






BMJ Open Web-based mindfulness and skills-based distress reduction for patients with cancer: study protocol of the multicentre, randomised, controlled confirmatory intervention trial Reduct

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ABSTRACT

Introduction Many patients with cancer experience severe psychological distress, but as a result of various barriers, few of them receive psycho-oncological support. E-mental health interventions try to overcome some of these barriers and the limitation of healthcare offers, enabling patients with cancer to better cope with psychological distress. In the proposed trial, we aim to assess the efficacy and cost-effectiveness of the manualised e-mental health intervention Make It Training-Mindfulness-Based and Skills-Based Distress Reduction in Oncology. Make It Training is a self-guided and web-based psycho-oncological intervention, which includes elements of cognitive behavioural therapy, mindfulness-based stress reduction and acceptance and commitment therapy. The training supports the patients over a period of 4 months. We expect the Make It Training to be superior to treatment as usual optimised (TAU-O) in terms of reducing distress after completing the intervention (T1, primary endpoint).

Methods and analysis The study comprises a multicentre, prospective, randomised controlled confirmatory interventional trial with two parallel arms. The proposed trial incorporates four distinct measurement time points: the baseline assessment before randomisation, a post-treatment assessment and 3 and 6 month follow-up assessments. We will include patients who have received a cancer diagnosis in the past 12 months, are in a curative treatment setting, are 18–65 years old, have given informed consent and experience high perceived psychological distress (Hospital Anxiety and Depression Scale ≥ 13) for at least 1 week. Patients will be randomised into two groups (Make It vs TAU-O). The aim is to allocate 600 patients with cancer and include 556 into the intention to treat analysis. The primary endpoint, distress, will be analysed using a baseline-adjusted ANCOVA for distress measurement once the intervention (T1) has been completed, with study arm as a binary factor, baseline as continuous measurement and study centre as an additional categorical covariate.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This prospective multicentre, randomised, controlled confirmatory intervention trial was developed using scientific evidence, theory and person-based practically orientated approaches.
- ⇒ The intervention of this study provides low-threshold, time-effective and cost-effective support.
- ⇒ The study only includes patients with access to the internet, as access is required in the intervention.

Ethics and dissemination The Ethics Committee of the Medical Faculty Essen has approved the study (21-10076-BO). Results will be published in peer-reviewed journals, conference presentations, the project website, and among self-help organisations.

Trial registration number German Clinical Trial Register (DRKS); DRKS-ID: DRKS00025213.

INTRODUCTION

In 2020, there were an estimated number of 19.3 million new cancer cases and almost 10.0 million cancer deaths occurred worldwide.¹ Many patients with cancer experience multiple physical and psychosocial problems during treatment and even for years afterward.² Every second patient with cancer is significantly distressed and one-third of all patients with cancer across tumour entities meet the criteria for at least one mental disorder at 4-week prevalence.^{3,4} The results from the study of Mehnert and colleagues reveal that 52.2% and 48.2% of patients with tumour stage 1 and 2 report elevated distress, respectively,³ indicating that, many patients in earlier tumour stages show high distress

levels. The meta-analysis from Mitchell *et al*, published in *Lancet Oncology* concluded that the distress levels of patients in palliative and non-palliative care are comparable.⁵ Concluding from these results, patients in palliative and non-palliative care are comparably burdened. However, the needs and demands are different between patients in palliative and non-palliative care. In patients with cancer, distress strongly affects all aspects of their lives (eg, work–life, family life), leads to decreased quality of life, causes financial problems and results in a 4.4-fold higher risk of suicide compared with the general population.^{6–8} In addition, adherence to cancer treatment can decrease due to severe distress.⁹

Patients with cancer who used e-mental health interventions experienced significantly reduced levels of distress, depression, pain, fatigue and anxiety.^{10–18} E-mental health interventions have proven to be feasible and effective in improving quality of life.^{10–18} Recent scientific findings extend their effectiveness by suggesting significant effects on well-being in terms of distress, depression and anxiety,^{11 16–20} especially for web-based interventions that included cognitive behavioural therapy (CBT) techniques, acceptance and commitment therapy (ACT) and mindfulness-based stress reduction (MBSR).^{10–22} Matis and colleagues conclude in their systematic literature review that mindfulness-based eHealth interventions are feasible and effective in improving different outcomes in patients with cancer.²³ Particularly in improving depression, anxiety and post-traumatic growth. Different e-mental health interventions combined CBT and mindfulness techniques to support patients with cancer. Internet mindfulness-based cognitive therapy showed promising results in terms of psychological distress, depression and anxiety symptoms and fear of cancer recurrence.²⁴ One trial evaluating a therapist-assisted internet-based MBCT intervention for breast and prostate cancer survivors showed reduced depression and anxiety symptoms at post-intervention.²² The effect was sustained for anxiety, but not for depression. In addition, two recent reviews on e-mental health interventions in (1) patients with breast cancer and (2) young adult patients emphasised the impact of e-mental health interventions and stressed the need for well-designed multi-centre randomised controlled trials (RCTs).^{25 26} Overall, interventions aiming to reduce distress in patients with cancer often make use of CBT, MBSR and ACT, as they are effective approaches adapted to the need of patients with cancer.²⁷ MBSR and ACT belong to the so-called ‘third-wave’ CBT approaches which means that they are commonly integrated into CBT to support the patients need with a more holistic view on mental health.²⁸ In the treatment of patients with cancer, a combination of these approaches seems promising, as they all contain different techniques that uniquely address the psychological burden associated with the disease.²⁷ Previous research shows that web-based interventions to reduce psychological distress in patients with cancer including CBT, MBSR or ACT have been proven to be effective.^{10–26}

Within these web-based interventions, different combinations such as CBT and MBSR, CBT and ACT or ACT and MBSR have been used.^{10–26 29 30} However, there is lack of research assessing the efficacy of web-based interventions using CBT, MBSR and ACT altogether in a RCT. Designing a web-based intervention based on an integrative approach seems promising, as it offers a holistic treatment to elevate psychological distress in patients with cancer. Based on these findings, we propose to conduct the first multicentre prospective RCT on the efficacy of a self-guided e-mental health intervention, including CBT, MBSR and ACT techniques, Make It Training—Mindfulness and Skills Based Distress Reduction Training in Oncology, tailored to reduce distress and achieve well-being in patients with cancer.

OBJECTIVES AND HYPOTHESES

The objective of the proposed trial is to address distress in patients with cancer and provide a low-threshold, cost-effective approach in the form of an e-mental health intervention. We aim to assess the efficacy of the e-mental health intervention Make It Training compared with treatment as usual optimised (TAU-O) in distressed patients with cancer.

Primary hypothesis

We expect the Make It Training to be superior to TAU-O in terms of reducing distress (T1) in patients with cancer.

Secondary hypotheses

We expect the Make It Training to be superior to TAU-O in terms of improving self-efficacy, quality of life, and mindfulness, and reducing depression and anxiety symptoms (T1, T2 and T3) as well as distress (T2 and T3) in patients with cancer.

Other study goals are to evaluate client satisfaction, usability, time to dropout and cost-effectiveness of the proposed intervention Make It Training compared with TAU-O. Furthermore, additional study aims are to establish and improve healthy coping mechanisms in patients with cancer and explore predictors of usage as well as analyse the usage behaviour of the Make It Training. Furthermore, we will explore relations between the observed usage behaviour and other study outcomes.

METHODS

This study protocol (V.1.0; 31 August 2021) is reported according to the Standard Protocol Items: Recommendations for Interventional Trials checklist (see online supplemental material I).³¹ In case of important protocol modification it will be reported to the sponsor (Federal Ministry of Education and Research), the ethics committees of the participating centres and the trial registration will be updated.

Table 1 Overview of the assessment schedule

Measures	Planned assessment time points					Drop-out
	Baseline (T0-month 0)	During treatment	End of treatment (T1-month 4)	3-month follow-up (T2-month 7)	6-month follow-up (T3-month 10)	
Primary outcome						
Distress						
HADS	x		x	x	x	x
Secondary outcomes						
Self-efficacy						
GSES	x		x	x	x	x
Quality of Life						
EORTC-QLQ-C30	x		x	x	x	x
EQ-5D-5L	x		x	x	x	x
Mindfulness						
FMI	x		x	x	x	x
Distress						
DT	x	x	x	x	x	x
HADS	x	x	x	x	x	x
Depression and anxiety						
PHQ-4	x	x	x	x	x	x
Internet-related variables						
Resource use	x			x	x	
Client satisfaction, usability and predictors of usage						
CSQ-I			x			x
SUS			x			x
UTAUT	x					
ETHSA			x			x
Usage behaviour*						
Self-generated items†	x	x	x	x	x	x
Demographic and medical characteristics‡						
	x					

*Usage behaviour refers to both groups. For the experimental group, it implies: time per day, type and number of modules started, type and number of modules finished, time since last log in, frequency of log in, frequency of each module, time for each module, % of each module completed, type and number of videos and audios started and type and number of videos and audios finished. For the control group, it implies: time per day, type and number of 'modules' displayed, time since last log in, frequency of log in, frequency of each 'module', time for each 'module', whereby a 'module' is defined as brief written psychoeducational information.

†Self-generated items on acceptability, satisfaction with the Make It Training, mindfulness, self-efficacy, coping and skills as well as eHealth-related variables (eg, internet experience).

‡Changes in the medical conditions and social demographic parameters of the patients will be continually assessed.

CSQ-I, Client Satisfaction Questionnaire adapted to Internet-based interventions; DT, Distress Thermometer; EORTC-QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L, European Quality of Life 5 Dimensions 5 Level Version; ETHSA, Evaluation Tool for Healthcare Smartphone Applications; FMI, Freiburg Mindfulness Inventory; GSES, General Self-Efficacy; HADS, Hospital Anxiety and Depression Scale; PHQ-4, Patient Health Questionnaire-4; SUS, System Usability Scale; UTAUT, unified theory of acceptance and use of technology model.

Study design

The study comprises a multicentre, prospective, randomised controlled confirmatory interventional trial with two parallel arms. The proposed trial incorporates four distinct measurement time points (see [table 1](#) and

[figure 1](#)): the baseline assessment (T0) before randomisation, a post-treatment assessment (T1) and 3-month and 6-month follow-up assessments (T2 and T3). Additionally, continuous assessments are planned during the experimental intervention (in-treatment assessment:

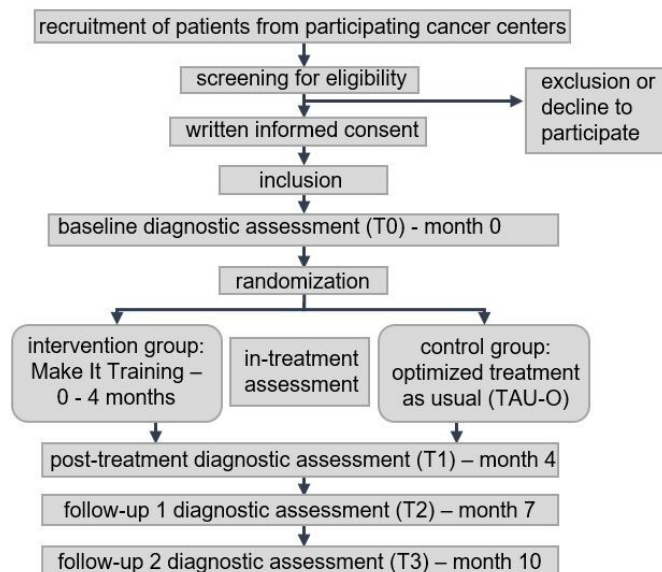


Figure 1 Trial flow of the Reduct trial.

usage behaviour, distress, depression and anxiety symptoms, mindfulness and self-efficacy). For the control group, data assessment during the control intervention (in-treatment assessments) is limited to measurement of distress, depression and anxiety symptoms. The medical data (eg, tumour entity, cancer treatment, tumour status, mental health diagnosis, previous mental health treatment, psychiatric medication; see online supplemental material II for the complete case report forms) are taken from the patient's medical records at T0. Changes in the medical conditions of the patients will be continually assessed. Participants who drop out (no login for 6 weeks is considered as a dropout) will be contacted (if written permission for this purpose has been given before trial start) and asked to complete a dropout assessment. Before participation, written informed consent must be given (see online supplemental material III for model informed consent form). [Table 1](#) displays the instruments used at each time point.

Participant eligibility and recruitment

We set the key inclusion and exclusion criteria in line with comparable and recent studies in psycho-oncology.^{10 11 32} Participants will be included if they have a confirmed diagnosis of cancer in the past 12 months (initial diagnosis, metastases or recurrence), are engaged in a curative treatment setting, have an age of 18–65 years, high perceived distress (Hospital Anxiety and Depression Scale (HADS) ≥ 13) for at least 1 week and have given their informed consent.

Patients with severe cognitive impairment and/or communication difficulties that compromise participation in the intervention, acute risk for suicide and/or severe depression according to clinical practice guidelines, other psychiatric or medical conditions requiring alternative treatment, known cerebral metastases, an age of >65 , no private internet access and/or regularly

contacting a mental health specialist will be excluded. We defined age of more than 65 years as an exclusion criterion because a German survey analysing the internet literacy of patients with cancer determined that while no significant differences regarding gender or age were seen, most of the patients with cancer were younger than 70 years old.³³ In addition, representative data on the daily internet use of the German population show that Internet use decreases with age.³⁴

The seven academic centres, which are involved in the recruitment, are University Hospital Essen, University Hospital Tübingen, University Hospital Erlangen, Freiburg University Hospital, University Medical Center Leipzig, University Medical Center of the Johannes Gutenberg – University Mainz and Klinikum rechts der Isar of the Technical University of Munich. Participants are going to be recruited by study personnel and involved clinic personnel. Flyers and posters will be spread. In addition, information about the study and the involved staff will be presented online via social media and the study homepage (reduct-studie.de). Interested patients are able to ask questions regarding the study, for example, its design and inclusion/exclusion criteria via email, phone or in persona.

Intervention

Eligible patients will be randomly assigned to either the experimental intervention or the control condition TAU-O. Both interventions last 4 months.

Experimental intervention: Make It Training

The psycho-oncological Make It Training is a self-guided and patient-oriented e-mental health intervention for patients with cancer to overcome distress and improve their well-being. In a previously published paper, the previous version of the intervention is described.³⁵ The Make It Training is based on the established, effective psychotherapeutic intervention techniques of MBSR, CBT and ACT approaches used during the treatment of patients with cancer. It aims to improve emotion management, mental strength, psychological resources, distress management and self-efficacy. The Make It Training is designed to accompany patients with cancer on their way for 4 months. The Make It Training consists of 16 modules. Each week, the patients are provided with a new module to help them to deal with the strains of the disease. Every module lasts approximately 30 min. The 16 interactive modules (8 mandatory modules, 8 optional modules, see [table 2](#)) involve various media, including tutorial videos, audio-guided mindfulness exercises, an individual skills box and an interactive skills training. At the beginning of each module, the patient is encouraged to focus on individually relevant issues, as each module starts with a short self-evaluation of their current distress level, skills and mindfulness. Furthermore, at the end of each module, patients receive an individual summary of the finished module with individual results, a mindfulness exercise plan and motivational notifications. During

Table 2 Overview of the 16 interventional modules

Module	Topic/skills	Mindfulness practice
1.	Technical introduction*	Quick introduction to the app and how to handle it
2.	Welcome to your path†	Introduction to the structure of the Make It Training and to Mindfulness
3.	Health-related behaviour*	Different aspects of promoting physical and mental health during cancer illness (diet, creating a daily structure, dealing with online health information).
4.	Emotions†	Accepting and dealing with emotions such as anxiety, depression, or anger as a part of processing the cancer illness.
5.	Fear*	Dealing with cancer-related fears including fear of progression.
6.	Pain†	Understanding and dealing with cancer illness-related and treatment-related pain.
7.	Sleep*	Foundations of restful sleep: Strategies and the role of thoughts and emotions with a cancer illness
8.	Activating resources†	Discovering and consciously using personal resources of strength during cancer disease.
9.	Positivity*	Making room for positive experiences; noticing accomplishments and step-by-step planning.
10.	Body awareness†	Dealing with cancer-related bodily changes by activating self-compassion and self-confidence.
11.	Exercise and relaxation*	Finding a healthy balance between exercise and relaxation as a part of recovery during a cancer disease.
12.	Stress management†	Mastering stressful cancer-related situations based on affirmative thoughts: The significance of thoughts for subjective experience and feelings of distress.
13.	Creativity*	Exploring creativity as a resource of strength during cancer illness.
14.	Self-care†	Self-appreciation and self-care and its importance in the context of cancer; strengthening the pillars of self-esteem.
15.	Relationships*	Personal relationships as a resource and communicating health information and needs toward family and friends during cancer illness.
16.	Looking back†	Review of Make It Training and helpful skills and using them beyond the training (Skillsbox).

*Additional module.
†Mandatory module.

each module, patients collect helpful skills and exercises in their individual skills boxes. The intervention also involves homework assignments and MBSR exercises that should be integrated into the daily routines of patients with cancer. Downloaded material can be used offline. Each Make It module is conceptualised to be completed within 1 week; after 1 week, the next module is delivered and trained. When a new module is available, patients receive a motivational notification via email. The training can be conducted on the patients' private PC, tablet or smartphone. See online supplemental material IV for screenshots of the web-based intervention.

Control intervention: TAU-O

In the proposed RCT, the intervention group will be compared with an active control group as a placebo or null intervention control group would be ethically

inappropriate. This refers to (1) standard treatments in the German healthcare system the patient can receive, (2) the support to access those treatments. Patients receive all the information that is routinely provided as part of inpatient or outpatient treatment (eg, how to find psychotherapy). In addition, the study team will help identify appropriate treatment options, if desired. (3) TAU-O also included an active contingent, which will function as the 'optimised' part of the control intervention, explained in the rest of this paragraph. Patients in the control group have access to selected sets of offered web-based information. These information sets will be based on CBT and contain written psychoeducational information. The topics of these information sets are equivalent to the topics of the mandatory sessions of the intervention group (see [table 2](#)). In total, the control

group will receive access to eight modules over the course of 4 months. Every 2 weeks, a new set of non-interactive written information will briefly inform patients about the benefits of these skills during the course of the disease and motivate them to use these skills. No exercises, interactive worksheets, videos, audio material and mindfulness exercises are given in the control condition, apart from the short psychoeducational information. The first information set contains an introduction to the treatment and support for finding access to selected treatments in Germany. We provided this structured information to make sure, every patient is informed about the various treatment offers of the German healthcare system. The topics of the other modules are emotions, pain, resources, body awareness, stress management and self-care. The last module is a retrospect of all the information sets offered and a reminder for applying the learnt aspects in daily lives. Before starting a module, patients in the control group are presented with some short questions about their current distress level, mindfulness and self-efficacy. All modules are designed to encourage patients to acquire further information on the relevant topics and to implement what they have learnt in their daily lives. In all modules, it is recorded at the end whether the patient is currently receiving psychotherapeutic treatment.

Reminders

To ensure intervention adherence and fidelity, all participants will receive notifications that inform them when a new module is available. Therefore, patients in the experimental intervention group will receive one notification every week about the new available module. Patients in the control group will receive a reminder every second week about the new available module. Patients in the experimental group and the control group receive additional reminders after 2 and 4 weeks of inactivity in order to enhance motivation to log in. All notifications and reminders are standardised and sent via email.

We do not expect serious or adverse events (see Ethical aspects section). In case of unexpected serious adverse events (eg, risk for suicide, severe depressive symptomatology), all participants can consult an expert of the study team at their centre to receive appropriate support. The experimental intervention and control intervention are considered complete when at least five of eight mandatory modules have been completed.

Outcomes

The primary outcome is distress at the end of the treatment (T1; see table 1). To measure distress, we will use the total score of the HADS.³⁶ The HADS was developed to assess possible distress in somatically ill patients. It is a valid and objective self-rating patient-reported outcome measure and is a common instrument in psycho-oncological trials. It consists of two subscales, assessing symptoms of anxiety and depression, with each subscale comprising seven 4-point scale items. A validated German

version is available and it is implemented in routine psycho-oncological care as well as in psycho-oncological research.³⁷

Large RCTs investigating the efficacy and effectiveness of psycho-oncological treatments have used distress as a primary or secondary outcome.^{10 11 22 38} Treatment guidelines for psycho-oncological treatment emphasise the importance of targeting and reducing distress in patients with cancer (e.g. Leitlinienprogramm Onkologie³⁹).

Secondary endpoints for this study include (1) self-efficacy, (2) quality of life, (3) mindfulness, (4) distress over four assessment points, (5) distress and its longitudinal course, (6) depression and anxiety symptoms, (7) client satisfaction, (8) time to dropout, (9) cost-effectiveness, (10) predictors of usage, (11) coping skills and (12) distress, mindfulness and self-efficacy. These outcomes have been chosen based on recommendations by current treatment guidelines (German Clinical Practice Guideline) or on their establishment in previous psycho-oncological and e-mental health trials.^{10 11 38 40} We will use validated instruments, self-generated items as well as usage data.

1. **Self-efficacy:** for the assessment of self-efficacy, we will use the German version of the General Self-Efficacy Scale (GSES).⁴¹ The GSES is a self-report measure of self-efficacy and optimistic self-beliefs related to coping with a variety of difficult demands in life as well as coping with all kinds of stressful life events. Responses are rated on a 4-point Likert scale for all 10 items. It is available in 33 languages, and it is objective and validated in the German language.
2. **Quality of life:** we will apply two questionnaires to measure quality of life in the proposed trial. First, the widely used European Quality of Life 5 Dimensions 5 Level questionnaire (EQ-5D-5L)⁴² will be used as a generic quality of life questionnaire and as the basis for cost-effectiveness analyses (see below). The EQ-5D-5L consists of five health-related dimensions, which can be scored on five levels. Additionally, the questionnaire includes one visual analogue scale to assess general health status. We will also use the European Organization for Research and Treatment of Cancer—Quality of Life Questionnaire (EORTC-QLQ-C30),⁴³ which was developed to assess the quality of life of patients with cancer. It is composed of 30 items and incorporates nine multi-item scales: five functional scales (physical, role, cognitive, emotional and social); three symptom scales (fatigue, pain, nausea and vomiting); and one global health and quality of life scale. Several single-item symptom measures are also included. Responses are given on a 4-point Likert scale except for the items that evaluate the overall quality of life (items 29 and 30), which are given on a 7-point Likert scale. We will use the validated and reliable German version.
3. **Mindfulness:** to assess mindfulness, we will use the validated German version of the Freiburg Mindfulness

- Inventory.⁴⁴ It consists of 14 items, and all responses are given on a 4-point Likert scale.
4. Distress over four assessment points: distress assessed with the HADS will be modelled over the whole treatment period of each patient, with measurements taken at T0 (baseline assessment), T1 (post-treatment assessment), T2 (3 months follow-up assessment) and T3 (6 months follow-up assessment; see also [table 1](#)). This will provide insights into changes of distress depending on various starting points of distress.
 5. Distress: distress and its longitudinal course measured via the Distress Thermometer (DT)⁴⁵ will be analysed over the whole trial of each patient, with measurements taken at T0 (baseline assessment), T1 (post-treatment assessment), T2 (3 months follow-up assessment) and T3 (6 months follow-up assessment). Furthermore, the DT will be applied in each module of the experimental and control intervention. DT is an efficient and convenient validated measurement of assessing distress. It is an established and rapid screening instrument for distress, which is presented as a visual thermometer using a scale from 0 (no distress) to 10 (extreme distress).
 6. Depression and anxiety symptoms: we will use the Patient Health Questionnaire-4 (PHQ-4)⁴⁶ in its validated German version to measure depression and anxiety symptoms. The PHQ-4 is an established short questionnaire, which consists of four items: two items on depression (PHQ-2) and two items on generalised anxiety (Generalised Anxiety Disorder Scale-2). Answers are rated on a 4-point Likert scale for all four items. The PHQ-4 will be applied over the whole trial of each patient with measurements taken at T0, T1, T2 and T3 (see also [table 1](#)). During the experimental intervention, it will be applied in each module in order to track changes in the level of depression and anxiety during the course of the intervention. The PHQ-4 will be used during the control intervention as well.
 7. Client satisfaction and usability: the Client Satisfaction Questionnaire adapted to Internet-based interventions⁴⁷ is an adapted German version of an eight-item client satisfaction questionnaire (ZUF-8)⁴⁸ used to assess the global satisfaction of participants with the internet-based intervention. Responses are given on a 4-point Likert scale for all items. Additionally, the German version of the System Usability Scale⁴⁹ is used to assess the usability of the Make It Training. This questionnaire comprises 10 items, which are to be rated on a 5-point Likert scale. Furthermore, self-generated items to evaluate specific aspects (eg, content, videos) will be used. On top of that, we will use a healthcare smartphone app evaluation survey to determine if our tool is reliable and useful.⁵⁰
 8. Time to dropout and usage behaviour will be defined based on the number and type of modules completed, time per day, type and number of modules started, time since last login, frequency of login, frequency of each module, time for each module, % of each module completed, type and number of videos and audios started and type and number of videos and audios finished. Patients who do not log in for 6 weeks are considered as dropouts.
 9. Cost-effectiveness: the aim of the economic evaluation is to analyse the cost-effectiveness of the Make It Training by performing a cost-effectiveness-analysis and a cost-utility-analysis from a payers' perspective. For the cost-utility analysis, quality-adjusted life years calculated based on utilities derived from the EQ-5D-5L questionnaire will be used as an effect measure. Resource use will be ascertained by questionnaire and will be evaluated in monetary units according to standards of health economics.
 10. Predictors of usage: it is very important to assess predictors of actual usage behaviour because interventions can only be beneficial to those patients using the intervention. Therefore, the predictors of actual usage behaviour/uptake of the Make It Training will be evaluated. To this end, a modified version of the model based on the Unified Theory of Acceptance and Use of Technology will be established.⁵¹ Furthermore, internet-related variables will be established.
 11. Coping skills: self-generated items to assess changes in coping skills will be used.
 12. Distress, mindfulness and self-efficacy will be assessed by single items before the start of each module in both groups. This way, it will be possible to assess the change in these outcomes throughout the intervention.

Trial procedure and timeline

An overview of the trial flow and assessment schedule is presented in [figure 1](#) and [table 1](#), respectively. Trial duration for participants comprises 10 months (including 4 months of intervention). Once the interested patient contacts the study staff, a screening for eligibility will be applied and the patient will receive an explanation about the study conditions, data storage and data safety (oral and written). The patient will receive an appointment for the baseline diagnostic assessment to check for eligibility, which will be handled by study team of the respective clinic. The patient will be included into the study, if inclusion criteria are met and exclusion criteria do not apply and the patient has given written informed consent. Once the patient is included into the study and the baseline assessment is completed, allocation into one of the following study groups will be applied via randomisation: Make It Training (experimental group) or TAU-O (control group). The patients will be informed about their group allocation result and will receive an email with the online link for the offered web-based programme and a code to log in into this programme and to be able to access the respective intervention (Make It Training or TAU-O).

After 4 months of experimental or control intervention a post-treatment diagnostic assessment and two follow-up diagnostic assessments will be implemented via a web-based survey 0, 3 and 6 months after the ending of the intervention. Patients receive reminder notifications (stepped intensity: email, phone call) in case of non-completion of the assessments. In case of a dropout (no login for 6 weeks) during the intervention, those patients receive an email with an online link for a short questionnaire assessing reasons for their dropout.

Sample size calculation

The sample size planning is based on the publication of van den Berg *et al.*¹¹ In this publication, a dropout rate of 25% was assumed for the planning of the study, but only a 5% dropout rate was observed at T1 (primary endpoint). In our project, we conservatively assume a dropout rate of 20%, which to us seems to be a realistic assumption for an e-mental health intervention. Furthermore, we assume an equal dropout rate in both arms of the study and zero difference (after imputation, statistical analysis) between dropouts in both arms in terms of the primary endpoint. In the end, assuming an effect size of d for compliant patients, the true effect size expected in our study would be $0.80 \times d$. Drawing on the paper of van den Berg *et al.*, we expect an effect size of 0.37 for a baseline adjusted analysis, drop outs excluded (the effect size of the unadjusted analysis was recalculated from table 2 of van den Berg *et al.*¹¹ 0.36, so there was no relevant difference between adjusted and unadjusted analysis). Due to a small effect to be expected by the active control condition, we conservatively assume an effect size of 0.30 in our study. In summary, we assume an effect size of $0.80 \times 0.30 = 0.24$. Accordingly, a sample size of 274 patients per group would be necessary. Note that dropouts are already included in this sample due to the effect shrinkage used in sample size calculation. To adjust for centre effects and baseline ($df=6+1$), we need a total of 556 recruited patients ($n=278$ per study arm). Therefore, the goal of the study is to allocate 600 patients and include 556 into the ITT analysis.

Randomisation and blinding

Randomisation will be applied via secuTrial (www.securial.com) using a standard computer algorithm. secuTrial will be provided by the Institute of Clinical Epidemiology and Applied Biostatistics (IKEaB), Medical Faculty Tübingen, Eberhard Karls University Tübingen. Stratification for study centres will be applied. The remaining prognostic factors are assumed to be balanced as a result of the randomisation process. The randomisation of participants and data monitoring will be ensured by the participating study centres.

Blinding for both patients and therapists will be impossible in the trial, although assessors and statisticians (primary analysis) will be blinded to group allocation to ensure objective analyses and audits.

Data management, data storage, and dissemination policy

To protect confidentiality, the participant's data will be pseudonymised and stored for at least 10 years. Independent data management is ensured by the IKEaB. In line with the EU General Data Protection Regulations, we will use the established and structured procedures implemented at Tübingen University Hospitals (databases: secuTrial). After the data-management plan (including digital data storing, archiving and regular plausibility checks) of the IKEaB, all standard operating procedures (SOPs) will be compliant with legal requirements. The data are entered electronically either by the study team or by the patients themselves. Paper-based source data will be entered to the electronic database. The conformity with the source data is monitored.

As per the guidelines of Good Clinical Practice (§13), all important trial data (including signed informed consents, patient identification lists and original records of clinical findings) will be archived for 10 years after completion or termination of the trial. Patient documents will be stored in accordance with the time permitted by the hospitals (at least 10 years). Data in terms of usage behaviour will be stored anonymously on a server, placed in the Clinic for Psychosomatic Medicine and Psychotherapy, LVR Hospital Essen. As per the guidelines of Good Clinical Practice (§13), usage behaviour data will be stored 10 years after completion or termination of the trial. Only authorised staff (project team) have access to the ICH/GCP-compliant validated system (secuTrial).

Data storage and sharing will be following Good Clinical Practice guidelines, Deutsche Forschungsgemeinschaft guidelines and the statements concerning data sharing in *The New England Journal of Medicine*.^{52 53} Data collected from the trial will be anonymously available in data repositories after the major results are published. The statistical analysis plan and all relevant documents will be stored and made available by request. Access to data storage will be restricted to authorised personnel. Patient consent forms will contain a section concerning the aforementioned aspects of data storage and data sharing.

We will set up a project homepage that will update the interested public on the progression of the trial, participation opportunities (eg, workshops, conferences) and major results. The website will remain live beyond the core funding period, acting as a central access point for future research work and outputs and as an avenue to a longer dissemination legacy. The main results of the trial will be submitted for publication in an open-access peer-reviewed journal and will be made publicly available in the clinical trial registry. In addition to presenting the results at national and international conferences, we will regularly communicate scientific results in lay language via press releases, social media and forums that are popular among patients. We will especially collaborate with our patient council and patient organisations in planning and implementing targeted and patient-oriented information campaigns to explain and disseminate the results

to cancer-affected persons and the public. For further dissemination and in-depth discussion of the results, we will involve the Comprehensive Cancer Center (CCC) network in Germany, and we will specifically rely on their expertise in promoting public awareness for psycho-oncological research.

Monitoring

Monitoring will be provided by the Centre of Clinical Trials (ZKS), an independent clinical research unit of the University Hospital Tübingen, which is independent of clinics performing the study. The ZKS is responsible for the methodological quality of the proposed trial. The ZKS has set the highest-quality criteria according to the legal requirements for medicines and medical devices as well as according to the Good Clinical Practice guidelines. The ZKS quality management system is certified under DIN EN ISO 9001:2015. All activities connected with the proposed trial will be conducted in accordance with the SOPs of the ZKS. The monitoring plan includes a pretrial visit, intermediate monitoring and a close-out visit in each recruiting centre. The data-monitoring plan includes the validation of written informed consent forms, documentation of (severe) adverse events, data validity of outcome measures with particular focus on source data transfer, validation of inclusion and exclusion criteria and documentation of the ending of treatment and dropouts.

Statistical methods

The primary aim of this trial is to demonstrate the superiority of the e-mental health intervention Make It Training in comparison to TAU-O in terms of distress in patients with cancer. The primary endpoint, distress, will be analysed using a baseline (T0 assessment)-adjusted ANCOVA for distress measurement once the intervention (T1) has been completed, with study arm as binary factor, baseline as continuous measurement, and study centre as an additional categorical covariate. The primary analysis will be in the intention-to-treat population, with imputation of missing data in the case of dropouts. Intention to treat will be defined as all patients for whom the HADS scale is available at baseline. Additionally, it is expected that patient age and gender will be documented, and these variables will be used to impute missing values. Imputation will be computed using the SPSS module for multiple imputations with 'monotone missing pattern' (as we will use complete data for gender, age and baseline). The number of imputations will be 3000, and the seed will be set to the date of analysis (ddmmyy). Furthermore, it is expected that endpoint measurements might be obtained from at least a subsample of dropouts, which might improve the accuracy of imputation procedures. An interim analysis is not planned. Secondary analyses include mixed models for overall change in distress; self-efficacy; mindfulness; coping; depression and anxiety; and quality of life including physical condition, tumour entity and treatment method; the analyses will use T0 as covariate and T1, T2 and T3 as dependent observations

with a predefined analysis: interaction of group with contrasts estimation of adjusted mean and 95% CI. Furthermore, secondary endpoints will be analysed using a χ^2 test and logistic regression for binary outcomes, t-tests and linear models for continuous outcomes. Time to dropout will be analysed as a secondary endpoint itself, using the Kaplan-Meier estimate and the Cox proportional hazard regression. Separate tabulations and line listings of adverse events and severe adverse events will be ensured to analyse safety. Ratio of changes in resource use and of changes in primary endpoint and in quality of life will generate point estimates for the incremental cost-effectiveness ratio; to determine deterministic and probabilistic sensitivity a respective analysis will be performed.

Ethical aspects

From our view, the trial poses no ethical concerns. We are unaware of specific risks or disadvantages that might affect patients during the trial, and we expect no specific adverse or serious adverse events. In case of unexpected adverse or serious adverse events they will be documented and reported by the responsible monitoring unit. During the trial, patients will have access to telephone/video consultation or face-to-face contact with a member of the study team (psychologist or physician) if indicated as needed.

We evaluated the risk of the proposed trial based on published literature in similar trials conducted before.^{10 11 54 55} Make It Training as well as TAU-O involves the chance of improvement of distress in patients with cancer. Side effects of evidence-based psychotherapies are fortunately rather rare. Possible undesired effects may include transient worsening of symptoms.

The Ethics Committee of the University Hospitals Essen have approved the study (21-10076-BO). Written informed consent is mandatory for all patients to participate and will be obtained after providing oral and written information and prior to randomisation. All participating patients can withdraw at any time without any disadvantage. The trial will be conducted in accordance with the tenets of the Declaration of Helsinki and the guidelines of Good Clinical Practice. Recruitment in the study centres will not begin until the relevant ethics committee has given its approval. A Data Safety and Monitoring Board (DSMB) has been implemented. The DSMB will supervise and monitor the proposed trial and is obliged to take appropriate actions where needed. The DSMB evaluates conformity of the trial with the study protocol as well as compliance with ethical criteria. The DSMB will decide whether practice is meeting the ethical criteria determined for this trial and/or whether the trial should be stopped. Adverse events and dropouts throughout the trial will be assessed and documented by the study team. The study team will be required to inform the DSMB if any adverse events or dropouts occur. Major events that need to be monitored include acute suicidality, suicidal acts and clinically relevant increased symptomatology.

Checks for causes of adverse events will be applied at each participating study centre.

Patient and public involvement

Patients were involved in developing the Make It Training (the content of the modules, recommendations for enhancing usability) and in planning the proposed trial. We have established a patient council (consisting of five members) and involved the self-help organisation Haus der Krebs-Selbsthilfe - Bundesverband e.V. to support the project team. Haus der Krebs-Selbsthilfe - Bundesverband e.V. is an established umbrella organisation of many different cancer self-help organisations in Germany and is primarily funded by the non-profit organisation German Cancer Aid Foundation. The patient council was consulted regarding research design, patient-friendly summaries and consent forms, as well as regarding dissemination of results among patients and in academic publications. A participatory decision-making process between the patient council and the researchers was implemented and followed. The final case report forms were tested regarding comprehensibility, illustration and duration of processing by the members of the patient council. During regular exchanges with the patient council, we will also mobilise different social media and self-help cancer groups to disseminate the trial's results. Patient involvement will be informed by the online resources of UK National Health Services (INVOLVE; <http://www.invo.org.uk/>). The public in the form of the Federal Ministry of Education and Research is the sponsor of this trial.

DISCUSSION

In our prospective, multicentre, randomised controlled confirmatory intervention trial (Reduct), we aim to assess the efficacy and cost-effectiveness of the e-mental health intervention Make It Training. The aim is to offer an evidence-based, efficient, cost-effective web-based psycho-oncological intervention in routine-care for individuals with cancer to reduce distress and enhance well-being.

The provision of care via e-mental health approaches aims to keep costs low for treating staff and premises, to offer care to many people at the same time, to promote continuity of care by being independent of time and place and to overcome the insufficient availability of specialised treatments by improving outreach. Thus, the training has socioeconomic and health-economic benefits. By evaluating the efficacy of the Make It Training, important findings for e-mental health interventions in general and in the context of somatic diseases could be derived. Accordingly, other patient groups could benefit from similar e-mental health approaches as well.

Treatment guidelines for psycho-oncology emphasise the importance of targeting and reducing distress in patients with cancer.³⁹ The initial results of e-mental health interventions have been promising for patients with cancer.^{10 11 56} Accordingly, RCTs are needed to evaluate e-mental health interventions in psycho-oncological

care—especially self-guided interventions, with low cost-intensity and with outreach to outlying regions with limited psycho-oncological offers.^{11 56–58} Given the increasing impact of digital technologies in daily life, the web-based Make It Training has the potential to reach high numbers of patients and to overcome barriers that patients face in analogue face-to-face care (eg, physical and psychological constraints due to cancer symptoms or treatments, limited psycho-oncological resources).⁵⁹ Because it is accessible everywhere at any time, the Make It Training enables patients with cancer to participate in psycho-oncological interventions regardless of barriers in the current healthcare system.⁶⁰ Younger patients with cancer generally report more unmet needs and utilise less likely psycho-oncological services⁶¹; the e-mental health intervention meets their demands and requirements.

In conclusion, we expect the results to contribute to the knowledge on e-mental health interventions in general and especially for patients with cancer and to overcome barriers or obstacles in everyday healthcare in order to offer significant benefits for both the patient and provider.

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which is responsible for quality assurance, monitoring and adherence to the study protocol. All authors contributed to refinement of the study protocol. AB drafted the manuscript and all coauthors critically reviewed it and approved the final version of the manuscript.

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