed-methods approach. Details of this analysis are described below in section 4. The detailed method of the entire trial is described elsewhere [Zwahlen et al., 2017].

3.1.2 Usability testing of STREAM

To ensure that online health interventions meet the needs of cancer patients and is accepted by them, structured usability testing to identify usability issues should be addressed early during development of a new program. For the preparation of the subsequent trial STREAM, the usability trial called “Usability testing of a newly developed stress management website for cancer patients” was conducted in cooperation with the computer laboratory of the Center of Human-Computer Interaction of the Department of Psychology at the University of Basel. The local ethics committee (EKBB) approved the trial (EKBB 251/13)[2]. The Swiss National Science Foundation (Grant No. PP00P3_139155/1 awarded to Viviane Hess; Grant No. PP00P1_144824

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[2] Note: Between the two projects (usability trial and the main STREAM trial), EKBB was renamed to Northwest and Central Swiss Ethics Committee (EKNZ).

awarded to Thomas Berger), and Swiss Cancer Research (Grant No. KFS-3260-08-2013 awarded to Corinne Urech) supported this study. Usability of a newly developed online stress management program was prospectively assessed in patients with solid tumors undergoing systemic treatment.

In an academic computer laboratory of the University of Basel, each patient completed 16 tasks concerning the key components of the program, e.g. website navigation, login-in to secure area, completing forms, accessing audio files, and contacting the trial team. Usability problems during these tasks were identified via the think-aloud method. This method encourages patients to think aloud while solving a problem, thereby giving observers an insight into the participant's cognitive processes. General usability was tested with the system usability scale (SUS). The usability testing process and key aspects of online intervention tools for the final version of STREAM are presented below.

3.1.3 Feasibility and efficacy testing of STREAM

The research project was entitled “Web-based stress management for newly diagnosed cancer patients (STREAM-1): a randomized, wait-list controlled intervention study”. The local Ethics Committee approved the study (EKNZ 339/13). The Swiss National Science Foundation (SNSF PP00P3_139155/1) and Swiss Cancer Research (KFS-3260- 08-2013) supported this study financially.

In this prospective, randomized, controlled intervention study (Figure 1), patients were randomized 1:1 (mixed randomization scheme using unequal block randomization) to either the intervention group or wait-list control group. Patients were stratified according to their baseline stress level (DT ≥5 vs <5; [Mehnert et al., 2006]). A total of 129 newly diagnosed adult (>18 years) cancer patients who had started first-line systemic treatment (including chemotherapy, hormonal treatment, or targeted therapy) or radiotherapy not longer than 12 weeks before were included after giving informed consent. Patients who underwent treatment for a first relapse of a tumor previously treated with curative intent were also eligible. Patients were required to read and write in German, have internet access, as well as basic computer skills. Assessment took place at three time points (see Figure 1). The intervention consisted of eight modules with weekly written feedback by a psychologist ("minimal contact") based on well-established stress management manuals including downloadable audio-files and exercises.

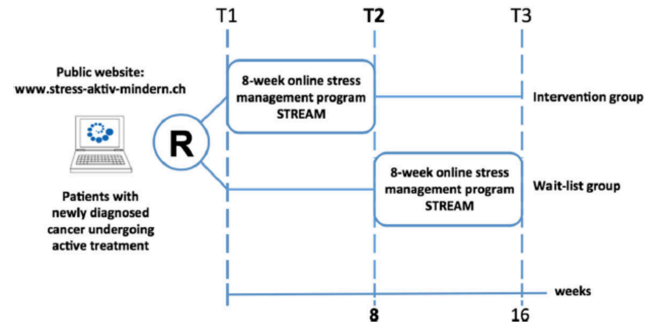


Fig. 1 Study design

Figure 1. Study design: Web-based stress management for newly diagnosed cancer patients (STREAM-1): a randomized, wait-list controlled intervention study, published in [Grossert et al., 2016].

The aim of this study was to evaluate efficacy in terms of improvement in QoL as well as decrease in anxiety and depression, as compared to patients in the wait-list control group. All analyses were done for the intention-to-treat (ITT) population defined as all patients who underwent randomization. The per-protocol (PP) population included all patients who completed the program in the intended time frame, i.e. a maximum of 16 weeks between the time of randomization and T2 assessment which was twice the minimal duration of the program.

To demonstrate a 9-point difference [Naumann et al., 2012] in the ‘Functional Assessment of Chronic Illness Therapy–Fatigue’ (FACIT-F) questionnaire total score between baseline and T2 (after 8 weeks) in the intervention group with a statistical power of 0.80 at a significance level of 0.05 (two-sided), 60 participants were required per group. Minimal ‘clinically meaningful differences’ are not well defined but have previously been set between 7 and 9 points, both as intra-individual changes and differences between groups [Cella et al., 2002; Temel et al., 2010]. Secondary endpoints included distress measured with the DT [Mehnert et al., 2006] and anxiety/depression measured with the Hospital Anxiety and Depression Scale (HADS; [Zigmond & Snaith, 1983]. Efficacy outcomes were modeled with analysis of covariance (ANCOVA), using the post-intervention score (T2) as dependent variable, the pre-score (T1) as covariate, and group allocation (intervention vs control) as independent variables. ANCOVAs were further adjusted for the stratification factor ‘distress’ (DT ≥5 vs <5). To assess the robustness of the results, sensitivity analyses were conducted for all outcomes in the PP population. For further details of the trial see study protocol [Grossert et al., 2016] in the appendix. The results were published in the Journal of Clinical Oncology [Grossert et al., 2018] and are presented in section 4.

3.2 STREAM

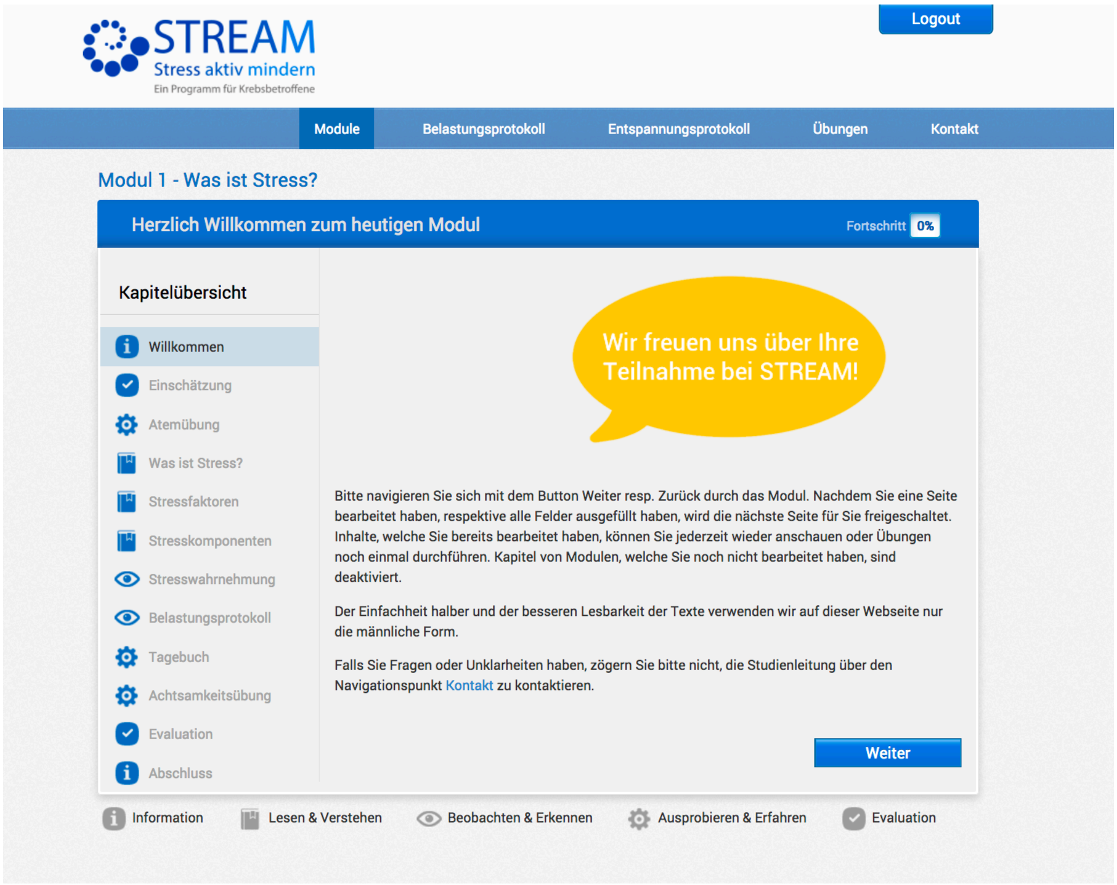
This section outlines the contents of the eight-week program, focusing on the topics covered in each part. We intended to develop a program for patients in the early phase of disease that diminishes their distress caused by the diagnosis and symptoms of their illness.

3.2.1 Structure

STREAM is an eight-module program covering the following sections: 1) overall introduction to stress; 2-4) specific nature of stress and coping with it on levels of the body, cognition, and emotions; 5) mindfulness and acceptance of thoughts and emotions; 6-7) activation of resources, and 8) summary. Table 1 provides an overview of the content and structure. Five icons guide the participants through the modules as well as the entire program (see Figure 2). The program is a guided intervention tool, which implies that guidance is provided page-by-page and module by module. Every edited page will remain accessible and visible during completion of the program. Each module should be completed in 60 to 90 min. Participants are asked to complete one module per week. Thus, completion of the full program takes eight weeks in total.

Module		Psychoeducation	Reflection on status	Strategies
1.	**Introduction: What is stress?**	Nature of stress in general and in specific cancer related situations	My individual stressor Stress protocol	Diary[b] Body scan[a] Stress protocol [b]
2.	**Body stress reduction**	Bodily sensations during stress and side-effects of anticancer treatment	Relaxation protocol	Progressive Muscle Relaxation [a] Strand promenade[a] Relaxation protocol[b]
3.	**Cognitive stress reduction**	Thoughts and their interaction with emotions and bodily sensations	My negative thought patterns	Negative thought cycle[a] Relationship of body position and thoughts[b] Thinking styles and reflextion[b] Thoughts on clouds[a]
4.	**Emotional stress reduction**	Feelings and cancer-related emotions as anxiety and worries were explained	My feelings and worries	Mountain meditation[a] Emotional emergency kit[a]
5.	**Mindfulness and acceptance of thoughts and emotions**	Meaning of mindfulness and acceptance and their implementation in daily life in contrast to the active strategies learned in modules 1-4	My definition and experiences with acceptance	Acceptance story [a,b] Body scan[a,b] Integration of mindfulness[b] Winter walk[a] Awakening spring[a]
6.	**Activation of resources: quality of life and pleasure**	Introduction of models of the balance between burden and resources	My individual resources	Health-cycle [b] Planning activities[b] Week planner [b] Friendly feelings with our own body[a] Enjoyment training[b]
7.	**Activation of resources: social network and communication skills**	Social network and the role of a supportive environment	My individual social network and current needs	Communication skills[b] Strand promenade[a] Winter promenade[a] Awakening spring[a]
8.	**Summary**	Concluding an overview and documentation of the last 7 weeks	My experiences with the program	Four seasons[a]

Table 1. Content of the web-based stress management program STREAM
a) Audio file: story, relaxation, or guided imaginary exercise, b) Instructions and worksheets



Bitte navigieren Sie sich mit dem Button Weiter resp. Zurück durch das Modul. Nachdem Sie eine Seite bearbeitet haben, respektive alle Felder ausgefüllt haben, wird die nächste Seite für Sie freigeschaltet. Inhalte, welche Sie bereits bearbeitet haben, können Sie jederzeit wieder anschauen oder Übungen noch einmal durchführen. Kapitel von Modulen, welche Sie noch nicht bearbeitet haben, sind deaktiviert.

Der Einfachheit halber und der besseren Lesbarkeit der Texte verwenden wir auf dieser Webseite nur die männliche Form.

Falls Sie Fragen oder Unklarheiten haben, zögern Sie bitte nicht, die Studienleitung über den Navigationspunkt Kontakt zu kontaktieren.

Figure 2. Welcome page of module 1, concerning the topic “What is stress”. The five icons (information; reading and understanding; observing and recognition; testing and experiencing; evaluation) navigate the user as required.

At the beginning of every module, distress level and actual motivation to work on the program is evaluated. Then, the specific contents are introduced, starting with a short mindfulness breathing exercise. The specific contents include (a) text-based psycho-education, (b) reflection on the current individual emotional status, and (c) acquisition of strategies including exercises. Within each module, exercises with respect to relaxation techniques and guided-imagery exercises are available as audio files that can be downloaded to various devices (e.g., PC/Mac, tablets, smart phones, MP3 players). Patients are encouraged to use the audio files daily. The final page of each module evaluates the anticipated therapeutic benefit and criteria of usability of the website.

3.2.2 Content

The STREAM program is based on well-described and established stress management intervention manuals [Angenendt et al., 2007; Antoni, 2003a; Geuenich, 2012; Kaluza, 2004; Weis et al., 2006], which we adapted to the participants' situation of suffering from cancer and its treatment as well as to the instrument's use as a web tool. The program primarily aims to improve intra- and interpersonal coping strategies to enhance QoL and reduce the distress perceived by newly diagnosed cancer patients. The breathing exercises suggested to the users before starting to work on the modules were specifically designed to help the patient focus on a new topic. The following paragraphs detail the contents of each module.

1. Overall introduction: This module focuses on the introduction and psycho-education of the nature of stress in general and cancer-related situations in particular. Patients are made aware of their individual stressors and the specific stress reaction to this severe disease. Apart from suggesting a breathing exercise, the module teaches a first relaxation technique and encourages participants to write a diary focusing on their daily stressors and emotions.

2. Body stress reduction: The reaction to stressful events of the body is addressed, and participants are encouraged to reflect on their individual perception. Information on side effects of the therapy and coping strategies are provided. Relaxation techniques such as visual imagery, progressive muscle relaxation, and mindfulness-based exercises are introduced.

3. Cognitive stress reduction: The cognitive model of adjustment and coping [Lazarus & Folkman, 1984] when faced with cancer are presented. Again, the focus is on detecting and identifying one's own helpful and unhelpful cognitive patters (e.g. all-

or-nothing thinking, selective abstractions, over-generalization). Exercises are provided to work on these unhelpful patterns and “stressful” thoughts. In this module, participants detect their automatic thinking in connection with their illness and learn to identify their negative thoughts. Strategies to provide alterative thought options in response to such automatic thinking are provided.

4. Emotional stress reduction: This module covers the emotional reaction to the disease and treatment by analyzing individual emotions and identifying strategies to cope with strong emotions.

5. Mindfulness and acceptance of thoughts and emotions: This module presents a more meaningful and acceptance-based approach as an additional coping strategy. Participants are encouraged to implement these strategies in their daily lives. In addition, patients learn how changes in their attitude can be helpful for coping with life under the new condition.

6. Activation of resources: QoL and pleasure: Some patients experience a complete change of their lives after their cancer diagnosis. Therefore, this module focuses on re-activating previous resources or developing new resources to improve their QoL. Exercises help patients to identify the most effective source of power at the moment and how to incorporate them in their everyday life in combination with weekly activity scheduling.

7. Activation of resources: Social network and communication skills: This module focuses on resources in connection with the patient’s social network. The patient’s disease affects not only his/her own life but tends to impact on the entire social network. Patients and their relatives and friends may have difficulty in communicating about the illness and its impact. This module introduces various communication strategies and suggests methods to cope with a deficient or absent social network.

8. Summary: This module provides an overview of the previous seven modules and encourages patients to reflect on their individual thought processes.

3.2.3. Minimal contact

As the program is a minimal-contact tool, the responsible therapist is due to respond by secure integrated e-mail after the participant has completed a module, i.e. after one week. Patients can use the secure chat function to contact the psychologist at any time, and an answer is provided within three working days. The underlying therapeutic attitude is based on a humanistic approach, with the therapist being empathetic and appreciative of the patient's problems with the ultimate aim to support the patient's self-efficacy. This semi-structured contact includes four sections: a) appreciation, b) understanding, c) embedding, supporting, and facilitating, and b) closing (see Table 1 for module contents). In case of persisting problems (e.g. suicidal ideation), clear recommendation for further assistance (e.g. face-to-face therapeutic support, psychiatric emergency care) is provided. Supervision and intervision of the therapists are conducted on a weekly basis.

3.2.4 Technical realization

The use of web-based healthcare interventions is growing rapidly, enabling certain aspects of mental healthcare to be delivered directly to the patient without face-to-face interactions. To develop a user-friendly program, we cooperated with the professional software engineering company YooApplication (Basel, Switzerland). The webpage was developed individual on the basis of Microsoft .NET Frameworks 4.5. The application is divided into a public, an user area and a back-end area for supervision and support. In the public area, information regarding the STREAM program and trial was presented[3]. Potentially interested participants were able to register using a digital contact form generating an e-mail to an official email account of the University Hospital

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[3] www.stress-aktiv-mindern.ch [STREAM, 2016]

of Basel (stream@usb.ch). This warranted secure data transfer using the Health Info Net (HIN) system from the provider side. Due to the confidential personal data, eligibility and assessment of the potentially interested persons took place outside the platform [Grossert et al., 2016]. After enrollment and group allocation participants got automatically generated login data and password for the user area[4]. On each internet page, the Secure Socket Layer (SSL) cryptographic technique with its own certificate warranted secure data transfer. At the back-end area for supervision and support, the responsible psychologist had read-only access to module progress and could write individual feedback.

Furthermore, the company VIZUAL Graphic&Code (Luzern, Switzerland) for the logo development (Figure 3) and Typo.d (Reinach, Switzerland) for design development professionally supported the visual appearance.

Figure 3. Logo.

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[4] For an inside into the program STREAM see section videos on http://www.stress-aktiv-mindern.ch/Medien [STREAM, 2016]

4. Summary of results - Publications

4.1 Focusing on cancer patients' intention to use psycho-oncological support: a longitudinal, mixed-methods study

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PAPER

WILEY

Focusing on cancer patients' intentions to use psychooncological support: A longitudinal, mixed-methods study

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Abstract

Objective: Distress screening programs aim to ensure appropriate psychooncological support for cancer patients, but many eligible patients do not use these services. To improve distress management, we need to better understand patients' supportive care needs. In this paper, we report the first key finding from a longitudinal study that focused on patients' intentions to use psychooncological support and its association with distress and uptake of the psychooncology service.

Methods: We conducted a prospective, observational study in an Oncology Outpatient Clinic and assessed distress, intention to use psychooncological support, and uptake of the psychooncology service by using the Distress Thermometer, a semistructured interview, and hospital records. We analyzed data with a mixed-methods approach.

Results: Of 333 patients (mean age 61 years; 55% male; 54% Distress Thermometer ≥ 5), 25% intended to use the psychooncology service (yes), 33% were ambivalent (maybe), and 42% reported no intention (no). Overall, 23% had attended the psychooncology service 4 months later. Ambivalent patients reported higher distress than patients with no intention (odds ratio = 1.18, 95% confidence interval [1.06-1.32]) but showed significantly lower uptake behavior than patients with an intention (odds ratio = 14.04, 95% confidence interval [6.74-29.24]). Qualitative analyses revealed that ambivalent patients (maybe) emphasized fears and uncertainties, while patients with clear intentions (yes/no) emphasized knowledge, attitudes, and coping concepts.

Conclusions: We identified a vulnerable group of ambivalent patients with high distress levels and low uptake behavior. To optimize distress screening programs, we suggest addressing and discussing patients' supportive care needs in routine clinical practice.

KEYWORDS

cancer, Distress Thermometer, health-care delivery, needs, oncology, psychological support, psychooncology, reasons, screening, uptake

1 | BACKGROUND

Cancer patients with untreated, high levels of psychosocial distress are at risk for nonadherence to cancer treatment,[1] reduced quality of life,[2] and comorbid mental disorders.[3-6] Psychooncological interventions can effectively reduce distress,[7] but many eligible patients do not take advantage of support services.[8,9] A third of all cancer patients show clinically significant levels of psychosocial distress,[3] but more than half of them do not want psychooncological support (42-75%),[10-15] although many patients with less distress do want support (10-44%).[11,15-17] Even patients who want and are offered psychooncological support do not always use these services.[18] Guidelines highlight the need to understand patients' supportive care needs to remove barriers and facilitate access to psychosocial services.[8,18-20]

Salmon et al[20] referring to Jonathan Bradshaw[21] recently brought patients' supportive care needs into focus by acknowledging that there is not only a *normative need* for support (defined by experts), indicated by an elevated distress score on the Distress Thermometer (DT) or other screening instruments, but also a *felt need* for support like a wish or desire that can become an *expressed need* for support, indicated, for example, by an expression of clear intent to use the known and available psychooncology service. Previous studies examined why a cancer patient's distress level did not always conform to their wish for support or adherence to services.[10,17,18,22-25] Most studies have focused on patients with high distress levels, and few used qualitative methods to understand patients' needs.[26,27]

We took an inductive, qualitative approach to understanding patients' supportive care needs without dividing them a priori into low- and high-distress groups. Our longitudinal mixed-methods design supplemented qualitative analysis with quantitative assessment of distress and uptake of the outpatient psychooncology service in a longitudinal mixed-methods design. We formulated 3 research questions: (1) What proportion of cancer patients intends, maybe intends, and does not intend to use the psychooncology service? (2) How are patients' intentions associated with distress and uptake of service? (3) Why do patients intend, maybe intend, and not intend to use the psychooncology service?

2 | METHODS

We report findings from a prospective, observational study in the Oncology Outpatient Clinic of the University Hospital Basel (Switzerland). Our methods are briefly outlined below; we have described them in more detail elsewhere.[28]

2.1 | Participants

Cancer outpatients who presented for the first time and used the outpatient oncological care at the clinic were eligible when fulfilling the inclusion criteria: ≥18 years, fluent in German, not being physically or cognitively impaired in a way that impedes study participation, and having at least 1 further consultation planned with an oncologist.

2.2 | Standard screening and referral procedure

Based on a stepped-care model,[19] patients were routinely screened with the DT at their first outpatient consultation for psychosocial distress. A nurse asked patients to fill in the DT, which patients then handed to the oncologist. All patients were given written information about the outpatient psychooncology service. The service is available for free and on short notice for all outpatients. Oncologists were briefed to address psychosocial distress during the first consultation and to recommend the service to patients, based on a clinically relevant distress level (DT ≥ 5), their clinical judgment, or the patient's wish.

2.3 | Study procedure

Oncologists screened cancer patients for interest to participate. The study team informed interested patients about the study, obtained informed consent, and interviewed participants an average of 15 days after the first consultation. Semistructured interviews were conducted in German and over the phone or face-to-face. Interviewers (TT and 7 Master's level students) relied on a manual. They were trained to use comprehension questions, reflection, and summaries to clarify mutual understanding; to take notes on participants' answers to open-ended questions during the interview, verbatim if possible; and to make postscripts of the interviews immediately afterward.[29] This study complied with the Declaration of Helsinki. The local ethics committee approved the study (Ethikkommission Nordwest-und Zentralschweiz, ref. no.: EK220/13).

2.4 | Measures

2.4.1 | Sociodemographic and clinical characteristics

Patients' sociodemographic data were recorded during the interview. Clinical data were collected from patients' medical records.

2.4.2 | Psychosocial distress screening

We used the German version of the National Comprehensive Cancer Network DT to assess self-reported psychosocial distress on a visual analogue scale from 0 to 10.[30] The 1-item screening tool shows good reliability and validity and has a cutoff value of ≥5 for clinically significant levels of psychosocial distress (from 0 “no distress” to 10 “extreme distress”).[30]

2.4.3 | Intention and reasons for uptake of psychooncological support

We asked the participants about their prospective intention during the interview: “Do you intend to uptake the outpatient psycho-oncological support service in the next months?” The interviewer categorized the participants' responses into 3 answers (yes/maybe/no), followed by an open-ended question: “What are the reasons why you do [may/not] intend to use the outpatient psycho-oncological support service?”

2.4.4 | Uptake of the outpatient psychooncology service

We defined uptake as having attended at least one appointment at the outpatient psychooncology service within 4 months after study entry and retrieved this information from hospital records.

2.5 | Data analyses

2.5.1 | Quantitative analyses

We conducted descriptive analyses for sociodemographic and clinical data. To determine the association between a priori selected sociodemographic variables, which are known to predict the use of psychological support, distress, and intention, we performed a multinomial logistic regression analysis. To determine the association between intention and uptake, we performed a logistic regression analysis. Results were presented as odds ratios with 95% confidence intervals. The level of significance was set at $P < .05$. Analyses were conducted by using SPSS Statistics version 22.0 (IBM, Armonk/NY, 2013).

2.5.2 | Qualitative analyses

We used content analysis to examine reasons for uptake of the psychooncology service.[31] This standardized, inductive approach analyzes qualitative data descriptively, adding a level of interpretation.[32] To guarantee high-quality content analyses, a team of trained researchers (AG, DZ, and TT) discussed the patients' reasons in a multistep procedure. First, we read the answers of the patients several times, divided the participants' answers into single reasons, and collected ideas about categories. Second, we gathered categories in a sample of 60 patients and refined them through an iterative process. Third, we coded reasons of all patients into categories, discussed inconsistence of assignment until consensus was reached, and assessed interrater- reliability by using Cohen kappa statistics (κ). Additionally, we identified main themes across categories. Analyses were conducted by using MAXQDA software version 12.2.0 (VERBI Software, Berlin, 2016).

3 | RESULTS

3.1 | Participant characteristics

Of 1240 outpatients who attended the clinic during 2013 to 2016 for an outpatient consultation, 484 were ineligible because of no further consultation, not being fluent in German, or being physically or cognitively impaired. Of all patients who attended the clinic, 756 (61%) were eligible for inclusion (Figure S1). In total, n = 333 patients completed the study (Table 1).

TABLE 1 Participants' sociodemographic and clinical characteristics

Participants (n = 333), Unless Otherwise Stated	n	%
Age, in Years		
Mean (SD)	60.5 (14.0)	
Range	19-93	
Sex		
Female	151	45.3
Male	182	54.7
Education		
Low (9th grade or less)	31	9.3
Middle (apprenticeship/high school)	186	55.9
High (diploma/university degree)	116	34.8
Living with a partner		
Yes	233	70.0
No	100	30.0
Living with children		
Yes	72	21.6
No	261	78.4
Distress thermometer[a]		
DT score 0-4	132	46.5
DT score 5-10	152	53.5
Time after initial cancer diagnosis, in weeks		
Median (range)	4 (0-264)	
Cancer type[b]		
Breast cancer	67	20.1
Thoracic malignancies	59	17.7
Hematologic malignancies	51	15.3
Genitourinary cancer	28	8.4
Melanoma/skin cancer	27	8.1
Gastrointestinal (noncolorectal) cancer	22	6.6
Central nervous system tumors	16	4.8
Others	64	19.2
Treatment approach		
Palliative	128	38.4
Curative	205	61.6
Current treatments (multiple treatments possible)		
Systemic treatment[c]	298	89.5
Radiotherapy	109	32.7
Surgery	34	10.2
No treatment/watch-and-wait/others	21	6.3

Abbreviations: SD, standard deviation; DT, Distress Thermometer.

[a] n = 284, DT from n = 49 patients missing due to nondelivery of the DT by clinical staff (n = 18), not being provided by patients (n = 22), and lost documents (n = 9).

[b] One participant with 2 cancer types.

[c] Systemic treatment includes chemotherapy, immunotherapy, hormone therapy, and targeted therapy.

3.2 | Distress, intention, and uptake of the psychooncology service

Of all participants, 53.5% showed high levels of psychosocial distress ($DT \geq 5$); distress was normally distributed among all participants. Overall, 83 patients (25%) intended to use the psychooncology service (yes), 111 patients (33%) were ambivalent (maybe), and 139 patients (42%) did not intend to use the service (no). We found high distress scores ($DT \geq 5$) in 71% of patients with yes, 56% of patients with maybe, and 42% of patients with no intention. After 4 months, 77 patients (23%) had used the service at least once (54 with yes intention [65% of all yes], 13 with maybe intention [12% of all maybe], and 10 with no intention [7% of all no]). Figure 1 shows distributions of uptake stratified according to levels of distress and intentions.

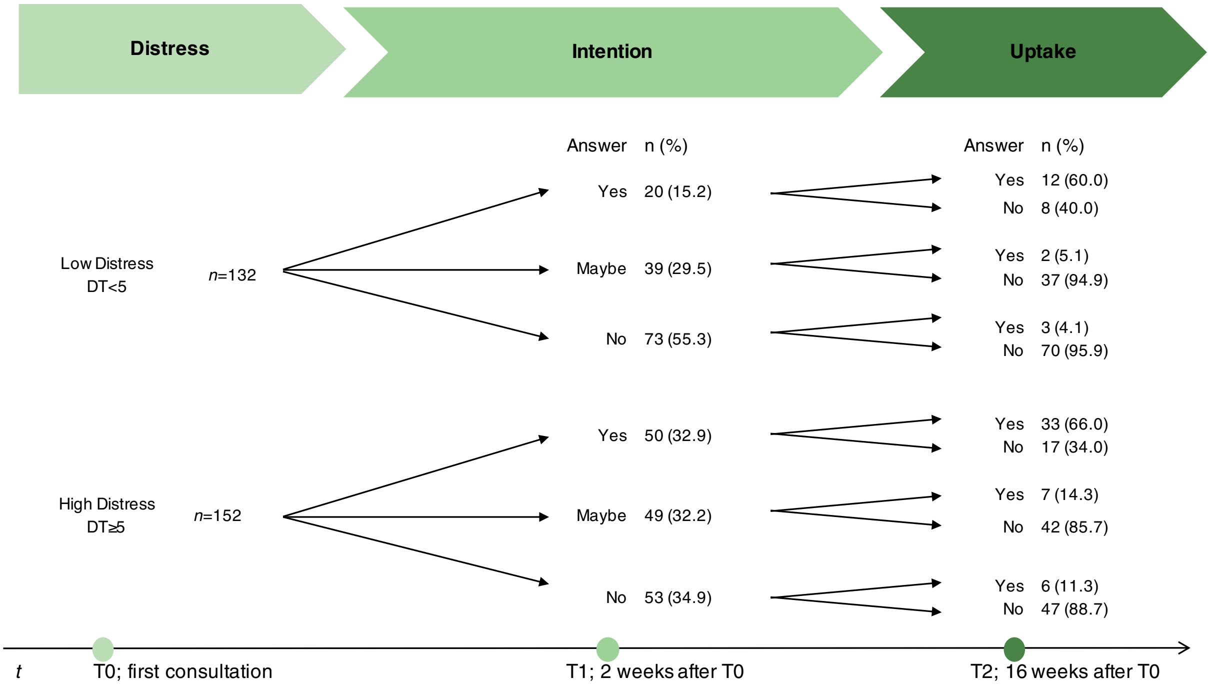

FIGURE 1 Description of patients' distress, intention, and uptake by distress level. Abbreviations: DT, Distress Thermometer; T0, screening; T1, baseline; T2, follow-up

In a multinomial logistic regression, patients with yes intention and patients with maybe intention were significantly more distressed than patients with no intention (yes: mean = 5.8 [SD = 2.4]; maybe: mean = 5.0 [SD = 2.6]; no: mean = 3.9 [SD = 2.7]). Age, sex, and education did not differ between intention groups (Table 2A). In a logistic regression analysis, patients with maybe and no intention showed significantly lower uptake behavior than patients with yes intention (Table 2B). This result did not materially change after adjustment for sociodemographic variables (data not shown).

3.3 | Reasons for yes, maybe, or no intention

Patients gave a total of 734 reasons, averaging 2.2 reasons per patient (min. 1, max. 6 reasons). Content analysis identified 32 categories of

TABLE 2 Associations among sociodemographic variables, distress, and intention as well as intention and uptake

(A) Multinomial Regression Analysis of Sociodemographic Variables and Distress on Intention

	Intention Yes vs No[a]			Intention Maybe vs No[a]			Intention Yes vs Maybe[b]		
	B (SE)	OR [95% CI]	*P* Value	*B* (SE)	OR [95% CI]	*P* Value	*B* (SE)	OR [95% CI]	*P* Value
Distress (DT 0-10)	0.28 (0.06)	1.32 [1.17-1.49]	<.001**	0.17 (0.06)	1.18 [1.06-1.32]	.003*	0.11 (0.06)	1.12 [0.99-1.26]	.078
Age	−0.02 (0.01)	0.98 [0.96-1.00]	.107	−0.01 (0.01)	0.99 [0.97-1.01]	.406	−0.01 (0.01)	0.99 [0.97-1.01]	.410
Sex (0 = male, 1 = female)	0.19 (0.32)	1.21 [0.65-2.24]	.553	0.20 (0.29)	1.22 [0.69-2.14]	.497	−0.01 (0.33)	0.99 [0.52-1.88]	.980
Education (0 = low, 1 = high)	−0.14 (0.33)	0.87 [0.46-1.66]	.672	−0.11 (0.30)	0.90 [0.50-1.62]	.722	−0.03 (0.34)	0.97 [0.50-1.88]	.924

(B) Logistic regression analysis of intention on uptake

	B (SE)	OR [95% CI]	*P* Value
Intention yes vs no[a]	3.18 (0.40)	24.02 [10.95-52.71]	<.001**
Intention maybe vs no[a]	0.54 (0.44)	1.71 [0.72-4.07]	.22
Intention yes vs maybe[b]	2.64 (0.37)	14.04 [6.74-29.24]	<.001**

Note. (A) Model χ^2 (8) = 28.94, $P < .001$, n = 284, Nagelkerke $R^2 = 0.110$. Education was dichotomized into "low/medium" (less than ninth grade/apprenticeship/high school) and "high" (diploma/university degree). (B) Model χ^2 (2) = 100.66, $P < .001$, n = 333, Nagelkerke $R^2 = 0.395$.

Abbreviations: *B*, Beta coefficient; SE, standard error; OR, odds ratio; CI, confidence interval; *P* value, significance level; DT, Distress Thermometer.

[a] Reference group *no* intention.

[b] Reference group *maybe* intention.

*$P < .05$.

**$P < .001$.

TABLE 3 Ranking order of categories of reasons for patients' (yes/maybe/no) intention to use the psychooncology service (n = 333)

Intention								
Yes (n = 83)			Maybe (n = 111)			No (n = 139)		
Rank	Categories	% (n)	Rank	Categories	% (n)	Rank	Categories	% (n)
1	[ATT1] Yes/psychooncologist is an expert	40% (33)	1	[DIS1] Maybe/fear of deterioration	46% (51)	1	[SUP2] No/social support (family and/or friends)	45% (62)
2	[COP1] Yes/support as means for empowerment and self-help	30% (25)	2	[SUP2] No/social support (family and/or friends)	25% (28)	2	[DIS8] No/subjective emotional and physical well-being	33% (46)
3	[DIS1] Yes/fear of deterioration	25% (21)	3	[DIS8] No/subjective emotional and physical well-being	24% (27)	3	[ATT9] No/psychologists are not helpful	19% (27)
4	[COP4] Yes/information and counseling	19% (16)	4	[DIS5] Maybe/uncertainty of current situation	14% (16)	4	[COP10] No/self-determination	19% (26)
5	[DIS2] Yes/bad news/shock	18% (15)	5	[DIS2] Maybe/bad news/shock	12% (13)	5	[COP9] No/self-management	14% (20)
6	[ATT6] Yes/recommendation	13% (11)	5	[ATT7] No/information is helpful and sufficient	12% (13)	6	[DIS7] No/favorable prognosis	13% (18)
7	[COP2] Yes/talking as catharsis	12% (10)	6	[DIS3] Maybe/uncertain medical situation	10% (11)	7	[SUP1] No/physician as main supporting partner	12% (16)
8	[ATT2] Yes/become acquainted with the psychooncologist	11% (9)	7	[COP9] No/self-management	9% (10)	8	[DIS1] Maybe/fear of deterioration	11% (15)
8	[COP5] Yes/disburden family	11% (9)	7	[COP4] Yes/information and counseling	9% (10)	9	[COP8] No/talking is not helpful	10% (14)
8	[DIS4] Yes/burdened family	11% (9)				10	[COP7] No/positive thinking	9% (13)
9	[ATT4] Yes/positive experience with psychological support	10% (8)						

Note. Categories are only listed above 9% of patients reporting (all categories are shown in Table S1). %, percentage of patients in this group reporting this category.

patients' reasons and 4 main themes. Interrater reliability was strong to moderate (κ = 0.70-0.89).[33] Table S1 contains a detailed description of all categories and number of reasons per group.

Four main themes emerged across groups: attitude (ATT), coping (COP), distress (DIS), and support (SUP). *Attitude* includes categories that describe patients' opinions about psychooncological support. *Coping* includes different strategies that patients say they used to handle a situation. *Distress* consists of several categories that describe either subjective distress or well-being as a reason for uptake or decline of support. Formal and informal support includes categories that describe support needs of patients.

Patients with a yes intention wanted to consult psychooncologists mainly because (1) they considered the psychooncologists to be experienced experts [ATT1], (2) they wanted support for self-empowerment [COP1], and (3) they wanted to prepare for potential physical or mental deterioration [DIS1]. Patients with no intention generally (1) felt supported enough by family and friends [SUP2], (2) reported mental and physical well-being [DIS8], and (3) did not think psychological support would be helpful [ATT9]. Ambivalent patients (maybe) combined reasons for and against support, and they often described a potential situation in which they would consider taking advantage of support services (ie, if-then thinking): (1) They wanted to use support if their physical or mental condition deteriorated [DIS1], (2) they currently felt supported enough [SUP2], and (3) they felt physically and emotionally well [DIS8]. Other reasons are listed in order of rank in Table 3 and Table S1.

4 | DISCUSSION

To the best of our knowledge, this study is the first longitudinal, observational study with prospective data along the distress screening pathway assessing cancer patients' distress, intention, and uptake of the psychooncology service focusing on patients' intentions by using mixed methods.

Our study had 3 key findings. First, with a trichotomous assessment of health-care service needs (yes/maybe/no), we identified a considerable number of ambivalent patients (33%), who had high mean distress levels but were less likely to use services. Second, we found an association between level of distress and patients' intentions, but 67% of patients with a high distress level did not intend to use support immediately. Third, qualitative analyses revealed different motives of ambivalent patients and patients with no or yes intention.

In line with previous research,[13,15,22,34] we found that the level of distress, but not age, sex, or education, was associated with the intention to use psychooncological support. However, about 35% of patients with high distress levels did not intend, whereas 45% of patients with low distress levels intended or maybe intended to use support. The general assumption that high distress equates with a need for support is based on a diagnostic model that recognizes patients who are at risk for mental disorders.[20,35] Predefining a cutoff value is a normative standard helpful for screening, but it must be used carefully, because we screen for *normative need* but not, per se, for patients' *felt* or *expressed needs*.[20]

Intention predicted uptake behavior, but 7% of patients with no intention used the service, and 35% of patients with an intention had not used the service after 4 months. Uptake behavior in ambivalent patients was low (12%). Further studies need to explore the barriers between intention and uptake.[18]

In the interview, patients with *no* intention emphasized social support and well-being, which supported our quantitative result on low distress values and aligned with previous research on highly distressed patients who declined support.[10] Patients' negative attitudes about psychological support and their strong emphasis on self-determination and self-management may indicate a patient concept avoiding help-seeking behavior, which is common in mental health-care settings.[10]

Similarly, positive attitudinal aspects, knowledge, and coping concepts were important for patients with an intention (yes). Attitudinal aspects and knowledge are relevant to support-seeking behavior.[24,36,37] Many of these patients had precise ideas of what they wanted and would get when asking for psychooncological support, which indicates that mental health literacy, knowledge, and patient empowerment is an important aspect for service use.[8,25]

However, attitudes, experiences, or knowledge about support services played a negligible role for most ambivalent patients (maybe). Ambivalent patients stated reasons for and against support: Fears and uncertainties were described as well as resources and well-being. Patients reported a lot of if-then thinking and seemed to be open to using the service at a later stage. In our clinical experience, a clear treatment plan, medical appointments, and a focus on going through the medical treatment psychologically stabilize patients. Dekker et al[38] argued that an increased distress level might indicate “adaptive emotional responses, which facilitate coping with cancer” instead of a maladaptive process. Further studies are needed.

Our study offers a novel, in-depth qualitative analysis of patients' supportive care needs, which revealed a threefold intention (yes/maybe/no) and a divergent pattern of motives for declining psychooncological support. Intention is relevant here because 67% of highly distressed patients did not want to make immediate use of the psychooncology service, but only 35% of these had no intention, and 32% were ambivalent (maybe).

Our study has several strengths. First, to our knowledge, it is the first study to monitor uptake behavior of patients after expressing supportive care needs in a longitudinal study. Second, we qualitatively analyzed patients' needs, a crucial extension of previous studies. Third, we assessed a large sample of cancer patients in the early phase of treatment with equal representation of men and women.

5 | STUDY LIMITATIONS

Our limitations are as follows: First, due to the large number of study participants, we decided against audio records. Instead, we used the qualitative method of taking notes during the interview and writing reflective postscripts afterward.[29] We countered possible interviewer bias by relying on a detailed interviewer manual and closely supervising interviewers. Second, this was a single center study. Our sample was representative for our clinic and other outpatient oncological settings that use a stepped-care model and integrate psychooncological care (eg, Comprehensive Cancer Centers). Third, oncologists did not inform 13% of all eligible patients about the study, 28% of eligible patients did not want more information about the study, and 12% refused to participate after being informed. We adopted a recruitment strategy where the consultant oncologist recruited the patients because it offered several advantages. Oncologists are the first and closest contact for outpatients, it is a naturalistic setting, and being invited by a physician to participate in a psychooncological study might reduce the stigma to accept the invitation. But there is also a risk of bias if oncologists are more inclined to inform interested, approachable patients about the study, or to invite patients with spare time, or who they judged healthy enough to participate.

6 | CLINICAL IMPLICATIONS

It is essential to integrate patients' supportive care needs into the clinical distress screening pathway. Patients with an ambivalent intention to use support might go unrecognized in clinical practice because supportive care needs are usually captured with a dichotomous response format.[13] We propose to assess the supportive care needs of patients by using a trichotomous response format (yes/maybe/no) at the same time as assessing psychosocial distress with the DT. The needs of highly distressed patients who do not intend to use support services (no) might be better met if approaches to these patients focused on reducing stigmatization and enhancing self-determination. In contrast, it might be better to address the needs of highly distressed, ambivalent patients (maybe) by taking an "if-then" approach to discussions about service uptake. Taking the right approach to meet the needs of each patient group could optimize psychooncological health-care delivery. Supportive cancer care should also always include providing detailed information to all patients about the work psychooncologists do and the benefits of psychooncological treatments.

7 | CONCLUSION

Our study reveals patients' subjective needs linked to psychosocial distress and uptake of a psychooncology service in cancer outpatients by using mixed methods. We identified a vulnerable group of ambivalent patients. To optimize distress screening programs, we suggest that patients' supportive care needs should be addressed and discussed in routine clinical practice.

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CONFLICT OF INTEREST

The authors declared no conflicts of interest. G.M. was a consultant for Janssen Research & Development, LLC.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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4.2 Usability testing of the online stress management intervention (STREAM) for cancer patients: results and implementations

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Usability Testing of the Online Stress Management Intervention (STREAM) for Cancer Patients: Results and Implementations

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Abstract

Background: Online health interventions are becoming increasingly frequent. However, to prove effective and satisfy the specific needs of cancer patients, the standardized steps of development are crucial. This includes structured usability testing to identify potential usability issues in the patient-specific context early during the development process of a new program.

Methods: Usability of a newly developed online stress management program was prospectively assessed in patients with solid tumors undergoing systemic treatment. In an academic computer-lab facility, each patient was asked to fulfill 16 tasks, which covered key components of the program including website navigation, login-in to secure area, filling-in forms, accessing audio files, and contacting the trial team. Usability problems during these tasks were identified via the think-aloud method and video recording and categorized. General usability was tested with the System Usability Scale (SUS).

Results: A total of 165 tasks from 11 patients were analyzed. Overall usability was high (mean System Usability Scale score 83.6) exceeding the pre-defined cut-off of 70. Participants solved 97% (160/165) of all tasks, the majority (76%) independently. A total of 122 specific usability problems were identified, predominantly concerning website functionality (50.8%) and navigation (29.5%).

Conclusions: Structured usability testing of a novel online intervention in the target population of cancer patients allowed for identification and subsequent correction of a significant number of usability problems. This crucial step allowed for a patient-friendly, self-explanatory online program with enhanced user-specific functionality, navigation and terminology before embarking on the subsequent randomized trial.

Keywords: *Cancer, internet-based, online, healthcare, usability, technical implications*

Introduction

The use of internet-based health care interventions is growing rapidly enabling certain aspects of mental health care to be delivered to the patient without the need for face-to-face interactions. Internet-based cognitive behavioral therapy for common mental health problems such as anxiety disorders and depression can provide effective, acceptable and practical health care for those who otherwise might remain untreated [1]. Internet interventions can also fill an important gap in cancer care. Cancer patients and their caregivers frequently use the Internet as a source of information [2, 3] and appropriately designed online tools can augment and increase the availability of psychosocial care by making participation convenient, confidential and less stigmatizing [2, 4]. Nevertheless, problems with high dropout rates [5, 6] and low level of engagement have been reported with some internet interventions [7]. The usability of an internet intervention is a key aspect that determines whether it will be used by the patient or not [7]. The few existing guidelines stress the importance of conducting formalized usability testing of internet-based health care interventions in the target population, hereby assessing whether the end user can work with the webpage during specific tasks [2]. Usability is defined as "the extent to which a product can be used by specified users to achieve specified goals with effectiveness, efficiency, and satisfaction in a specified context of use' (ISO 9241-11) [8]. In formalized usability testing the observed usability problems are grouped to identify flaws within the system, ultimately leading to design improvements that remove these barriers [9].

Aim of our study

Usability testing was conducted as part of the development process of the web-based stress management program for newly diagnosed cancer patients undergoing treatment "STREAM" (*STRess Aktiv Mindern*; Active Stress Reduction). The aim was to improve the final website (www.stress-aktiv-mindern.ch) specifically for use by cancer patients in a subsequent randomized trial. Here we describe the usability testing process, and identify key aspects of online intervention tools that are relevant for the development process of other online interventions for cancer patients.

Patients and Methods

Cancer patients (Table 1) who were undergoing systemic anti-cancer treatment at the Medical Oncology outpatient department of the University Hospital Basel were invited to participate in this study. The usability trial was conducted at the computer laboratory of the Center of Human-Computer Interaction of the Department of Psychology at the University of Basel. The Ethics Committee northwest/central Switzerland (EKNZ) approved the study and informed consent was obtained from all participant.

Patients first completed a pre-test questionnaire that assessed socio-demographic data, medical history, and computer skills. Patients then executed 16 tasks (for an overview see Table 2) on the website using the 'think-aloud' method. This method encourages patients to think aloud while solving a problem, thereby giving observers an insight into the participant's cognitive processes. A task designed to familiarize patients with the think-aloud method was also included. The 16 tasks covered the most important steps within the public area of the website (including the website overview, registration, and login function) and included a sample module of the secured area of the website that covered website navigation, filling-in forms, use of audio files, and contacting the trial team. Literature suggests that the majority of usability problems and flaws can be identified with as few as eight to ten subjects [9]. Overall usability was assessed with the validated System Usability Scale (SUS) questionnaire [10]. All usability tasks were videotaped and the recordings were used to assess usability. A coding manual for the analyses of behavior and performance was created by consensual expert judgment and later applied by these experts to each participant and task.

Effectiveness was measured by task success and characterized by the degree of help needed ("some help" and "a lot of help"). Problems were categorized in terms of terminology, navigation, content, functionality, and 'others'. The severity of each specific usability problem was rated by a usability expert based on the impact each problem had on the user [9]. Major problems were defined as those that had a large impact on the user's interaction such as creating significant delay and frustration or had an impact on a persons' workflow and were experienced by many users. Medium problems were those experienced by only a few users that had a large impact on the user interaction, or those experienced by many users but with a small impact on the user interaction. Efficacy was assessed by measuring the time-on-task and the time for navigating to the right place for task completion. Self-reported data concerning satisfaction with the STREAM tool were collected using a Likert Scale (1–6) and after every task.

Results

Data from 11 participants (Table 1) who solved 165 tasks (Table 2) were analyzed. Data analyses according to pre-specified age groups (<65/ ≥65 years) did not reveal any significant differences (data not shown).

Overall usability

The mean SUS score was 83.6 indicating that the overall usability of the STREAM web-based stress management program clearly exceeded the pre-defined cut-off for good overall usability of 70 [11].

Effectiveness and efficacy

Participants solved 97% (160/165) of all tasks (Table 2). Thereof, 76% (121) tasks were solved independently, 16% (26) with some help, and 8% (13) with a lot of help. The mean time spent on tasks was 39 minutes 47 seconds (SD: 78: 03; range 26: 13–64: 47 minutes).

Specific usability problems

A total of 122 specific usability problems were identified (Table 2). These predominantly concerned website functionality (50.8%) and navigation (29.5%).

Satisfaction

Participants indicated they were satisfied with the platform with an overall rating of 4.91 (on a scale 1–6). They described the intervention as clear, structured, and professional. Moreover, 73% (8/11) of the participants indicated that they would continue to use the program themselves and all participants stated they would recommend the platform to other cancer patient.

Discussion and implications

Our results show that structured usability testing with the target population is an important step during the standardized development of online health interventions. Our online stress management program STREAM is aimed at cancer patients who are undergoing active treatment. The overall usability of the STREAM website was rated as good and well above the pre-defined cut-off for usability; however, our analysis identified 122 specific usability problems.

A multidisciplinary team consisting of an oncologist, psychologists, human-computer interaction researchers, and software engineering specialists analyzed and subsequently solved these problems. The solutions to these problems were all relatively straightforward. Therefore, the crucial step is to first identify the problems, and this is greatly facilitated by evaluating the usability of the tool by the target patient population. Interestingly, usability in terms of solving tasks independently (effectiveness), the time spent on tasks (efficacy), and user satisfaction did not differ between young (<65 years) and older (≥65 years) patients. The likely explanation for this is that participants in both age groups had a similar frequency and duration of Internet use (Table 1). The specific usability problems identified in this analysis allow some general recommendations: First, it is essential to introduce simple but specific wording and use it consistently throughout the program. Second, users should be able to view the entire page without using the scroll function. To enable this, text should be concise and written in simple to understand language. Third, the intuitive use of a webpage is essential and this will solve the majority of minor usability problems (Table 2). Finally, a close collaboration with the software engineering specialist is extremely important to find good and affordable implementation solutions. A limitation of this study is that the testing was done in the laboratory and may not reflect the use of the program at home. If problems occurred during the use of the online program, participants were able to ask for assistance. Second, the small sample size may also limit the generalizability of our results. However, it is important to note that usability tests are qualitative methods that aim to reveal the most important issues that may arise during a patient's interaction with a webpage.

Table 1. Information on socio-demographics, medical history, internet skills and usage

Demographics		**Age group <65 years (N = 5)**	**Age group ≥ 65 years (N = 6)**	**Total (N = 11)**
Age	Mean (SD), range	**51 (10.4), 37–63**	**70.5 (3.4), 68–77**	**61.64 (12.35), 37–77**
Gender	Female	**2**	**3**	**5**
	Male	**3**	**3**	**6**
Highest educational level	Apprenticeship	**2**	**-**	**2**
	Business Academy	**2**	**3**	**5**
	College	**-**	**3**	**3**
	University	**1**	**-**	**1**
Medical information				
Cancer type	Breast Cancer	**2**	**2**	**4**
	Prostate Cancer	**-**	**1**	**1**
	Lung Cancer	**-**	**2**	**2**
	Ovarian Cancer	**-**	**1**	**1**
	Colon Cancer	**1**	**-**	**1**
	Glioblastoma	**1**	**-**	**1**
	Hodgkin Lymphoma	**1**	**-**	**1**
Current treatment[a]	Surgery	**1**	**3**	**4**
	Radiotherapy	**-**	**1**	**1**
	Chemotherapy	**3**	**4**	**7**
	Hormonal treatment	**2**	**2**	**4**
	Other	**1**	**2**	**3**
Ongoing side effects		**5**	**5**	**10**
Internet skills				
Internet Usage (Years)	Mean (SD), range	**15.8 (9.0), 5–35**	**16.17 (7.37), 8–25**	**16 (7.71), 5–30**
Internet Usage (Frequency)[b]	Mean (SD), range	**3 (0), 3–3**	**2.67 (.52), 2–3**	**2.82 (.41), 2–3**

[a] *Patients might undergo more than one treatment*

[b] *0 = several times per month, 1 = once a week, 2 = several times per week, 3 = daily*

In conclusion, our study highlights the importance of conducting a professional usability test with the target population during the development of an online intervention, as recommended by current guidelines [2]. This preparative step allowed for identifying several important but easy to resolve usability problems by integrating the end user (cancer patients) with the development of the STREAM online program. It influenced the development process and enabled us to implement a revised version of this tool prior to launching the randomized controlled trial (clinicaltrials.gov NCT02289014) assessing the efficacy and feasibility [12, 13] of the STREAM tool for newly diagnosed cancer patients.

Table 2. Overview of usability problems and implications

Overall Usability Problems	**Number of problems (N = 122)**		***100%***	
Category				
Terminology (T)	**11**		**9.0**	
Navigation (N)	**36**		**29.5**	
Content (C)	**5**		**4.1**	
Functionality (F)	**62**		**50.8**	
Other (O)	**8**		**6.6**	
Problem description	**Number of users affected**	**Category**	**Severity[a]**	**Implications**
Overall				
• Required form fields were not filled out	**10 /11**	**F**	**I**	Mark mandatory form fields using color or asterisks
• Unclear error messages	**6 / 11**	**T**	**I**	Define terms clearly and use them consequently
• Text was not read	**3 / 11**	**C/T**	**II**	Reduce text to a minimum and use simple-to-understand language
• Cursor orientation (e.g. participants started typing while mouse cursor was not yet in a form field)	**5 / 11**	**F/ N**	**II**	Automatically place the cursor in the first form field
Specific for public area				
• Substantial information was overlooked	**4 / 11**	**C**	**I**	Display important information within user's view, without the need to scroll
• Label confusion (e.g. "sign up" versus "register")	**7 / 11**	**T**	**I**	Define terms clearly and use them consistently
Specific for private area				
• Unintentional logouts	**6 / 11**	**F**	**I**	Prevent unintentional logouts
• No feedback was given upon successful saving processes	**4 / 11**	**F**	**I**	Give feedback to inform the user about the system's current status
• System feedback was not noticed	**5 / 11**	**F**	**I**	Place system feedback within users focus of attention
• Sequentially navigation within module was not intuitive	**11 / 11**	**N**	**I**	Use color to differentiate between visited subsites and not yet visited subsites
• New interaction possibility (e.g. lightbox) caused disorientation	**6 / 11**	**F**	**II**	Use known and established interaction patterns
• Mapping between labels and form field unclear	**6 / 11**	**N**	**II**	Place labels visually close to the form field
• Scale labeling unclear	**2 / 11**	**T**	**II**	Define terms clearly and use them consistently

[a] *Classification of problem severity: (I) Major problems that have a large impact on the user's interaction and are experienced by many users = Immediate changes needed; (II) Medium problems experienced by only a few users but with a large impact on the user interaction or experienced by many users but with a small impact on the user interaction = Should be changed*

Authorship

Grossert A: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing

Heinz S: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing

Müller L: Data Curation, Formal Analysis, Investigation, Writing – Review & Editing

Gaab J: Writing – Review & Editing

Urech C: Writing – Review & Editing, Financial support

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Hess V: Conceptualization, Formal Analysis, Methodology, Validation, Writing – Original Draft Preparation, Writing – Review & Editing, Financial support

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Abbreviations

STREAM	*STRess Aktiv Mindern*; Active Stress Reduction
EKNZ	Ethics Committee northwest/central Switzerland
SUS	System Usability Scale

Competing interests

The authors declare that they have no conflicts of interest.

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4.3 Web-based stress management for newly diagnosed patients with cancer (STREAM): a randomized, wait-list controlled intervention study

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Web-Based Stress Management for Newly Diagnosed Patients With Cancer (STREAM): A Randomized, Wait-List Controlled Intervention Study

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ABSTRACT

Purpose
Being diagnosed with cancer causes major psychological distress; however, a majority of patients lack psychological support during this critical period. Internet interventions help patients overcome many barriers to seeking face-to-face support and may thus close this gap. We assessed feasibility and efficacy of Web-based stress management (STREAM [Stress-Aktiv-Mindern]) for newly diagnosed patients with cancer.

Patients and Methods
In a randomized controlled trial, patients with cancer who had started first-line treatment within the previous 12 weeks were randomly assigned to a therapist-guided Web-based intervention or a wait-list (control), stratified according to distress level (≥ 5 *v* < 5 on scale of 0 to 10). Primary efficacy end point was quality of life after the intervention (Functional Assessment of Chronic Illness Therapy–Fatigue). Secondary end points included distress (Distress Thermometer) and anxiety or depression (Hospital Anxiety and Depression Scale). Treatment effect was assessed with analyses of covariance, adjusted for baseline distress.

Results
A total of 222 of 229 screened patients applied online for participation. Between September 2014 and November 2016, 129 newly diagnosed patients with cancer, including 92 women treated for breast cancer, were randomly assigned to the intervention (n = 65) or control (n = 64) group. Adherence was good, with 80.0% of patients using ≥ six of eight modules. Psychologists spent 13.3 minutes per week (interquartile range, 9.5-17.9 minutes per week) per patient for online guidance. After the intervention, quality of life was significantly higher (Functional Assessment of Chronic Illness Therapy–Fatigue: mean, 8.59 points; 95% CI, 2.45 to 14.73 points; $P = .007$) and distress significantly lower (Distress Thermometer: mean, −0.85; 95% CI, −1.60 to −0.10; $P = .03$) in the intervention group as compared with the control. Changes in anxiety or depression were not significant in the intention-to-treat population (Hospital Anxiety and Depression Scale: mean, −1.28; 95% CI, −3.02 to 0.45; $P = .15$). Quality of life increased in the control group with the delayed intervention.

Conclusion
The Web-based stress management program STREAM is feasible and effective in improving quality of life.

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ASSOCIATED CONTENT

Appendix
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Data Supplement
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INTRODUCTION

Diagnosis of cancer elicits high levels of distress in a majority of patients,[1] which is associated with decreased quality of life as well as diminished treatment tolerance[2,3] and potentially worse disease course.[4,5] Psychosocial support for patients with cancer is effective in alleviating distress and improving quality of life, including fatigue, the most common complaint of patients with cancer.[2,6] However, a majority of newly diagnosed patients with cancer lack psychosocial support because of constraints on the part of both providers and patients.[6,7] Use of the Internet, which has become an integral part of our lives, has the potential to change this. At least 70% of patients with cancer use the Internet as a source of information shortly after diagnosis,[8] making it a powerful platform for reaching these patients. Recent approaches to integrating the Internet into patient care range from patient forums to information sites and even therapeutic games.[9,10] Internet programs based on cognitive behavioral techniques with patient guidance via regular online contact with a health care professional (ie, therapist-guided programs or guided self-help) have emerged as particularly effective options. For a range of psychological disorders, including anxiety disorders and depression in those without cancer,[11,12] therapist-guided online interventions seem similarly effective as face-to-face interventions.[13] The success of Web-based guided self-help in psychological disorders[9,13] coupled with the need to further improve access to psychosocial support for patients with cancer, especially outside of inner cities with large cancer centers,[6] has boosted interest in online interventions in oncology. Numerous piloted and ongoing trials in patients with cancer seek to define suitable indications, formats, and settings.[14] The few larger published randomized controlled trials[15-17] show encouraging results, with improvement in a number of relevant psychosocial domains, including coping with cancer,[15] sexual functioning,[16] and distress[17] in breast cancer survivors.

We designed the STREAM (Stress-Aktiv-Mindern) intervention specifically for the particularly vulnerable period immediately after first diagnosis of cancer.[18] The rationale behind this early intervention was three-fold. First, distress in patients with cancer peaks shortly after diagnosis,[18] irrespective of cancer type. Second, the time after diagnosis is busy with appointments for diagnostics and treatment. Therefore, the self-management of time and location allowed by Web-based interventions[9] might be of particular value. Third, successful early psychosocial interventions have shown potential to affect disease course beyond psychosocial outcomes.[19] We assessed feasibility and efficacy of our therapist-guided Web-based stress management program STREAM for newly diagnosed patients with cancer receiving first-line treatment.

PATIENTS AND METHODS

Details are provided in the Appendix (online only) and the published protocol.[20] We included adult patients (age ≥ 18 years) with newly diagnosed cancer who started first-line treatment (either systemic treatment, including chemotherapy, hormonal treatment, or targeted therapy, or radiotherapy) no longer than 12 weeks before study registration. Patients were required to provide written informed consent, read and write in German, and have Internet access as well as basic computer skills. The ethics committee approved the study (EKNZ339/13). Patients were recruited online via the STREAM Web site of STREAM. We randomly assigned eligible patients at a ratio of one to one using blocked randomization with randomly selected block sizes to an intervention group or a wait-list control group (Fig 1). Patients were stratified according to baseline distress using an internationally accepted cutoff of ≥ 5 points on the 10-point visual analog scale (VAS) of the Distress Thermometer (DT).[21]

Intervention

We developed the Web-based intervention STREAM[20] based on established stress management intervention manuals[22] that incorporate cognitive behavioral– and mindfulness-based stress reduction techniques, which we adapted to the Web context. STREAM consists of eight modules (Appendix Table A1, online only), which can be completed in 60 to 90 minutes each. Daily use of downloadable audio files with relaxation and guided-imagery exercises was encouraged. Participants were asked to complete one module per week. Our therapists provided weekly written feedback via integrated secured e-mail.

Patients in the control group underwent their cancer treatment locally as planned and were recontacted by the study team 8 weeks after random assignment (T2; Fig 1). After T2 assessments, they received access to the online program. For patients in both groups, cancer treatment was determined locally, and supportive care according to local standards may also have included face-to-face psychosocial support and psychotropic drugs.

Assessments

Assessments were conducted electronically directly within the Web-based program via the open source application LimeSurvey at baseline (T1) and after the intervention or waiting period (control group), respectively (T2). In addition, 2-month follow-up (T3) was performed in both groups.

Efficacy End Points

Primary end point was quality of life at T2, assessed using the validated German version of the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) questionnaire.[23] Minimal clinically meaningful differences are not well defined but have previously been set between 7 and 9 points, both as intraindividual changes and differences in groups.[19,24]

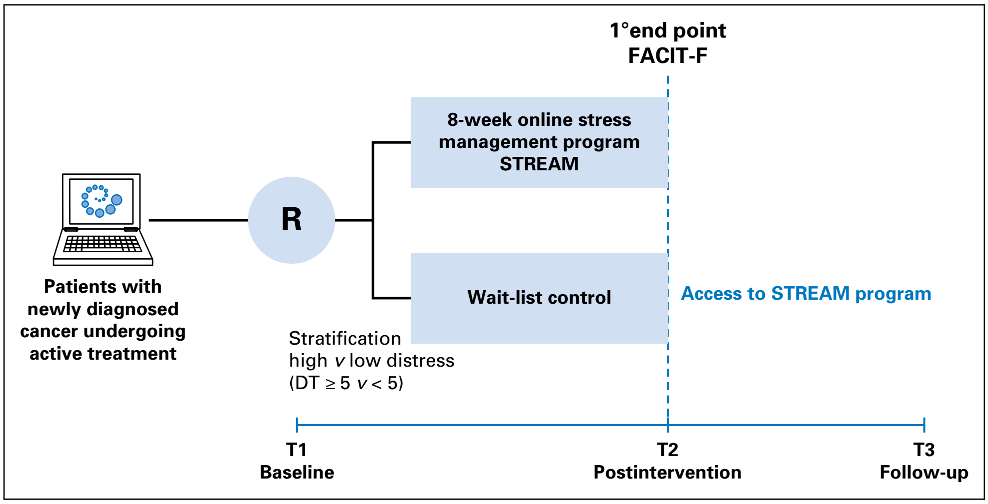

Fig 1. Trial design. DT, Distress Thermometer; FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue; STREAM, Stress-Aktiv-Mindern.

Secondary efficacy end points were assessed at the same points in time and evaluated psychological distress and anxiety or depression using the validated German versions of the National Comprehensive Cancer Network DT[21] and the Hospital Anxiety and Depression Scale (HADS),[25] respectively. Effect sizes are expressed as partial eta squared (η^2_p),[26] with the following cutoffs to categorize effect sizes into small (0.01), medium (0.06), and large (0.14), as suggested by Cohen.[27]

Assessments During Intervention

Usability was evaluated after the first and last module with the System Usability Scale; scores > 70 represent good usability.[28] Therapeutic alliance between patients and the online therapist was assessed using the Working Alliance Inventory in its short form (12 items)[29] after each module. Total score ranges from 0 to 5, and scores > 3.5 have been rated as good working alliances.[30]

Statistical Analyses and Sample Size Calculation

All analyses were performed in the intention-to-treat (ITT) population defined as all patients who were randomly assigned. The per-protocol (PP) population included all patients who underwent the program in the intended timeframe (ie, the time between random assignment and T2 assessments did not exceed 16 weeks, which is twice the minimal duration of the program). To demonstrate a 9-point difference[31] in FACIT-F total score between baseline and T2 (after 8 weeks) in the intervention group with a statistical power of 0.80 at a significance level of .05 (two sided), 60 participants were needed in each of the two conditions.

Efficacy Analyses

Efficacy outcomes were modeled with analysis of covariance (ANCOVA), using postscore (T2) as the dependent variable, prescore (T1) as the covariate, and group allocation (intervention *v* control) as the independent variable. ANCOVAs were further adjusted for the stratification factor distress (DT ≥ 5 *v* < 5). For the follow-up period, score changes from T2 to T3 were analyzed with paired *t* tests, separately for each group (no between-group comparisons). Multiple imputations (n = 99) by chained equations[32] using predictive mean matching[33] incorporating all variables of the linear models underlying ANCOVA were used to impute missing outcome values.[34] To assess the robustness of the results, sensitivity analyses were conducted for all outcomes in the PP population. In addition, sensitivity analyses were carried out using other methods for handling missing data; more specifically, complete-case analyses and last observation carried forward analyses, as specified in the protocol,[20] were computed for all outcomes in both the ITT and PP populations.

RESULTS

We screened 229 patients, of whom 129 were randomly assigned between September 11, 2014, and November 24, 2016 (Fig 2). All patients received first-line cancer treatment, which they started a median of 17 days (interquartile range [IQR], 6-22 days) and 14 days (IQR, 7-20 days) after signing informed consent in the intervention and control groups, respectively. Patients were residents of Switzerland (n = 64), Germany (n = 59), Austria (n = 5), and the United Kingdom (n = 1). Medical, psychological, and socioeconomic baseline characteristics are listed in Table 1 and were balanced between the groups. All 21 patients (control group, n = 10; intervention group, n = 11) who scored 1 point in the Beck Depression Inventory suicide item at baseline were immediately contacted by telephone, but they clearly distanced themselves from acute suicidal intent.

The intervention was designed to be feasible within 8 weeks. However, median duration of the online intervention (between first login to module one and postintervention assessment at T2) was 11.7 weeks (IQR, 9.1-18.6 weeks). In the intervention group, 52 patients (80.0%) used at least six modules, and 49 (75.4%) worked with all eight modules. Our psychologists spent a median time of 165 minutes (IQR, 127-210 minutes) for administering the online intervention (ie, 13.3 minutes [IQR, 9.5-17.9 minutes] per patient each week). Usability of the program was rated high, with a mean System Usability Scale score of 87.5 (IQR, 81.2-95.0) after module one and of 90.0 (IQR, 82.5-95.0) after module eight. As a measure of the therapeutic relationship between patient and online therapist, patients reported a mean score in the Working Alliance Inventory questionnaire of 3.77 (IQR, 3.38-4.14), similar to that of previously reported online working alliances.[30]

Primary and secondary efficacy outcomes are listed in Table 2 and illustrated in Figures 3 and 4. Quality of life (FACIT-F) after the intervention (T2; the primary end point) was significantly higher in the intervention group as compared with the control group (ANCOVA $P = .007$; Table 2). With a mean increase in total FACIT-F score of 8.59 (95% CI, 2.45 to 14.73; $P = .007$) in the ITT population and of 10.71 (95% CI, 4.49 to 16.94; $P = .001$) in the PP population, changes were clinically meaningful.[19,24] Effect sizes were medium[27] ($\eta^2_p = 0.063$ and 0.114 in the ITT and PP populations, respectively; Table 2). Increased scores within the fatigue (4.51; 95% CI, 1.81 to 7.22; $P = .002$), physical well-being (2.01; 95% CI, 0.43 to 3.59; $P = .01$), and functional well-being subscales (1.53; 95% CI, 0.11 to 2.95; $P = .04$) were major contributors to the increase in total FACIT-F score, whereas social well-being and emotional well-being scores were not (Table 2.).

Distress on the VAS (scored from 0 to 10) of the National Comprehensive Cancer Network DT was significantly lower at T2 in the intervention group as compared with the control (−0.85; 95% CI, −1.60 to −0.10; $P = .03$). As summarized in Table 2, anxiety and depression (HADS) after the intervention (T2) were not significantly lower in the intervention as compared with the control group ($P = .15$) in the ITT population. However, decrease in HADS score was statistically significant in the PP population (−2.09; 95% CI, −4.03 to −0.16; $P = .03$). All results were confirmed in the prespecified sensitivity analyses (Appendix Table A2). Figure 4 shows the percentage of patients who reported any changes in scores between baseline and T2 for all three assessment tools.

During the 2-month follow-up period of the intervention group (T2 to T3), quality of life (FACIT-F T2 to T3: mean, 4.69; 95% CI, −0.74 to 10.12; $P = .09$), distress (DT T2 to T3: mean, −0.29; 95% CI, −1.03 to 0.44; $P = .4$), and mood (HADS T2 to T3: mean, −0.82; 95% CI, −2.28 to 0.65; $P = .27$) did not change significantly. In the follow-up phase (ie, after T2), 51 (79.7%) of 64 patients randomly assigned to the control arm opted to start the STREAM program. For this group of patients, T2 represents the assessments immediately before and T3 the assessments immediately after the online program. In an ITT analysis (n = 64), quality of life increased significantly (FACIT-F T2 to T3: mean, 10.95; 95% CI, 6.18 to 15.71; $P < .001$) and distress decreased significantly (DT T2 to T3: mean, −1.25; 95% CI, −1.95 to −0.55; $P = .001$) between T2 and T3. Self-reported anxiety and depression were also lower (HADS T2 to T3: mean, −2.83; 95% CI, −4.29 to −1.36; $P < .001$). Again, results were confirmed in the prespecified sensitivity analyses (Appendix Table A3, online only).

Data for individual patients and group means are shown in Appendix Figure A1 (online only).

DISCUSSION

In this randomized controlled trial, newly diagnosed patients with cancer reported significantly better quality of life and lower distress on the DT after participating in the therapist-guided Web-based stress management program STREAM. Recruitment to the STREAM study via online channels was successful, and patients in three countries, corresponding to a geographic area twice as large as the United Kingdom, were reached. Thus, dissemination of psychosocial interventions beyond urban centers, where face-to-face psychosocial interventions are available,[35] can be facilitated by a Web-based approach. The STREAM intervention was feasible in our population of patients during a period of active treatment of different types of cancer with good adherence; 80% of patients worked with at least six of the eight modules.[16]

Although it is indisputable that quality of life matters, it is also inherently difficult to measure.[36] To ensure robust and clinically relevant data, we rely on well-validated and standardized questionnaires.[1,23,25]

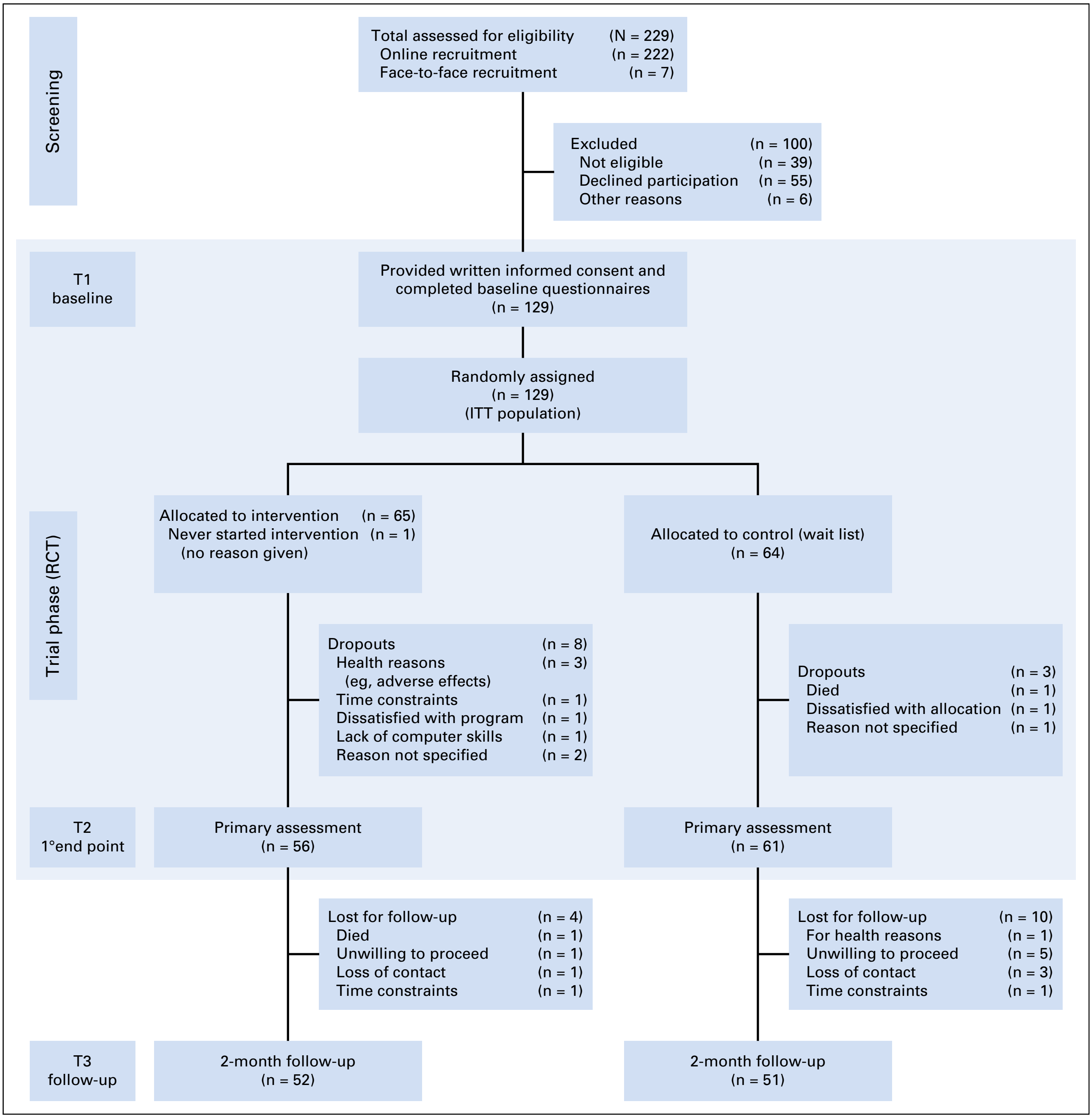

Fig 2. Patient flow (CONSORT diagram). ITT, intention to treat; RCT, randomized controlled trial.

Table 1. Baseline Demographic and Clinical Characteristics

	No. (%)		
Characteristic	All Patients (N = 129)	Control Group (n = 64)	Intervention Group (n = 65)
Age, years			
Median	52	53	51
IQR	46-58	46-58	46-57
Sex			
Female	109 (84.5)	56 (87.5)	53 (81.5)
Male	20 (15.5)	8 (12.5)	12 (18.5)
Tumor origin			
Breast	92 (71.3)	47 (73.4)	45 (69.2)
Gynecologic tract	7 (5.4)	5 (7.8)	2 (3.1)
Lung	5 (3.9)	3 (4.7)	2 (3.1)
CNS/head and neck	4 (3.1)	1 (1.6)	3 (4.6)
Lymphoma	11 (8.5)	4 (6.2)	7 (10.8)
Skin/soft tissue	1 (0.8)	1 (1.6)	0 (0.0)
GI tract	7 (5.4)	2 (3.1)	5 (7.7)
Urogenital tract	2 (2.0)	1 (1.6)	1 (1.5)
Disease stage			
Localized	111 (86.0)	55 (85.9)	56 (86.2)
Metastatic	18 (14.0)	9 (14.1)	9 (13.8)
Treatment			
Radiotherapy	16 (12.4)	8 (12.5)	8 (12.3)
Chemotherapy	75 (58.1)	40 (62.5)	35 (53.8)
Hormonal therapy	32 (24.8)	14 (21.9)	18 (27.7)
Radiochemotherapy	4 (3.1)	1 (1.6)	3 (4.6)
Other	2 (1.6)	1 (1.6)	1 (1.5)
Treatment goal			
Curative	117 (90.7)	58 (90.6)	59 (90.8)
Palliative	12 (9.3)	6 (9.4)	6 (9.2)
Marital status			
Married	81 (62.8)	39 (60.9)	42 (64.4)
Married, separated	2 (1.6)	1 (1.6)	1 (1.5)
Single	26 (20.2)	12 (18.8)	14 (21.5)
Divorced	16 (12.4)	9 (14.1)	7 (10.8)
Widowed	4 (3.1)	3 (4.7)	1 (1.5)
Highest education			
Compulsory school	2 (1.6)	1 (1.6)	1 (1.5)
Apprenticeship	32 (24.8)	16 (25.0)	16 (24.6)
College	44 (34.1)	19 (29.7)	25 (38.5)
University	48 (37.2)	25 (39.1)	23 (35.4)
Other	3 (2.3)	3 (4.7)	0 (0.0)
Monthly household income, € (n = 107)			
< 1,200	2 (1.9)	0 (0.0)	2 (3.8)
1,200-2,500	7 (6.5)	6 (11.1)	1 (1.9)
2,500-4,900	35 (32.7)	18 (33.3)	17 (32.1)
4,900-8,100	36 (33.6)	18 (33.3)	18 (34.0)
8,100-12,200	19 (17.8)	9 (16.7)	10 (18.9)
> 12,200	8 (7.5)	3 (5.6)	5 (9.4)
Using complementary medicine (n = 116)			
Yes	31 (26.7)	17 (30.4)	14 (23.3)
No	51 (44.0)	23 (41.1)	28 (46.7)
I don't know	34 (29.3)	16 (28.6)	18 (30.0)
Currently seeing a therapist			
Yes	45 (34.9)	27 (42.2)	18 (27.7)
No	84 (65.1)	37 (57.8)	47 (72.3)
Currently using psychotropic drugs			
Yes	17 (13.2)	11 (17.2)	6 (9.2)
No	111 (86.0)	53 (82.8)	58 (89.2)
I don't know	1 (0.8)	0 (0)	1 (1.5)
Baseline FACIT-F score			
Median	106.0	108.3	101.0
IQR	84.2-123.0	87.8-124.0	81.0-120.0
Baseline distress (DT)			
Low	30 (23.3)	14 (21.9)	16 (24.6)
High (score ≥ 5)	99 (76.7)	50 (78.1)	49 (75.4)
Baseline HADS score			
Median	12	12	13
IQR	7-17	7-16	7-18

NOTE. No significant differences ($P < .05$) between groups were identified for any category (as determined by Wilcoxon or Kruskal-Wallis test or Pearson χ^2 test).

Abbreviations: DT, Distress Thermometer; FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue; HADS, Hospital Anxiety and Depression Scale; IQR, interquartile range.

There is no clear cutoff for clinically meaningful increases in overall quality of life in the FACIT-F score. However, on the basis of previous studies, changes reported in the postintervention scores of this trial were in a range that is considered highly noticeable to patients.[19,24] Quality-of-life analyses are often complicated by a large number of missing data. In our study, the low number of missing data (90.7% of all randomly assigned patients completed the primary assessment at T2) and robustness of the sensitivity analyses (Appendix Tables A2 and A3), increase reliability of patient-reported outcomes.

Although the primary efficacy end point of better quality of life after the STREAM intervention was clearly met, the effect of the intervention on distress is less clear cut. The DT is an assessment tool that allows patients to summarize all subjective aspects of distress in a single number (VAS, 0 to 10). In its simplicity, the DT therefore has the advantage of covering various dimensions of distress, including physical, functional, social, socioeconomic, spiritual, and emotional distress.[21] However, the weight that patients assign, whether consciously or not, to each dimension is not discernible from the DT score. In contrast, the HADS questionnaire covers exclusively the emotional dimension of distress, but it does so in greater depth.[25] Whereas self-reported distress on the DT was lower after STREAM, with a small to medium effect size[27] ($\eta^2_p = 0.043$ and 0.069 in the ITT and PP populations, respectively), emotional distress as assessed by HADS did not change. This leads to the hypothesis that STREAM primarily affects dimensions of distress other than anxiety or depression. Of note, in our population, HADS scores at baseline were rather low (mean, 12; IQR, 7-17), whereas baseline DT scores were high (mean, 6; IQR, 5-8). It is therefore conceivable that a potential impact of STREAM on the emotional dimension of distress (anxiety and depression) cannot be assessed conclusively in our population. A study tailored specifically toward patients with high baseline levels of anxiety or depression would be more appropriate to answer this specific question.

Although STREAM was designed for and open to all newly diagnosed patients with cancer, women with breast cancer undergoing curative treatment represented the vast majority of the study population. This leaves uncertainty regarding generalizability

Table 2. Efficacy Outcomes

Measure	ITT Population (n = 129)			PP Population* (n = 95)		
	Δ Means† (95% CI)	*P*	ES (η^2_p)‡	Δ Means† (95% CI)	*P*	ES (η^2_p)‡
Quality of life including fatigue (FACIT-F; 40 items; score, 0-160)	8.59§ (2.45 to 14.73)	.007	0.063	10.71 (4.49 to 16.94)	.001	0.114
Physical well-being (seven items; score, 0-28)	2.01 (0.43 to 3.59)	.01		2.64 (1.02 to 4.25)	.002	
Social well-being (seven items; score, 0-28)	0.44 (−0.95 to 1.82)	.53		0.41 (−1.13 to 1.96)	.60	
Emotional well-being (six items; score, 0-24)	0.24 (−0.77 to 1.25)	.64		0.68 (−0.38 to 1.75)	.21	
Functional well-being (seven items; score, 0-28)	1.53 (0.11 to 2.95)	.04		1.65 (0.04 to 3.26)	.05	
Fatigue score (13 items; score, 0-52)	4.52 (1.81 to 7.22)	.002		5.26 (2.37 to 8.16)	.001	
DT (score, 0-10)	−0.85 (−1.60 to −0.10)	.03	0.043	−1.11 (−1.95 to −0.26)	.01	0.069
HADS (14 items; score, 0-42)	−1.28 (−3.02 to 0.45)	.15	0.019	−2.10 (−4.03 to −0.16)	.03	0.049

NOTE. Results of analysis of covariance for postintervention scores (T2), with baseline scores (T1) as covariates, adjusted for baseline distress (stratification factor).

Abbreviations: DT, Distress Thermometer; ES, effect size; FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue; HADS, Hospital Anxiety and Depression Scale; ITT, intention to treat; PP, per protocol.

*PP population was defined as all patients for whom time between random assignment and T2 assessments did not exceed 16 weeks.

†Treatment effects estimated by analysis of covariance are reported as difference (Δ) in scores of group means for intervention *v* control group.

‡ESs are expressed as partial eta squared, with the cutoffs small (0.01), medium (0.06), and large (0.14). Multiple imputations were used to handle missing data. Results did not change significantly with other methods for handling of missing data (complete-case (CC) analysis or last observation carried forward (LOCF) analysis; Appendix Table A2, online only).

§Primary end point of the trial.

of the results, particularly toward men and toward the palliative setting. Women with breast cancer are known to have the largest social media network in the cancer community, which likely allowed for effective online recruitment. The presence of other cancer groups in the Internet community is only emerging, with platforms such as that created by the Movember Foundation for men with cancer.[37] Such platforms may allow for integrating more men into future studies. If targeted specifically, men with prostate cancer also seem to be reachable via the Internet, as shown by an Australian self-help online program, which integrated a patient forum called My Road Ahead.[38]

At baseline, before random assignment, more patients in the control group reported face-to-face psychological support and use of psychotropic drugs than in the intervention group, although the number was not statistically significant. Data on the amount of time spent face to face with local psychologists during the course of the trial were not collected; hence, potential bias cannot be quantified. In contrast, attention bias toward the intervention group, possibly introduced by the time our STREAM psychologists spent online with the patients, may have affected outcome inversely. Because we opted for a care-as-usual (ie, wait-list) rather than active control, this will need to be differentiated in future studies.

A wait-list controlled design is generally accepted to control for the effect of time on the outcome of interest. However, the duration of the wait and consequently the timing of assessments (T2) for the control group are prospectively defined and rigid, whereas the timing of assessments (T2) in the interventions group is dependent on the duration of the intervention and therefore more variable. Hence, time sensitivity is only partially accounted for. This is also true for our study, where median time between T1 and T2 was 9.4 weeks (IQR, 8.6-12.1 weeks) for the intervention group but was shorter in the control group (median, 8.7 weeks; IQR, 8.3-9.3 weeks). Dynamic wait-list controlled designs have been proposed to minimize this potential bias.[39]

Another shortcoming of our trial is that we only show a benefit in distress and quality of life for patients early after

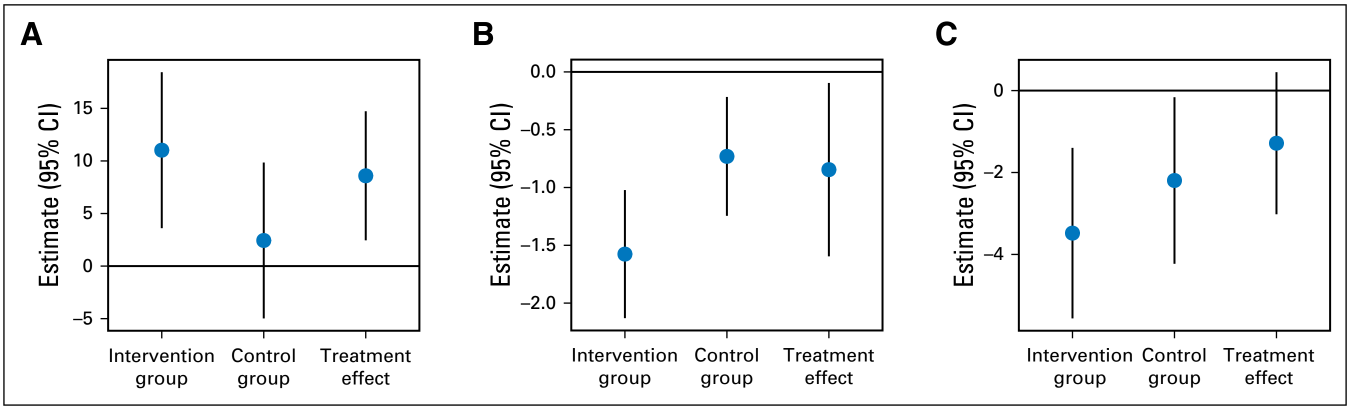

Fig 3. Treatment effects. Mean changes in scores (95% CIs) postintervention (T2) for (A) quality of life (Functional Assessment of Chronic Illness Therapy–Fatigue), (B) distress (Distress Thermometer), and (C) anxiety/depression (Hospital Anxiety and Depression Scale) for the intervention and control groups and their differences (treatment effects) based on analyses of covariance with prescores (T1) as covariates.

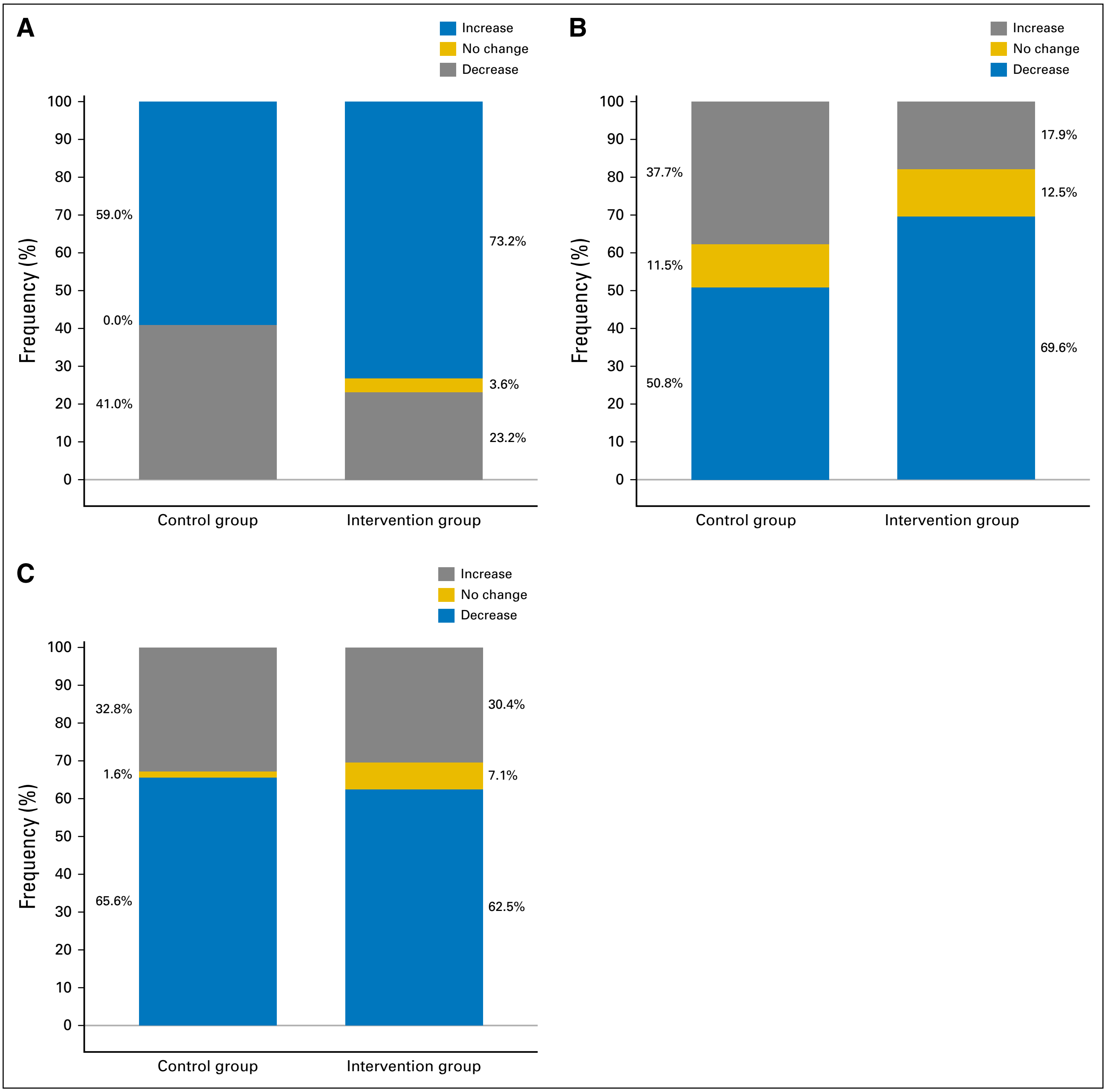

Fig 4. Percentage of patients with any increase or decrease or no change in total scores between T1 and T2 in (A) quality of life (Functional Assessment of Chronic Illness Therapy–Fatigue), (B) distress (Distress Thermometer), and (C) anxiety/depression (Hospital Anxiety and Depression Scale), where blue represents amelioration and gray deterioration within the respective assessment tool.

diagnosis, with a limited follow-up. It is conceivable, however, that such an early intervention[19] may be of particular importance to prevent chronification of distress.[40] Whether lower distress and increased quality of life after STREAM translate into better treatment tolerance and favorable disease course warrants additional studies.

The unique and common feature of study participants in this trial was a recent diagnosis of cancer. In contrast, the few reported randomized controlled trials on online support for patients with cancer have mainly focused on cancer survivors (ie, interventions later in the disease trajectory). In a randomized, wait-list controlled trial, breast cancer survivors (on average, 3 years after initial diagnosis) who participated in an online program in a similar therapist-guided format as presented here reported significantly improved sexual functioning (the primary end point of the trial) as compared with the wait-list control group.[16] Breast cancer survivors were also the target population in the randomized trial for the Coping With Cancer Workbook.[15] Women who participated in this Web-based self-help program reported better self-efficacy in coping with cancer. Overall quality of life was not reported. The BREATH (Breast

Cancer eHealth) intervention,[17] a Web-based intervention based on cognitive behavioral techniques but without therapist guidance, led to reduced distress in breast cancer survivors; however, it was not sustained during the 10-month follow-up.

In conclusion, with digital natives approaching an age that places them at risk for developing age-associated diseases, including cancer, use of the Internet in the health care setting will likely further increase. In this randomized trial, we found that a Web-based, guided self-help intervention resulted in a clinically meaningful improvement in quality of life. Our results indicate that Web-based, guided self-help has potential to efficiently support newly diagnosed patients with cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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Web-Based Stress Management for Newly Diagnosed Patients With Cancer (STREAM): A Randomized, Wait-List Controlled Intervention Study

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Appendix

Patients and Methods

Patient Eligibility Criteria and Recruitment

Rationale and design of this randomized trial have been published.[20] We included adult patients (age ≥ 18 years) with newly diagnosed cancer who started first-line treatment (either systemic treatment, including chemotherapy, hormonal treatment, or targeted therapy, or radiotherapy) no longer than 12 weeks before study registration. Patients were required to provide written informed consent, read and write in German, have Internet access, and have basic computer skills. To obtain informed consent, a therapist provided detailed information about the study via telephone and went point by point through the informed consent form. The informed consent form was then sent to the patient, who, if in agreement, sent the signed paper form back via post mail. The Ethics Committee of Northwestern and Central Switzerland approved the study (EKNZ 339/13). The trial is registered at ClinicalTrials.gov (ClinicalTrials.gov identifier: NCT02289014).

For safety reasons, patients were assessed at baseline for suicidal tendency by the suicide item of the Beck Depression Inventory (Green KL, et al: J Clin Psychiatry 76:1683-1686, 2015). Our online program was not designed to support suicidal patients in acute crises; therefore, patients with a score higher than 1 were contacted by telephone and referred to immediate local support.

Information on medical history was obtained from the patients during baseline assessments and confirmed by their treating physicians, who we contacted by e-mail or telephone.

Patient Recruitment

Patients were recruited via the public Web site of STREAM (Stress-Aktiv-Mindern). To foster recruitment, we linked and distributed information about the trial via the following channels: links from health-related Web sites, such as cancer leagues, cancer hospitals, and patient advocate Web sites to the public Web site of STREAM; distribution of flyers in hospitals and during cancer conferences; communication to medical lay press; and paid advertisement via Google and Facebook.

Study Design

We randomly assigned eligible patients at a ratio of one to one using blocked randomization with randomly selected block sizes to an intervention group or a wait-list control group (Fig 1). Patients were stratified according to baseline distress, using an internationally accepted cutoff of ≥ 5 points on the 10-point visual analog scale of the Distress Thermometer.[21]

Intervention

We developed the Web-based intervention STREAM[20] based on established stress management intervention manuals[22] that incorporate cognitive behavioral– and mindfulness-based stress reduction techniques, which we adapted to the Web context. STREAM aims at improving intra- and interpersonal coping strategies, thereby reducing perceived stress, anxiety, and fatigue as well as enhancing quality of life. STREAM consists of eight modules (Appendix Table A1), which can be completed in 60 to 90 minutes each. Each module starts with a short mindfulness breathing exercise followed by text-based psychoeducation, reflection on current individual emotional status, and acquisition of coping strategies including several exercises and worksheets. Daily use of downloadable audio files with relaxation and guided-imagery exercises was encouraged. Participants were asked to complete one module per week. Access to the next module was provided after the weekly online feedback of a therapist. Patients who had to interrupt the program for medical or personal reasons were regularly contacted and offered continuation. The total duration of the program was not limited. Therapists monitored participants' progress in the program and contacted the participants via an integrated and secured e-mail system to provide feedback and structure. Patients could use the integrated e-mail system to contact their therapist whenever they felt the need to and were informed that the therapist would answer within 3 working days. Whenever patients did not log in to the program for 7 days, therapists sent an e-mail reminder.

Therapists were four female psychologists with Master's degrees in clinical psychology and clinical experience in psycho-oncology. Three of them were in postgraduate psychotherapy training programs, and one was a licensed psychotherapist (C.U.). This core team was supported by seven psychologists with Bachelor's degrees in psychology, who worked under supervision of the licensed psychotherapist. All therapists were trained by the psychological study team leaders (A.G., C.U.) in applying the STREAM program and met for weekly discussions, with input by a medical oncologist (V.H.), to align procedures and strategies. For data protection, the program is password protected and secured by Secure Socket Layer encryption.

Control

Patients in the control group underwent their cancer treatment locally as planned and were recontacted by the study team 8 weeks after random assignment (T2; Fig 1). After T2 assessments, they received access to the online program. For patients in both groups, cancer treatment was determined locally, and supportive care, according to local standards, may also have included face-to-face psychosocial support and psychotropic drugs.

Assessments

Assessments were conducted electronically directly within the Web-based program via the open source application LimeSurvey at baseline (T1) and after the intervention or waiting period (control group), respectively (T2). In addition, 2-month follow-up (T3) was performed in both groups. Feasibility was assessed at two different levels: feasibility of online recruitment and feasibility for patients to participate in the STREAM program while undergoing first-line treatment. According to the study protocol, feasibility of online recruitment was confirmed when 120 patients (ie, the number needed to assess the primary efficacy outcome) were recruited within a 2-year period; feasibility of participation during treatment was prespecified as a descriptive end point—more specifically, the percentage of completers' in the intention-to-treat (ITT) population, where completers' were defined as patients who worked with at least six of eight modules.

Efficacy End Points

Primary end point was quality of life at T2, assessed in the validated German version of the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) questionnaire.[23] The first 27 items are common to all Functional Assessment of Cancer Therapy (FACT) questionnaires and cover different domains of quality of life, specifically physical well-being (seven items), social well-being (seven items), emotional well-being (six items), and functional well-being (seven items). The last 13 items focus on various aspects of fatigue, a key aspect of quality of life in patients with cancer, particularly during active treatment.[6] FACIT-F total score ranges from 0 to 160. Higher scores represent better quality of life. Minimal clinically meaningful differences are not well defined but have previously been set between 7 and 9 points, both as intraindividual changes and differences in groups.[19,24] For our sample size calculation, we relied on the more stringent definition of 9 points. We chose FACIT-F, rather than the distress thermometer (DT), as primary outcome because overall well-being, reflected by the multidimensional FACIT-F questionnaire, seems clinically more important than changes in a single domain.[23] Also, FACIT-F is better validated as outcome measure than DT, which often serves as screening tool.[21]

Secondary efficacy end points were assessed at the same points in time and evaluated psychological distress and anxiety and depression using the validated German versions of the National Comprehensive Cancer Network DT[21] and the Hospital Anxiety and Depression Scale (HADS),[25] respectively. Effect sizes are expressed as partial eta squared (η_p^2),[26] with the following cutoffs to categorize effect sizes into small (0.01), medium (0.06), and large (0.14), as suggested by Cohen.[27] Subgroup analyses are highly explorative and, therefore, not part of this report.

Assessments During the Intervention

Usability was evaluated after the first and last module with the System Usability Scale (SUS), where scores > 70 represent good usability.[28] Therapeutic alliance between patients and online therapist was assessed using the Working Alliance Inventory (WAI) in its short form (12 items),[29] adapted with 2 additional items specific to the online context after each module. Total score ranges from 0 to 5, and scores > 3.5 have been rated as good working alliances.[30]

Statistical Analyses and Sample Size Calculation

R version 3.4.0 software (R Foundation for Statistical Computing, Vienna, Austria) was used for all analyses. All analyses were performed in the ITT population defined as all patients who were randomly assigned. The per-protocol (PP) population included all patients who completed the program in the intended timeframe (ie, the time between random assignment and T2 assessments did not exceed 16 weeks, which is twice the minimal duration of the program).

To demonstrate a 9-point difference[31] in FACIT-F total score between baseline and T2 (after 8 weeks) in the intervention group with a statistical power of 0.80 at a significance level of .05 (two sided), 60 participants were needed in each of the two conditions. We assumed normally distributed data in both groups with a standard deviation of ± 18 (Pandey M, et al: World J Surg Oncol 3:63, 2005). Data preparation of all continuous dependent variables included tests for normality, homogeneity of variances, and examination of outliers.

Efficacy Analyses

Efficacy outcomes (primary end point of FACIT-F; secondary end points of DT and HADS) were modeled with analysis of covariance (ANCOVA), using the postscore (T2) as dependent variable, the prescore (T1) as covariate, and group allocation (intervention *v* control) as independent variable. ANCOVAs were further adjusted for the stratification factor distress ($DT \geq 5$ *v* < 5). Multiple imputations ($n = 99$) by chained equations[32] using predictive mean matching[33] incorporating all variables of the linear models underlying ANCOVA were used to impute missing outcome values.[34] To assess the robustness of the results, sensitivity analyses were conducted for all outcomes in the perprotocol population. In addition, sensitivity analyses were carried out using other methods for handling missing data; more specifically, CC analyses and LOCF analyses, as specified in the protocol,[20] were computed for all outcomes on both the ITT and PP populations.

2-Month Follow-Up Analyses

For the follow-up period, score changes from T2 to T3 were analyzed with paired *t* tests separately for each group (no between-group comparisons). Again, multiple imputations were used for missing data. Sensitivity analyses were conducted using CC and LOCF analyses in the ITT and PP populations.

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The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Table A1. Content of Web-Based Stress Management Program STREAM

Module	Psychoeducation	Reflection on Status	Strategies and Exercises
Introduction: What is stress?	Nature of stress in general and specifically in relation to cancer	My individual stressors	Diary,* body scan†
Bodily stress reduction	Bodily sensations during stress and adverse effects of anticancer treatment, focus on fatigue	My individual bodily stress reactions	Stress protocol*
Cognitive stress reduction	Thoughts and their interaction with emotions and bodily sensations	My negative thought patterns	Progressive muscle relaxation†
Emotional stress reduction	Feelings and cancer-related emotions such as anxiety and worries	My feelings and worries	Walk on the beach,† relaxation protocol,* negative thought cycle,† relationship of body position and thoughts,* thinking styles and reflection*
Mindfulness and acceptance of thoughts and emotions	Meaning and implementation of mindfulness and acceptance in daily life (as opposed to active strategies learned in modules one to four)	My definition and experiences with acceptance	Thoughts on clouds,† mountain meditation,† emotional emergency kit†
Activation of resources: quality of life and pleasure	Introduction of models for balance between burden and resources	My individual resources	Acceptance story*†
Activation of resources: social network and communication skills	Social network and the role of a supportive environment	My individual social network and current needs	Body scan*†
Summary	Overview and documentation of the last 7 weeks	My experiences with the program	Integration of mindfulness,* winter walk,† spring awakening,† health cycle,* planning activities,* week planner,* friendly feelings toward our own body,† enjoyment training,* communication skills,* walk on the beach,† winter walk,† spring awakening,† four seasons†

Abbreviation: STREAM, Stress-Aktiv-Mindern.
*Instructions and worksheets.
†Audio file: story, relaxation, or guided imaginary exercise.

Table A2. Sensitivity Analyses for Efficacy Outcomes

Measure	Mean (95% CI) *P*					
	ITT/MI	ITT/CC	ITT/LOCF	PP/MI	PP/CC	PP/LOCF
FACIT-F (dependent variable: T2)						
FACIT-F (T1)	0.61 (0.47 to 0.74) *P* < .001	0.61 (0.48 to 0.74) *P* < .001	0.67 (0.54 to 0.79) *P* < .001	0.66 (0.52 to 0.79) *P* < .001	0.66 (0.52 to 0.79) *P* < .001	0.66 (0.52 to 0.79) *P* < .001
DT (T1) ≥ 5: true − false	2.50 (−5.27 to 10.27) *P* = .53	2.21 (−5.62 to 10.04) *P* = .58	3.07 (−4.27 to 10.40) *P* = .41	4.15 (−3.56 to 11.86) *P* = .29	4.15 (−3.56 to 11.86) *P* = .29	4.15 (−3.56 to 11.86) *P* = .29
Group allocation: intervention group − control group	8.59 (2.45 to 14.73) *P* = .007	8.70 (2.53 to 14.88) *P* = .007	7.23 (1.38 to 13.07) *P* = .02	10.71 (4.49 to 16.94) *P* < .001	10.71 (4.49 to 16.94) *P* < .001	10.71 (4.49 to 16.94) *P* < .001
Observations	129	117	129	95	95	95
DT (dependent variable: T2)						
DT (T1)	0.18 (0.01 to 0.35) *P* = .04	0.18 (0.01 to 0.35) *P* = .04	0.27 (0.11 to 0.43) *P* = .002	0.14 (−0.04 to 0.33) *P* = .14	0.14 (−0.04 to 0.33) *P* = .14	0.14 (−0.04 to 0.33) *P* = .14
Group allocation: intervention group − control group	−0.85 (−1.60 to −0.10) *P* = .03	−0.87 (−1.61 to −0.12) *P* = .03	−0.79 (−1.51 to −0.08) *P* = .04	−1.11 (−1.95 to −0.26) *P* = .02	−1.11 (−1.95 to −0.26) *P* = .02	−1.11 (−1.95 to −0.26) *P* = .02
Observations	129	117	129	95	95	95
HADS (dependent variable: T2)						
HADS (T1)	0.55 (0.43 to 0.67) *P* < .001	0.55 (0.43 to 0.67) *P* < .001	0.60 (0.49 to 0.72) *P* < .001	0.56 (0.43 to 0.68) *P* < .001	0.56 (0.43 to 0.68) *P* < .001	0.56 (0.43 to 0.68) *P* < .001
DT (T1) ≥ 5: true − false	0.70 (−1.45 to 2.84) *P* = .52	0.71 (−1.43 to 2.86) *P* = .51	0.57 (−1.45 to 2.59) *P* = .58	0.38 (−1.95 to 2.71) *P* = .75	0.38 (−1.95 to 2.71) *P* = .75	0.38 (−1.95 to 2.71) *P* = .75
Group allocation: intervention group − control group	−1.29 (−3.02 to 0.45) *P* = .15	−1.29 (−3.02 to 0.44) *P* = .15	−0.92 (−2.56 to 0.71) *P* = .27	−2.09 (−4.03 to −0.16) *P* = .04	−2.09 (−4.03 to −0.16) *P* = .04	−2.09 (−4.03 to −0.16) *P* = .04
Observations	129	117	129	95	95	95

NOTE. Results of analyses of covariance for postintervention scores (T2) with baseline scores (T1) as covariate, adjusted for stratification factor distress in FACIT-F and HADS but not in DT because this would result in model overspecification. First column (ITT/MI): primary analyses in the ITT population with MI for missing data. Other columns: sensitivity analyses in ITT and PP populations using MI, CC analyses, and LOCF analyses for missing data. Note that the models for the PP population are identical because there were no missing data.

Abbreviations: CC, complete case; DT, Distress Thermometer; FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue; HADS, Hospital Anxiety and Depression Scale; ITT, intention to treat; LOCF, last observation carried forward; MI, missing imputation; PP, per protocol.

Table A3. Sensitivity Analyses for Follow-Up Assessments

Measure	Mean (95% CI) *P*					
	ITT/MI	ITT/CC	ITT/LOCF	PP/MI	PP/CC	PP/LOCF
Follow-up intervention group						
FACIT-F (dependent variable: T3 − T2	4.69 (−0.74 to 10.12) *P* = .09	4.69 (−0.86 to 10.25) *P* = .10	3.75 (−0.68 to 8.19) *P* = .10	2.19 (−4.10 to 8.48) *P* = .49	2.32 (−4.04 to 8.68) *P* = .47	2.26 (−3.93 to 8.45) *P* = .47
Observations	65	52	65	38	37	38
DT (dependent variable: T3 − T2)	−0.29 (−1.03 to 0.44) *P* = .43	−0.27 (−1.03 to 0.49) *P* = .49	−0.22 (−0.82 to 0.39) *P* = .48	−0.15 (−0.98 to 0.69) *P* = .73	−0.14 (−0.96 to 0.69) *P* = .75	−0.13 (−0.94 to 0.67) *P* = .75
Observations	65	52	65	38	37	38
HADS (dependent variable: T3 – T2)	−0.82 (−2.28 to 0.65) *P* = .27	−0.88 (−2.35 to 0.58) *P* = .24	−0.71 (−1.88 to 0.46) *P* = .24	−0.10 (−1.60 to 1.40) *P* = .90	−0.14 (−1.65 to 1.38) *P* = .86	−0.13 (−1.61 to 1.34) *P* = .86
Observations	65	52	65	38	37	38
Follow-up control group with delayed intervention						
FACIT-F (dependent variable: T3 − T2)	10.95 (6.18 to 15.71) *P* < .001	12.03 (7.39 to 16.68) *P* < .001	9.59 (5.72 to 13.46) *P* < .001	11.68 (6.83 to 16.53) *P* < .001	11.85 (7.12 to 16.58) *P* < .001	10.39 (6.14 to 14.65) *P* < .001
Observations	64	51	64	57	50	57
DT (dependent variable: T3 − T2)	−1.25 (−1.94 to –0.55) *P* < .001	−1.31 (−2.02 to –0.61) *P* < .001	−1.05 (−1.62 to –0.47) *P* < .001	−1.25 (−1.94 to –0.56) *P* < .001	−1.24 (−1.94 to –0.54) *P* < .001	−1.09 (−1.71 to −0.46) *P* < .001
Observations	64	51	64	57	50	57
HADS (dependent variable: T3 − T2)	−2.83 (−4.30 to −1.36) *P* < .001	−2.63 (−4.13 to −1.12) *P* < .001	−2.09 (−3.31 to −0.87) *P* = .002	−2.86 (−4.41 to −1.31) *P* < .001	−2.62 (−4.16 to −1.08) *P* = .002	−2.30 (−3.66 to −0.94) *P* = .002
Observations	64	51	64	57	50	57

NOTE. Results of paired *t* tests for 2-month follow-up scores (T3) with T2 scores as baseline. First column (ITT/MI): primary analyses in the ITT population with MI for missing data. Other columns: sensitivity analyses in ITT and PP populations using MI, CC analyses, and LOCF analyses for missing data.

Abbreviations: CC, complete case; DT, Distress Thermometer; FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue; HADS, Hospital Anxiety and Depression Scale; ITT, intention to treat; LOCF, last observation carried forward; MI, multiple imputation; PP, per protocol;

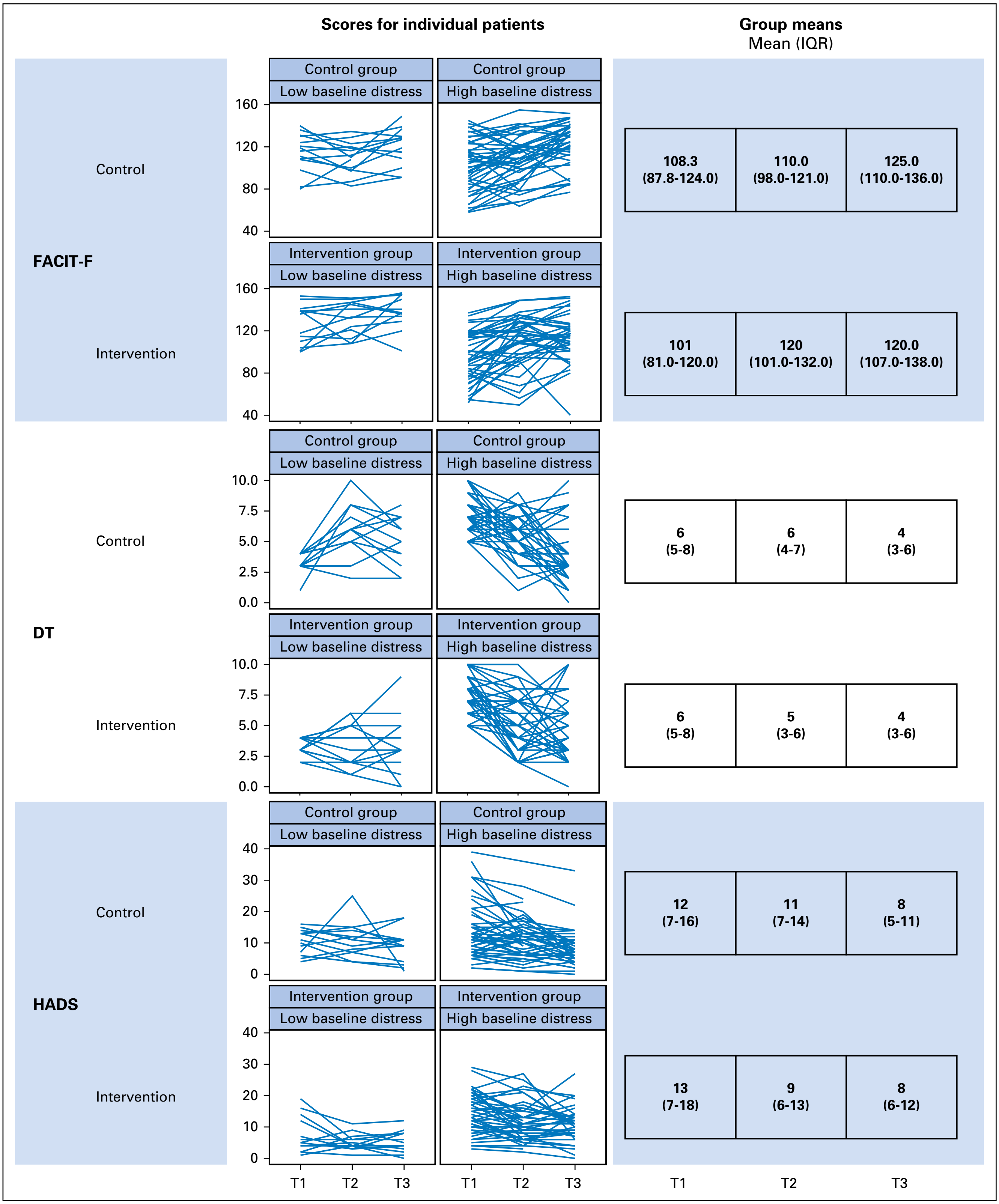

Fig A1. Individual patients' scores and group means for all time points. DT, Distress Thermometer; HADS, Hospital Anxiety and Depression Scale; IQR, interquartile range; FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue.

5. Discussion

The studies presented in this thesis succeeded to identify patients with a need for support. We first identified a vulnerable group of ambivalent patients with high distress levels and 'low uptake behavior', i.e. those patients who had refrained from psycho-oncological support. Secondly, we successfully developed the tailor-made online intervention tool STREAM for newly diagnosed cancer patients. Usability of STREAM was tested, and the results were taken into account for the finalization of the STREAM program. Third and most importantly, we demonstrated the feasibility and efficacy of STREAM in a randomized, controlled clinical trial in the target population during active treatment of various types of cancer. Newly diagnosed cancer patients reported significantly better QoL and less distress after participating in STREAM. Detailed discussion of the individual studies is provided in the publications attached (section 4). Below, some findings that should be integrated into routine clinical practice are briefly summarized.

5.1 Identifying patients with a need for support

Focusing on the patients' intention to seek support and their actual use of psycho-oncological assistance, we identified a vulnerable group of ambivalent patients with high distress levels and low uptake behavior. The distress indicator DT was used with a dichotomous answering option (yes/no). By means of qualitative content analyses, we detected the "maybe" group which was lost when using the dichotomous approach. Ambivalent patients stated reasons for and against support. Therefore, patients with an ambivalent intention to accept support might stay unrecognized in clinical practice when using the dichotomous answering option as their answer to this question is usually "no".

It is difficult to systematically capture emotional turmoil due to the highly variable conditions of cancer patients. Type of disease and treatment as well as survival perspectives are highly heterogeneous in this patient population. Thus, the clinical implication of our results is that the need of supportive care in these patients should be assessed by using a trichotomous response format with the answer possibilities “yes”, “maybe”, and “no” within the DT assessment. In response to our research results, we are currently testing this approach at the University Hospital Basel. Moreover, we suggest to routinely re-evaluate the distress levels of patients to more fully understand the changes in the patients’ willingness to accept mental support. Assessment of the needs of psycho-oncological patients is hampered by the "emotional rollercoaster rides" experienced by many patients. Moreover, cancer patients with untreated psychosocial distress are at risk of non-adherence to cancer treatment [DiMatteo et al., 2000; Kennard et al., 2004; Markovitz et al., 2017], poorer QoL [Stark et al., 2002], and psychiatric comorbidities [Kissane, 2014; Mitchell et al., 2011; Zabora et al., 2001]. In addition, clinical embedding of the mental health aspect of physically ill patients might be helpful to overcome stigmatization of psychological face-to-face care in routine practice [Tondorf et al., 2018]. If the resistance to face-to-face support is pronounced, a low-threshold option, such as the STREAM program, would be of particular merit.

5.2 Tailored online intervention - the impact of usability testing

To detect even small flaws of an online intervention program, structured usability testing in the target population is of critical importance. As pointed out in the literature [Leykin et al., 2012], the usefulness and effectiveness of online tools hinges on the easy and reliable handling of the underlying technology.

The aim of this study was to adjust the final website to the specific use by our target population. In this preparative step, we detected as many as 122 specific usability problems [Grossert et al., 2019]. These predominantly concerned website relevant topics of functionality (50.8%) and navigation (29.5%).

A multidisciplinary team consisting of an oncologist, psychologists, human-computer interaction researchers, and software engineering specialists analyzed the problems and subsequently solved them. The specific usability problems identified in this analysis allow some general recommendations. First, it is essential to use simple but specific wording and to use it consistently throughout the program. Second, users should be able to view the entire page without having to use the scroll function. Thus, the text should be concise and written in a language that is readily understood. Third, the intuitive use of a webpage is essential, and this will solve the majority of minor usability problems. Finally, close collaboration with the software engineering specialist is indispensable to find effective and affordable solutions.

By removing the sources of these errors, we were able to implement a revised version of the STREAM tool prior to launching the randomized, controlled trial assessing the efficacy and feasibility of the program. Reliable technical use provided the foundation for the modest dropout rate (i.e. less than 10%) and highly satisfactory outcome of the trial [Grossert et al., 2018].

5.3 Feasibility and efficacy of STREAM

5.3.1 Feasibility

Feasibility of the STREAM program was assessed on the basis of successful recruitment, high completion rate with a low dropout rate, as well as the established therapeutic alliance. Recruitment to the STREAM study was successful, and we reached patients in the German-speaking countries Switzerland, Germany, and Austria. For detailed patient characteristics please see Table 1 of the publication [Grossert et al., 2018] in section 4.

Recruitment was successful with 129 included patients. Although recruitment of a sufficiently high number of patients was a crucial step. Our recruitment strategy included online advertising (e.g. Google AdWords) since we were aware that one of the most frequent reasons for trial discontinuation is poor recruitment. Clearly, premature trial discontinuation is accompanied by a waste of administrative and financial resources as well as distorted perception of a specific research field because of unpublished results [Kasenda et al., 2014]. As a subproject, we contrasted inclusion rate and costs of two online advertising channels (Google AdWords [GAW] and Facebook advertisement [FA]) over a period of 2 months with those associated with traditional recruitment strategies (e.g. flyers, posters, advertisement in magazines, and word-of-mouth). Overall, GAW performed better than FA and resulted in significantly higher registration rates (n_{GAW} 32 vs. $n_{FA}=19$) and inclusion rates ($n_{GAW}=14$ vs. $n_{FA}=8$). During the 2-month control period before implementation of any active online advertisement, the recruitment rate was markedly lower (registration $n_{control}=9$; inclusions $n_{control}=4$). The cost per included patient was CHF 265.17 for GAW and CHF 459.86 for FA. Our results are in line with those of a review [Lane et al., 2015] identifying Google to be the more effective platform for the recruiting of trial subjects, whereas Facebook performed better when recruiting younger participants (age <25 years). These evaluations provided insight into the reachability of cancer patients via online advertisement (publication in preparation).

The STREAM program was completed by 80% (n=52) of participants. Completion was defined by finalizing three-quarters of the program consisting of 8 modules. Remarkably, 75% (n=49) of patients in the intervention group completed all 8 modules. Moreover, time to completion of the STREAM program (i.e. the time between the start of module 1 and post-intervention assessment) was approx. 12 weeks (mean 11.7 weeks; IQR 9.1 to 18.6). The program was intended to be completed within 8 weeks, but it turned out that due to the burden caused by the therapies and side effects, a somewhat longer period was required to complete the modules. However, the dropout rate was low (n=11; 8.5%). Thus, we achieved a high completer rate and low dropout rate, which is impressive when the context of the disease and demands on the patients are considered. In the literature, high dropout rates are documented in this patient population [Melville et al., 2010; Wootten et al., 2014a]. While female gender, sufficient time, and personalized intervention are predictors for higher compliance with the online intervention [Beatty & Binnion, 2016], illness factors (specifically side effects of cancer treatment), distress, and technical barriers appear to be the main reasons for poor compliance [Beatty et al., 2017; Brebach et al., 2016; Christensen et al., 2009]. Moreover a good adherence and therefore low dropout rate has an important clinical implication – poor adherence limits exposure to the full STREAM program, thus diminishing their psycho-oncological support [Eysenbach, 2005]. In turn, this may impact on psychological health outcomes [Donkin et al., 2011]. In addition, patients may be at risk of entering a vicious circle; higher distress leads to lower compliance, and this may result in more side effects and even shorter overall survival.

A possible reason for the high completion rate is the successful development of a therapeutic working alliance. STREAM has been designed as a minimal-contact program; this includes a weekly written contact with a psychologist. The overall therapeutic working alliance between patient and therapist was good (WAI mean 3.77 [IQR 3.38 to 4.14], [Berger, 2016]). As stipulated in the literature [Rehse & Pukrop, 2003], a psychosocial intervention should be planned for at least 12 weeks, which is approximately the duration required for a stable relationship.

Besides the good and stable working alliance, we observed an improvement of the working alliance during the program between the modules, with the highest rate achieved in the final module. In-depth analysis of the dynamics of the working alliance has not yet been conducted. From the patient's perspective, criteria of a good working alliance are trust, empathy, sympathy, sufficient time, a solution-oriented approach, and a respectful interaction [Hermer & Röhrle, 2008]. We took these criteria into account when developing the STREAM program, based on the notion that a good therapeutic relationship is a key predictor of successful psychological treatment in general [Grawe et al., 1994]. The presence of a therapeutic relationship between the patient and healthcare professional in online interventions is well established [Anderson et al., 2012;

Bisseling et al., 2019; Klasen et al., 2013; Knaevelsrud & Maercker, 2007; Preschl et al., 2011].

Interestingly, the time per patient spent by psychologists in the STREAM program was low. The psychologists spent a median time of 165 (IQR 127 - 210) min for administering (e.g. time for administration, reading the module progress and formulating written answers) the online intervention with an average of 13.3 (IQR 9.5 to 17.9) min per patient each week. Our findings support the suggestion that the length of time devoted to patients during online interventions can be considerably reduced, and that the extent of support (e.g. number of messages) does not affect the working alliance [Andersson et al., 2008; Klein et al., 2009]. The provision of support and feedback when requested seems to be satisfactory [Andersson, 2016]. These aspects were of critical importance to us during the conduct of the clinical trial and support of the participants.

5.3.2 Efficacy: QoL and distress improvement

In our randomized, controlled trial, newly diagnosed patients with cancer reported significantly better QoL and lower distress after participating in the therapist-guided online stress-management intervention. We discussed our finding in detail in the publication [Grossert et al., 2018]. Below, some aspects relevant to the existential dimension of a cancer diagnosis are summarized.

We showed that QoL measured with the FACIT-F at the post-intervention time point was significantly higher in the intervention group than the control group. When compared to findings in published studies [Cella et al., 2002; Temel et al., 2010], the changes seen in our study can be assumed to be clinically meaningful with a mean increase in total FACIT-F score of 8.59 (95%CI 2.45 to 14.73; $p=0.007$) in the ITT population and of 10.71 (95%CI 4.49 to 16.94, $p=0.001$) in the PP population. The most distinct improvement was seen in the subscales ‘fatigue’, ‘physical wellbeing’, and ‘functional wellbeing’. A good QoL consists of a balance between resources, hopes, and burdens, while fatigue is a subjective sensation of weakness, lack of energy, or tiredness [Stone et al., 1998]. Fatigue is reported to be the most common complaint among cancer patients [Carlson et al., 2004; Duijts et al., 2011]. A recent meta-analysis conclude that exercise and psychological interventions are effective for reducing cancer related fatigue during and after cancer treatment, and are significant better than the available pharmaceutical options [Mustian et al., 2017].

The STREAM program offers an approach to focus on individual processes to adapt to the disease and its fundamental threats. The content includes psychoeducation, reflection, and acquisition of coping strategies. Amongst others, these include the fostering of a more efficient use of one's own resources, in line with published results that both behavioral techniques and physical exercise improve psychosocial functioning and QoL [Duijts et al., 2011].

Distress measured with the DT at the post-intervention time point was significantly lower in the intervention group than the control group (-0.85; 95%CI -1.60 to -0.10; p=0.03). Systematic recording of distress and QoL in cancer patients is well established [Mehnert et al., 2018; Pearce et al., 2008]. While it is indisputable that QoL is of substantial importance, it is inherently difficult to measure [Testa & Simonson, 1996]. When interpreting the results, the conceptual overlap with distress caused by the existential threat of the illness must be taking into account. The DT itself is a simplified and widely used assessment tool of general distress with a single number (VAS 0-10) representing distress [National Comprehensive Cancer Network, 2019].

There has been considerable scientific interest in the psychological adjustment to a sudden threat of mortality [Baker et al., 2016; Vehling & Kissane, 2018]. Fears of dying, suffering, loss of body parts and functionality, and loss of autonomy play an important role during adjustment to the disease [Parle et al., 1996]. Velikova and colleagues investigated the impact of recording QoL in cancer patients and concluded that attentiveness and feedback are important components of a therapeutic intervention’s effectiveness [Velikova et al., 2004]. Moreover, the authors found that regular assessment of QoL itself favorably affected the physician-patient communication and resulted in better QoL and emotional functioning in some patients [Velikova et al., 2010]. It seems that the regular attention to an individual’s QoL might be an effectiveness factor itself. Thus, future attention should be directed towards placebo research, which offers a potential for improvement of fatigue [Zhou et al., 2019]. Our study did not address this specific question, and further studies specifically focusing on these issues are needed.

For the sake of completeness, the potential positive impact of cancer should be mentioned. A severe life event can be an opportunity for positive personal growth as well as distress [Aldwin & Sutton, 1998; Parkes, 1971]. The positive aspect of suffering from cancer, often referred to as post-traumatic growth, has been gaining interest in the last decade. Such post-traumatic growth has been defined as a positive psychological change experienced as a result of the struggle with highly challenging life circumstances [Calhoun & Tedeschi, 2001]. We did not evaluate the potential of any positive impact of the illness on QoL and distress in our randomized, controlled trial.

Another matter of importance is the timing of administering the intervention. STREAM was implemented in the early phase of the course of disease, i.e. at the time of starting antitumor therapy. Previous studies suggested that QoL data recorded early in the course of disease and treatment are a possible cue for optimized treatment. Stickel and Goerling proposed the use of QoL as an early warning system [Stickel & Goerling, 2018]. Therefore, interventions targeting QoL at an early stage are of substantial interest. Published results indicate that QoL is the most common patient-recorded outcome showing an association with overall survival in cancer patients [Gotay et al., 2008; Quinten et al., 2009]. Moreover, the association between distress and cancer was investigated for decades without a clear understanding of the underlying mechanism. With the rapid development of successful immunotherapies, these research questions have gained new momentum. Recently, Obradovic et al. published data from mice modeling on glucocorticoid receptor activity assuming that stress management in breast cancer patients plays a role in survival-time prolongation [Obradovic et al., 2019]. Further longitudinal studies are needed to confirm whether improved QoL after completion of STREAM translates into improved treatment tolerability and/or even favorable disease course.

Our results may allow estimations about the potential public health impact of the STREAM program. Psycho-oncology with specific interventions is gaining increasing interest. Within a short time, some promising programs have been developed, addressing QoL and distress in cancer patients [Bao et al., 2019; Beatty et al., 2016; van den Berg et al., 2015; van den Berg et al., 2012; Willems et al., 2017]. Hummel and colleagues developed a promising internet-based CBT addressing sexual functioning with improvement in body image. In this trial, no significant effects of distress and QoL were found [Hummel et al., 2017]. It is hoped that the successful implementation of these programs will provide insight into future possibilities and limitations of psycho-oncological support delivered online. Moreover, guidelines [Proudfoot et al., 2011] for executing studies and reporting data enable researchers to repeat and compare studies. This, in turn, may lead to an improvement of programs and patient care in the future.

In conclusion, STREAM offers a comprehensive intervention addressing QoL enhancement and distress reduction in cancer patients. STREAM is an alternative to face-to-face interventions in the psycho-oncological care landscape. Furthermore, this form of support may overcome the resistance to psychological help among patients with time constraint and high distress levels as well as those who live in places far removed from medical and psychological facilities.

5.4 Clinical integration of STREAM

Digitalization in the healthcare sector is progressing rapidly with a benefit for all populations, especially those living far away from medical and psychological facilities. As Hesse formulates it, "*in theory, the internet should help solve the last mile problem by making the best knowledge in the world available to everyone worldwide at a low cost and no delay"* [Hesse, 2019]. With STREAM, we developed a treatment option using online delivery for patients living outside of urban centers. Besides the advantage that the internet intervention bridges an actual local distance, it also supports individuals in maintaining their subjective boundaries in their contact option with a professional therapist.

Although the reasons for none or ambivalent acceptance of an intervention are multifaceted [Tondorf et al., 2018], one important factor for patients to consult a professional psycho-oncologist is their personal inhibition threshold. Many patients have difficulties in addressing integrity disturbances directly and verbally in a professional therapeutic context since they are ashamed of exposing their (perceived) weakness [Kaul & Fischer, 2016]. Individuals have a good sense of their own felt boundaries as an area defined by unconscious proprioception in its extension, which gives them a feeling of security and wholeness [Scaer, 2014]. The perception of boundaries comprises a spatial and physical closeness and distance on the one hand and an emotional closeness and distance on the other hand [Kaul & Fischer, 2016].

For patients with a clear need of support who refuse such help because of their intra-individually perceived suffering and integrity disturbance, online therapy may have a double benefit. First, more patients may undergo psycho-oncological therapy due to a lower inhibition threshold. Second, the effectiveness of their therapy is increased as individual contact boundaries are respected due to written contact. Beyond the general effect of lowering the inhibition threshold, online therapy may also have specific benefits for patients with a life-threatening diagnosis, such as cancer. A cancer diagnosis threatens the fundamental assumptions about a person’s own control of his or her life, often leading to the questioning of all aspects of his or her life, including the individual’s self-perception of being invulnerable or even immortal [Janoff-Bulman, 1999]. These changes might result in “existential distress” [Vehling & Philipp, 2018]. In the course of dealing with one's own life or mortality, the known, mostly unconscious regulatory patterns of proximity and distance often shift, and patients may find it difficult to continue the familiar daily routine that provides security [Salander, 2018].

In the early course of the disease, the struggle with regulating closeness and distance might be worsened by the many hospital and physician visits and difficult treatment decisions patients have to make. Patients may fear to lose their autonomy by having to accept inpatient stays with reduced privacy and invasive treatments, such as drug injections and infusions [Norskov et al., 2019]. The standardized diagnostic and therapeutic procedures leave little room for individual decisions since they depend on established schemes used by the treatment center. This might result in an "excess" of emotional, cognitive, and physical stimuli, and violations of individual needs seem inevitable. According to Lazarus and Folkman, the reactions to this are highly individual and depend on available coping strategies [Lazarus & Folkman, 1984]. Patients experience distress and diminished QoL, which negatively affects their mental health [Penedo et al., 2013; Rehse & Pukrop, 2003] and therapy compliance [Chambers et al., 2012; Park & Gaffey, 2007].

Under these stressful conditions, an additional appointment with a psycho-oncologist may not be fully effective as the patient is not receptive to additional treatment due to high stress levels. Psycho-oncological online support with minimal contact has the benefit to let patients feel more in control of their life. Online therapy may therefore be more effective by overcoming the challenges of stress-inducing face-to-face consultations.

The following two statements by participants underline the empowerment factor in delivering coping strategies: *"The program showed me how to deal better with my emotional world, the ups and downs. The modules have given me many very good different ways to deal with stress phases".* Another participant stated, *"It makes me feel good to do something for myself and not just do nothing".* Online support in the form of STREAM (guided self-help, minimal-contact) represents a good compromise between no support at all and regular face-to-face consultations and thus supports patients in their self-efficacy in dealing with cancer. Moreover, the tool might support ambivalent patients by protecting and respecting their needs for closeness (indigence) and distance (autonomy). Online interventions are often accused of sacrificing the important therapist-patient relationship. This notion has been refuted in recent years as stated by Cuijpers: "*It seems safe to conclude that guided self-help and face-to-face treatments can have comparable effects. It is time to start thinking about implementation in routine care"* (p. 1, [Cuijpers et al., 2010].

I postulate that respecting the patient's boundaries – physical and emotional - supports an effective therapy. Further research is needed to validate this speculation, as our study design was not dedicated to this question. However, our randomized, controlled trial achieved exceptionally high adherence values, which may indicate that patients were well supported by the minimal-contact format. These promising data should encourage new specific research on the balance between closeness and distance for effective therapy.

5.5 Limitations

The project entitled "Understanding why cancer patients accept or turn down psycho-oncological support: A prospective observational study including patients' and clinicians' perspectives on communication about distress" was a single-center study conducted in a large cancer center at a major Swiss university hospital. Single-center studies are common in the medical literature (e.g. [Ellis et al., 2009], and can provide valuable heuristic information. However, they may not be representative of the population worldwide as they are likely to reflect national and cultural variations.

A limitation of the STREAM usability pre-study was that we tested it in the laboratory, which may not fully represent the use of the program at home. If problems occurred during the use of the online program, participants were able to ask for assistance. Second, the small sample size may also limit the generalizability of our results. However, it is important to note that usability tests are qualitative methods that aim to reveal the most important issues that may arise during a patient's interaction with a website. Published literature suggests that the majority of usability problems and flaws can be identified in small samples of up to 10 subjects [Tullis & Albert, 2013].

Shortcomings of the main project entitled “Web-based stress management for newly diagnosed cancer patients (STREAM-1): a randomized, wait-list controlled intervention study” include the following: First, STREAM was designed for newly diagnosed cancer patients. Nevertheless, women with breast cancer undergoing curative treatment represented the vast majority of the study population. This renders the generalizability of the results questionable, particularly for male patients and patients in the palliative setting. There is evidence that also men experience a benefit in distress reduction [Wootten et al., 2014b]. Second, more patients in the control group than the intervention group reported face-to-face psychological support and use of psychotropic drugs at baseline, although the difference was not statistically significant. Because we did not collect data on the time spent with psychologists during the trial, the potential bias cannot be quantified. Third, we opted for a wait-list (care-as-usual) controlled design. A wait-list controlled design is generally accepted to assess the effect of time on the outcome of interest. However, the post-intervention assessment time points for the control group were rigid and defined prospectively, whereas the post-intervention assessment time points in the interventions group depended on the duration of the intervention and were therefore more variable. Hence, time sensitivity is only partially accounted for. Dynamic wait-list controlled designs have been proposed to minimize this potential bias [Brown et al., 2006].

Another shortcoming of our trial was that we showed a benefit for distress and QoL for patients only early after diagnosis with a limited follow-up. It is conceivable, however, that such an early intervention [Temel et al., 2010] may be of particular importance to prevent chronification of distress [Enns et al., 2013]. The question whether reduced distress and improved QoL after STREAM translate into better treatment tolerability and favorable disease course warrants additional studies.

Thereby, it is important to take into account the extent to which psychological stress is a risk factor for cancer disease progression, as it is for the development of psychological disorders. This includes the investigation of biological variables such as cortisol levels, which was found to affect overall survival in breast cancer patients [McGregor & Antoni, 2009]. Despite numerous epidemiological studies, the underlying mechanism is not yet clarified [Rensing & Rippe, 2009].

Moreover, we did not consider the potential positive impact of a cancer diagnosis itself. Post-traumatic growth has been defined as a positive psychological change and adaption as a result of the struggle with highly challenging life circumstances [Calhoun & Tedeschi, 2001]. The inclusion of post-traumatic growth will be an important aspect for further investigations.

5.6 Outlook

The prevalence of cancer will continue to rise. The incidence in 2030 is estimated at over 20 million people worldwide [Arndt et al., 2016; Global Cancer Observatory, 2019]. Due to the improved treatment options, the number of long-term cancer survivors will also increase. The psycho-oncological services are constantly being expanded and are routinely offered to and strongly recommended in patients with marked distress. This leads to an increasing number of patients seen by a psycho-oncologist. Due to the rapid technical changes, online support will continue to grow and will find its way into standard care of cancer patients. Moreover, online support modules have a considerable potential to support large numbers of cancer patients in a broadly accessible and cost-effective manner [McAlpine et al., 2015]. Online minimal-contact programs can be used as a source of information, form of communication, and therapeutic tool.

The upcoming ICare project funded by European Union’s Horizon 2020 research aims to establish a comprehensive model of promoting mental health in Europe. ICare is designed to improve existing healthcare models, open new access paths, and overcome traditional implementation barriers. This large project brings together mental health experts from all of Europe [Jacobi & Partners, 2019]. Other initiatives are currently being developed to tailor information and support to a larger community of cancer patients and their relatives (e.g. https://.kanker.nl in the Netherlands, and https://lebensheldin.de/ in Germany). In the next few years, it remains to be seen whether internet-based support in routine application can confirm the promising research results.

Cancer-related fatigue is one of the five top high-priority research areas designated by the National Cancer Institute Clinical Oncology Research Program in the United States [Mustian et al., 2017]. STREAM has the potential to be linked to these platforms, especially addressing patients suffering from reduced QoL and cancer-related fatigue. Currently, we are working on its implementation in the German-speaking healthcare sector with the perspective to translate its contents into different languages. Since our feasibility and efficacy results for STREAM proved positive [Grossert et al., 2018], further implementation of the tool and larger clinical studies can now be planned.

Future investigations of online interventions will aim to complete the picture of effectiveness and to better understand underlying processes. Moreover, social change with the increasing influence of new technical possibilities will also be reflected in the psychological support of patients. In addition, the debate about the daily influence of new media and their fast technical development and innovation (e.g. virtual reality, artificial intelligence) will continue to challenge individuals, care givers, patients, and the entire society.

5.7 Conclusion

Despite improved diagnostic and therapeutic options, the diagnosis of cancer remains an enormous threat, and QoL of affected individuals is inevitably impaired. Oncology was one of the first areas in which the assessment of health-related QoL was systematically measured to describe the patient's condition and functional status during the course of disease. Our studies offer a novel method to analyze the supportive care needs of cancer patients. The pre-study findings highlighted the importance of conducting a professional usability test in the target population during the development of an online intervention tool. These assessments were an important step in the planning of the randomized, controlled clinical trial. To the best of our knowledge, this is the first efficacy study testing a German web-based stress-management intervention tool for newly diagnosed cancer patients. The needs of cancer patients and cancer survivors are changing continuously, and psycho-oncological support has become a standard treatment option. Our results confirmed that web-based self-help guidance has the potential to efficiently support and empower newly diagnosed cancer patients and hopefully pave the way for new interventions to enrich the psycho-oncology landscape.

“A tree with deep roots is not bending by the wind.”
Korean proverb, author unknown

6. References

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7. Appendix

A Study protocol

Web-based stress management for newly diagnosed cancer patients (STREAM-1): a randomized, wait-list controlled intervention study

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Web-based stress management for newly diagnosed cancer patients (STREAM-1): a randomized, wait-list controlled intervention study

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Abstract

Background: Being diagnosed with cancer causes major psychological distress, yet the majority of newly diagnosed cancer patients lack psychological support. Internet interventions overcome many barriers for seeking face-to-face support and allow for independence in time and place. We assess efficacy and feasibility of the first web-based stress management intervention (STREAM: STREss-Aktiv-Mindern) for newly diagnosed, German-speaking cancer patients.

Methods/design: In a prospective, wait-list controlled trial 120 newly diagnosed cancer patients will be included within 12 weeks of starting anti-cancer treatment and randomized between an immediate (intervention group) or delayed (control group) 8-week, web-based intervention. The intervention consists of eight modules with weekly written feedback by a psychologist ("minimal-contact") based on well-established stress management manuals including downloadable audio-files and exercises. The aim of this study is to evaluate efficacy in terms of improvement in quality of life (FACT-F), as well as decrease in anxiety and depression (HADS), as compared to patients in the wait-list control group. A sample size of 120 patients allows demonstrating a clinically relevant difference of nine points in the FACT score after the intervention (T2) with a two-sided alpha of 0.05 and 80 % power. As this is the first online stress management intervention for German-speaking cancer patients, more descriptive outcomes are equally important to further refine the group of patients with the largest potential for benefit who then will be targeted more specifically in future trials. These descriptive endpoints include: patients' characteristics (type of cancer, type of treatment, socio-demographic factors), dropout rate and dropout reasons, adherence and satisfaction with the program.

Discussion: New technologies open new opportunities: minimal-contact psychological interventions are becoming standard of care in several psychological disorders, where their efficacy is often comparable to face-to-face interventions. With our study we open this field to the population of newly diagnosed cancer patients. We will not only assess clinical efficacy but also further refine the target population who has the most potential to benefit. An internet-based minimal-contact stress management program might be an attractive, time- and cost-effective way to effectively deliver psychological support to newly diagnosed cancer patients and an opportunity to include those who currently are not reached by conventional support.

Trial registration: ClinicalTrials.gov NCT02289014.

Keywords: Stress, Depression, Anxiety, Online, Web-based, Cancer, Stress-management intervention, Minimal-contact

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Background

Impact of cancer on mental health

Every second cancer patient suffers from clinically relevant psychosocial distress [1]. Psychosocial distress encompasses emotional lability, rearranging of roles and responsibilities, changing of future plans, fear of recurrence, depression and anxiety and is associated with decreased quality of life [2–4]. In addition, high levels of distress lead to reduced compliance with treatment and more side effects [5, 6]. Conversely, side effects of cancer treatment like fatigue, nausea and pain may trigger distress and, therefore, impact psychological adjustment.

Efficacy of psycho-oncological interventions and Utilization of psycho-oncological support

Cognitive behavioural techniques, including relaxation techniques [7] and mindfulness based stress reduction [8], significantly reduce distress, depression and fatigue and increase quality of life in cancer patients, albeit effect sizes in randomized controlled trials are small to medium [9]. Moreover, psycho-oncological interventions may reduce side effects of cancer treatment [7, 9–13]. Yet many patients do not seek or have access to psycho-oncological support, even when high levels of distress are experienced [14]. This seems especially true for male patients [15, 16] and patients with cancer other than female breast cancer [15].

Web-based interventions in psycho-oncology

The internet has the potential to reach patients and to overcome barriers towards using psycho-oncologic support (e.g. stigma and privacy concerns, geographical distance form providers, time constraints to adhere to additional appointments during office hours) [17]. The vast majority of cancer patients already uses the internet as a source of information [18]. Furthermore, from the providers' perspective, internet interventions are time- and cost-effective, and thus are of special interest for the health care system. Scientific interest in internet interventions for non-cancer patients has grown rapidly over the last decade. Efficacy of this novel treatment format has been demonstrated for a variety of mental disorders in a substantial number of randomized controlled trials (RCTs). Reviews and meta-analyses show moderate to large effects, post-treatment [19–22]. Studies directly comparing internet interventions with face-to-face therapy report similar outcomes across various mental disorders (e.g. anxiety disorders, depression) and health concerns associated with bodily symptoms (e.g. tinnitus, sexual dysfunction) [23]. There are also a few long-term follow-up studies showing lasting effects over as much as five years post-treatment [24]. Data on web-based interventions for cancer patients are scarce [25, 26]. There is no cancer-specific stress management program for cancer patients in German. Also, little is known on the characteristics (including age, sex, education, type of cancer) of patients who participate and benefit from a web-based intervention.

Objective and research questions

In a prospective randomized wait-list controlled trial we assess the efficacy of a minimal-contact online intervention in newly diagnosed cancer patients. More specifically, we assess whether patients who undergo the online intervention report a better quality of life (FACIT-F), are less anxious and depressive (HADS-D), less stressed (DT), and cope better with their disease (FAH II) as compared to patients in the wait-list control group. This is the first online stress management intervention in German for cancer patients (STREAM: **STRE**ss **A**ktiv **M**indern). Moreover, since it is novel to recruit patients via the internet rather than face-to-face, we set out to determine patients characteristics for participation and benefit. These descriptive outcomes include: patients' characteristics (type of cancer, type of treatment, sociodemographic factors), patients' adherence as well as satisfaction with the program.

Methods/design

In a prospective randomized controlled intervention study (Fig. 1) patients are randomized 1:1 (mixed randomization scheme using unequal block randomization) between the intervention group and the wait-list control group. Patients are stratified according to baseline stress level (distress thermometer $\geq$ *vs* < 5 [27]). A total of 120 newly diagnosed adult (>18 years) cancer patients who started first-line treatment (either systemic treatment - including chemotherapy, hormonal treatment or targeted therapy - or radiotherapy) no longer than 12 weeks earlier are included after giving informed consent. Patients who undergo treatment for a first relapse of a tumor previously treated with curative intent are also eligible. Patients are required to read and write in German, have internet-access as well as basic computer skills.

Patients are recruited via the public website of STREAM [28]. We adopt an *active* recruitment strategy in the German speaking countries Switzerland, Germany, and Austria via the following channels: a) Links to the public website of STREAM on health related websites, such as Cancer Leagues, Cancer Hospitals, Patient advocate websites b) distribution of flyers in hospitals and during cancer conferences, c) active communication to the media d) advertisement via Google Ad and Facebook Ad. The Northwest and Central Swiss Ethics Committee has approved the study (EKNZ 339/13).

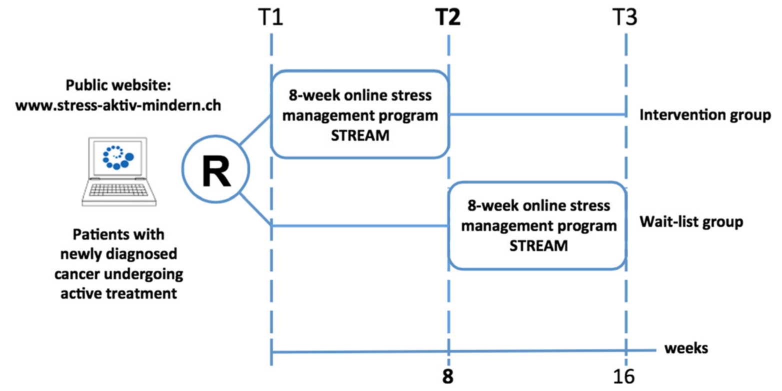

Fig. 1 Study design

Intervention

We developed the web-based intervention STREAM based on well-described and established stress management interventions manuals [29–33], which we adapted to the web-context. The program aims at improving intra- and interpersonal coping strategies, reducing perceived stress and anxiety as well as enhancing quality of life. We assessed the usability of the program in the target population of cancer patients in a previous study (Grossert A, et al. Usability evaluation of the web-based stress management program STREAM for newly diagnosed cancer patients. submitted. 2016).

STREAM consists of eight modules (Table 1) which can be completed in 60 to 90 min each. Participants are asked to work through one module per week, i.e. the intervention takes 8 weeks in total. Every module starts with a short mindfulness breathing exercise and includes (a) text-based psycho-education, (b) reflection on the current individual emotional status and (c) acquisition of strategies including several exercises. Within each module exercises on relaxation techniques and guided-imagery exercises are available as audio files and can be downloaded to various devices (e.g. PC/Mac, tablets, smart phones, MP3 Players). Patients are encouraged to use the audio files daily. Participants receive weekly feedback and individual support by a psychologist from the study team via secure integrated e-mail (=”minimal-contact”). Patients can use the secure chat function to contact the psychologist.

Assessments

Assessments are summarized in Table 2 and are conducted via an open source survey application [34] at baseline (T1), after the 8-week intervention or wait (control group), respectively (T2), as well as after an additional 8 weeks (T3, follow-up for the intervention group or after the delayed intervention for the wait-list group, respectively (Fig. 1)).

Socio-demographic information is self-reported and includes age, gender, marital status and partnership, children, education, monthly household income and employment status.

Medical history includes information regarding tumor diagnosis, time since diagnosis, past and current cancer treatments (curative or palliative setting), past and current psychosocial support and psychopharmacological medication and is obtained from both patients and their treating physicians.

Efficacy outcomes

The main efficacy outcome is quality of life (FACT) including assessment of fatigue (FACT-F) [35] at T2. We use the validated German Version **functional assessment of chronic illness therapy-fatigue (FACIT-F)** which is freely available from the website www.facit.org.

To assess anxiety/depression and psychological distress the **hospital anxiety and depression scale (HADS)** [36] and the **distress thermometer (DT)** in the German version [27] are used, respectively. Patients are stratified based on their level of baseline distress. A score of five or higher at the DT visual analogue scale is a cut-off score for a clinically significant level of distress [27]. To longitudinally describe psychological coping with cancer we use ‘the acceptance and action questionnaire (AAQ)’ in its German version ‘***Fragebogen zur Akzeptanz und Handeln* (FAH II)’** [37], which we adapted specifically for cancer patients with three additional items concerning their coping with the disease.

The online support program STREAM is not designed to support suicidal patients in acute crises. For safety reasons, **suicidal tendency** is assessed by the single suicide item out of the Beck Depression Inventory (BDI) [38]. Patients with a score higher than one are contacted by telephone to reassess suicidal ideation and, if needed, patients are instructed to call for local psychiatric support.

Table 1 Content of the web-based stress management program STREAM

Module		Psychoeducation	Reflection on status	Strategies
1.	Introduction: What is stress?	Nature of stress in general and in specific cancer-related situations	My individual stressors	Diary[b]
			Stress protocol	Body scan[a]
				Stress protocol [b]
2.	Body stress reduction	Bodily sensations during stress and side effects of anticancer treatment	Relaxation protocol	Progressive muscle relaxation [a]
				Beach promenade[a]
				Relaxation protocol[b]
3.	Cognitive stress reduction	Thoughts and their interaction with emotions and bodily sensations	My negative thought patterns	Negative thought cycle[a]
				Relationship of body position and thoughts[b]
				Thinking styles and reflection[b]
				Thoughts on clouds[a]
4.	Emotional stress reduction	Feelings and cancer-related emotions as anxiety and worries were explained	My feelings and worries	Mountain meditation[a]
				Emotional emergency kit[a]
5.	Mindfulness and acceptance of thoughts and emotions	Meaning of mindfulness and acceptance and their implementation in daily life in contrast to the active strategies learned in modules 1–4	My definition and experiences with acceptance	Acceptance story [a,b]
				Body scan[a,b]
				Integration of mindfulness[b]
				Winter walk[a]
				Spring awakening[a]
6.	Activation of resources: quality of life and pleasure	Introduction of models of the balance between burden and resources	My individual resources	Health-cycle [b]
				Planning activities[b]
				Week planner [b]
				Friendly feelings with our own body[a]
				Enjoyment training[b]
7.	Activation of resources: social network and communication skills	Social network and the role of a supportive environment	My individual social network and current needs	Communication skills[b]
				Beach promenade[a]
				Winter promenade[a]
				Spring awakening[a]
8.	Summary	Concluding an overview and documentation of the last 7 weeks	My experiences with the program	Four seasons[a]

[a]Audio file: story, relaxation or guided imaginary exercise, [b]Instructions and worksheets

Evaluation of the intervention

To evaluate the therapeutic alliance between patient and therapist the **short version of the working alliance inventory (WAI-SR)** with subscales for bond, tasks and goals is used in its German version [39] weekly after each module. Usability and user satisfaction is assessed with the **system usability scale (SUS)** [40] and the Client Satisfaction Questionnaire (CSQ-8; in its German version: *Fragebogen zur Messung der Patientenzufriedenheit* ZUF-8; [41]. Satisfaction with the online therapeutic contact will be assessed with predefined questions described by Knaevelsrud and Maerker [42]. In addition, after each module, patients' satisfaction with the module is assessed with an open question. Data on adherence (frequency and duration of logins, website activity, using/downloading different exercises, and the number of modules completed) are collected via the backend functions of the online program STREAM.

Statistical analyses and sample size calculation

Based on previous studies [43] including recent data on cancer patients [44], a difference of nine points in the FACT score is both, clinically significant and realistic. In order to demonstrate a 9-point difference between baseline and T2 (after 8 weeks) in the intervention group with a statistical power of 0.80 at a significance level of 0.05 (two-sided), 60 participants are needed in each of the two conditions. We assume normally distributed data in both groups with a standard deviation of ±18 [45]. Data preparation of all continuous dependent

Table 2 Schedule of assessment

Instrument	T1		T2	T3
	Baseline	Weekly during intervention	Post intervention	Follow up
Socio-demographics	x			
Medical history	x		x	x
Distress Thermometer (DT)	x	x	x	x
Functional Assessment of Chronic Illness Therapy-Fatigue (FACT-F)	x		x	x
Hospital anxiety and depression scale (HADS)	x		x	x
Suicidal tendency (Suicid Item Beck Depression Inventory BDI)	x		x	x
Acceptance and Action Questionnaire (AAQ)	x		x	x
Working Alliance Inventory (WAI-SR)		x		
System Usability Scale (SUS)		x[a]		
Client Satisfaction Questionnaire (CSQ-8)			x[b]	x[b]

[a] Assessed twice (after the first and last module); [b] Assessed post-intervention: for intervention group to T2, for control group to T3

variables will include tests for normality, homogeneity of variances, and examination of outliers. If not normally distributed, variables will be subjected to adequate transformation. Intent-to-treat samples will be used to analyze data. The choice of statistical approach depends on the amount of missing data at T2 and T3. If less than 12 % of data are missing, the Last Observation Carried Forward (LOCF) method will be applied to estimate effects. Then, the outcome will be computed with an analysis of covariance (ANCOVA), using the pre-scores as a covariate and the post-scores as the dependent variable. If more than 12 % of data are missing, we will use linear mixed models. This method is recommended for intent-to-treat-analyses with a high amount of dropouts due to its potential to reduce bias caused by missing data. Regression analyses will be used to identify predictors of treatment outcome.

Discussion

Psychological distress associated with cancer diagnosis and treatment is high. Yet, psycho-oncological support is often lacking –due to barriers on the patients' side or to insufficient resources on the providers' side [15]. Online-interventions with regular psychologist-contact (minimal-contact) -already established in several psychological disorders- might reduce this gap. In our prospective, randomized controlled study we assess the first minimal-contact, online stress management program for German-speaking, newly diagnosed cancer patients.

Our study will yield information on the efficacy of the intervention with respect to quality of life and stress/ anxiety. In addition, it will show whether cancer patients are ready to use new technologies to further increase the range of treatment options at their disposal, and -even more importantly- whether patients who are in need of support but slip through the net of the current system can be reached. Conversely, the time- (and indirectly the cost-) effectiveness of administering support in a minimal-contact online intervention will be assessed from the providers' perspective – an outcome with important implications for the health care system.

On a different level, the contribution of various and novel recruitment strategies (flyers, "conventional face-to-face", internet links, Google Ads, Facebook Ads, You tube) will be described allowing for conclusions for future online study portals.

One of the limitations of the study is the heterogeneity of newly diagnosed cancer patients with respect to tumor type, treatment type and treatment strategies (curative, palliative). However, the distress of a new cancer diagnosis is their common denominator, and a stratification factor. Also, since this is the first online stress management program for newly diagnosed cancer patients, we deliberately aim at reaching a broad population to avoid missing a small but important group of patients with potential benefit from this intervention. The results of this study will allow characterizing the patient population(s) with respect to age, sex, diagnosis and treatment that will then be studied more specifically in follow-up trials. Our trial represents a first step in expanding the much-needed psychological support for newly diagnosed cancer patients towards the promising approaches that come with new technical possibilities which have become integral part of our lives.

Trial status

Trial start date: 1th July 2014; Currently recruiting ($N_{current} = 80$ as of March 17, 2016).

Abbreviations

AAQ: Acceptance and action questionnaire; ANCOVA: Analysis of covariance; BDI: Beck depression inventory; CSQ: Client satisfaction questionnaire; DT: Distress thermometer; FACIT-F: German Version Functional Assessment of

Chronic Illness Therapy-Fatigue; FACT (–F): Functional Assessment of Cancer Therapy including Fatigue; FAH II: Fragebogen zur Akzeptanz und Handeln; HADS: Hospital anxiety and depression scale; LOCF: Last observation carried forward; RCT: Randomized controlled trial; STREAM: STREss Aktiv Mindern; SUS: System usability scale; WAI-SR: Short version working alliance inventory; ZUF-8: Fragebogen zur Messung der Patientenzufriedenheit

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Availability of data and materials

With this manuscript we provide the study protocol but no patient data. Within the trial, data are electronically stored on the secure server of Basel University Rechenzentrum. Patient data are anonymized with a 3-digit UPN.

Authors' contributions

AG contributed to the study design, development of the intervention, patient recruitment, the conduct of the intervention and the writing of the manuscript. CU contributed to the study design, development of the intervention, patient recruitment and funding. As principal investigator she is also responsible for the conduct of the study and the supervision of the intervention. JA contributed to the study design and development of the intervention. JG contributed to the study design. TB contributed to the study design including statistical advice, development of the intervention and writing of the manuscript. VH initiated the study (sponsor-investigator) and contributed to the study design, development of the intervention, patient recruitment, funding and the writing of the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Ethics approval and consent to participate

The Northwest and Central Swiss Ethics Committee has approved the study (EKNZ 339/13). Each participant gives written informed consent before participating in the trial.

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