Study protocol with rudimentary statistical analysis plan

The original study protocol was approved by the Swedish Ethical Review Authority on August 16th 2023 on the condition that *"in the information for the study participants, the identifier for the approval of the Swedish Ethical Review Authority shall be reported (id: 2023-04056-01)"*.

Internet-Delivered Psychological Treatment for Cancer Survivors (IN-FACT-1)

ClinicalTrials.gov identifier: NCT06046586

Study protocol

Towards an evidence-based Internet-delivered psychological treatment for cancer survivors with clinically significant psychiatric symptoms

A randomized factorial pilot study (IN-FACT-0) and trial (IN-FACT-1)

Summary

Negative psychological effects of cancer are common, but cancer survivors are rarely offered psychological treatment. Most existing treatments have modest effects. Internet-delivered treatments have shown some promise, but specific treatment components have not been empirically evaluated which means that it is not clear which therapies that should be prioritized. In this randomized factorial trial at Karolinska Institutet, Stockholm, Sweden, 400 cancer survivors with psychiatric symptoms are enrolled in variations on a 10-week therapist-guided online psychological treatment intended to address the negative psychological long-term effects of cancer. The aim is to determine the contribution of treatment components to the overall effect. Key therapeutic targets include anxiety, depression, the fear of cancer recurrence, bodily distress, and existential considerations. The outcome is analyzed using a fully factorial statistical model. In secondary analyses, cost-effectiveness and possible mediating variables are explored. A factorial pilot study (N=48) is first conducted to inform details pertaining to the design of the full-scale trial. We expect the full scale trial to illustrate what components that should be prioritized for beneficial outcomes in the treatment of long-term psychological distress in cancer survivors.

Overview of the field (background)

Need to address the negative psychological long-term effects of cancer

The long-term effects of cancer on quality of life and other psychological outcomes such as anxiety and depression are widely believed to be substantial. Approximately one third of cancer survivors report long-term distress related to existential themes, and report difficulty moving on with life (1). About 22-87% develop a chronic and significant fear of cancer recurrence (2), and approximately 25-38% have been estimated to suffer from clinically significant health anxiety (3, 4). This results in increased in health care consumption and a substantial long-term reduction in quality of life, including in cancer forms such as breast cancer, testicular cancer, and differentiated thyroid cancer where the postoperative long-term prognosis is relatively good (3, 5). Patients are often reassured that they suffer from a “good” cancer (6), without further clinical intervention, despite findings indicating that depression and anxiety are predictive of recurrence and mortality (7). Cancer survivors suffering from long-term mood disturbance are rarely offered psychological treatment (8).

Potential benefits of incorporating knowledge from health anxiety research

A 2019 systematic review and meta-analysis (9) found that the typical effects of existing treatments for recurrent fear and anxiety in cancer survivors are relatively small (g=0.33 vs rudimentary controls) in comparison to the typical effects of broader modern psychological treatments for health anxiety (g=0.54-1.08 vs rudimentary controls) (10). Whereas research on the fear of cancer recurrence has developed primarily in recent years, the field of psychiatry has seen ca 35 years of research on health anxiety in a broader sense, i.e., a multifaceted trait characterized by a fear or preoccupation with having or developing serious health condition (11-14). This highlights the potential benefits of making use of lessons learned from the broader field of health anxiety for interventions more specifically aimed at cancer survivors.

Need for stringent evaluations of treatment components
Most promising psychological interventions for the negative psychological long-term effects of cancer are multicomponent protocols that involve several treatment components such as behavioral activation, exposure and response prevention, mindfulness exercises, and self- or stress management techniques (15, 16). Randomized controlled trials have usually employed rudimentary control conditions. Because treatment components have rarely if ever been evaluated against each other, it is yet unclear which components that contribute the most to beneficial effects of multicomponent therapies, and how components are best combined.

Factorial experiments enable the evaluation of components
Randomized trials are commonly referred to as "factorial" if participants are assigned more than one property (independent variable) (17). That is, rather than to assign each participant to one condition (a, b, or c), participants are assigned a combination of conditions (e.g., a, b, c, a+b, a+c, b+c, or a+b+c). A key advantage of a factorial experiment is that the contribution of several treatment components, and their combinations, to the effect of an overarching, broad, multicomponent treatment can be efficiently evaluated in one and the same clinical trial. While modelling the contribution of all treatment components and their interactions in the same statistical model, the added effect of a specific component to the average treatment effect can be estimated by comparing conditions that included the component to conditions where the component was not included. The randomized factorial trial maintains the advantage of guarding against confounding, and usually includes a null-component attention control reference group, which is similar to a conventional randomized controlled trial.

Potential benefits of the online treatment format
It is increasingly recognized that therapist-guided Internet-delivered treatments can have large mean effects that often approximate those of face-to-face treatment (18, 19). Also, therapist-guided treatments delivered via the web have shown promise specifically for cancer survivors (15, 16, 20). Online therapies typically require less therapist time than face-to-face treatment, can be delivered regardless of geographical distances, and also do not require patients to work with their therapy during any particular time of the day. The structured online format is ideal for researching treatment components and mechanisms, considering that educational content can easily be standardized and there is little room for unintended deviations from the protocol.

Summary of background
In summary, a substantial proportion of cancer survivors experience long-term distress in terms of anxiety, depressive symptoms, and existential concerns. Still, access to treatment is poor. There have been several attempts at developing psychological treatments, but effects have usually been modest. There could be much to learn from the broader field of health anxiety. There is also a need for the systematic evaluation of treatment components, for example using factorial trial designs. Certain promising treatments have been administered online with therapist support. The conventional online format offers advantages in terms of scalability and a form factor ideal for the evaluation of treatment components.

Aim of the study

The overarching aim of this trial is to evaluate the unique contribution of common treatment components – (a) behavioral activation, (b) systematic exposure with mindfulness training, and (c) self-management techniques – to the overall efficacy of online psychological treatment for long-term psychological distress in cancer survivors. More specifically, in a fully factorial randomized trial, we aim to assess the incremental effect of adding treatment

components on the reduction in depression (PHQ-9) and general anxiety (GAD-7) up to the post-treatment assessment, as modeled over 11 weekly measurement points (primary outcome; see Table 2). Secondary analyses concern cost-effectiveness and possible mediators of the treatment effects. Other key secondary outcomes include effects on the fear of cancer recurrence, quality of life, adverse events, and participant satisfaction with the treatment.

Hypotheses:

- The addition of behavioral activation leads to a larger average reduction in depression.
- The addition of exposure and mindfulness training leads to a larger average reduction in anxiety.
- All combinations of treatment components are rated as credible and will lead to adequate satisfaction, with no statistically significant differences in this regard.
- The optimal combination of treatment components is cost effective compared to the attention control null group.
- The effect of the behavioral activation component is mediated by an increase in behavioral activation, the effect of the exposure and mindfulness training component is mediated by a reduction in symptom preoccupation, and the effect of the self-management component is mediated by increased physical activity and self-efficacy.

A factorial pilot study (N=48) mirroring the design of the full-scale trial is first completed to develop content and a credible framework. In the pilot study, we aim to assess the feasibility of the online treatment in terms of interest in the study, patient-reported credibility of the intervention, adherence to the treatment protocol, satisfaction with the treatment, acceptability of the measurement strategy, missing data rates, adverse events, and preliminary efficacy on anxiety, depression, the fear of recurrence, and health-related quality of life (Table 1).

Table 1. Key aspects of feasibility assessed within this randomized factorial pilot study.

Specific aim	**Key outcome**
To assess the feasibility of a randomized factorial design	Experience of study administrators and therapists tasked with the assignment and delivery of treatment variants.
To assess the credibility of the treatment as perceived by patients.	The Credibility/Expectancy scale (C/E scale) (21)
To assess the adherence to the treatment protocol.	Number of completed modules. Number of completed exercises.
To assess the acceptability of the online measurement strategy.	Number of measurements completed. Perceived strain caused by the measurement strategy.
To assess the patient's satisfaction with the treatment.	The 8-item Client Satisfaction Questionnaire (CSQ-8) (22) Free text item with suggestions for improvement. Likert items pertaining to satisfaction with components.
To assess the rate of adverse events and negative experiences	Adverse events questionnaire used in previous clinical trials (e.g., ClinicalTrials.gov: NCT04511286) The 20-item Negative Events Questionnaire (NEQ-20) (23)
To assess preliminary efficacy in terms of within-group improvement.	Efficacy outcomes focusing on general anxiety, depressive symptoms, the fear of cancer recurrence, and quality of life

Methods

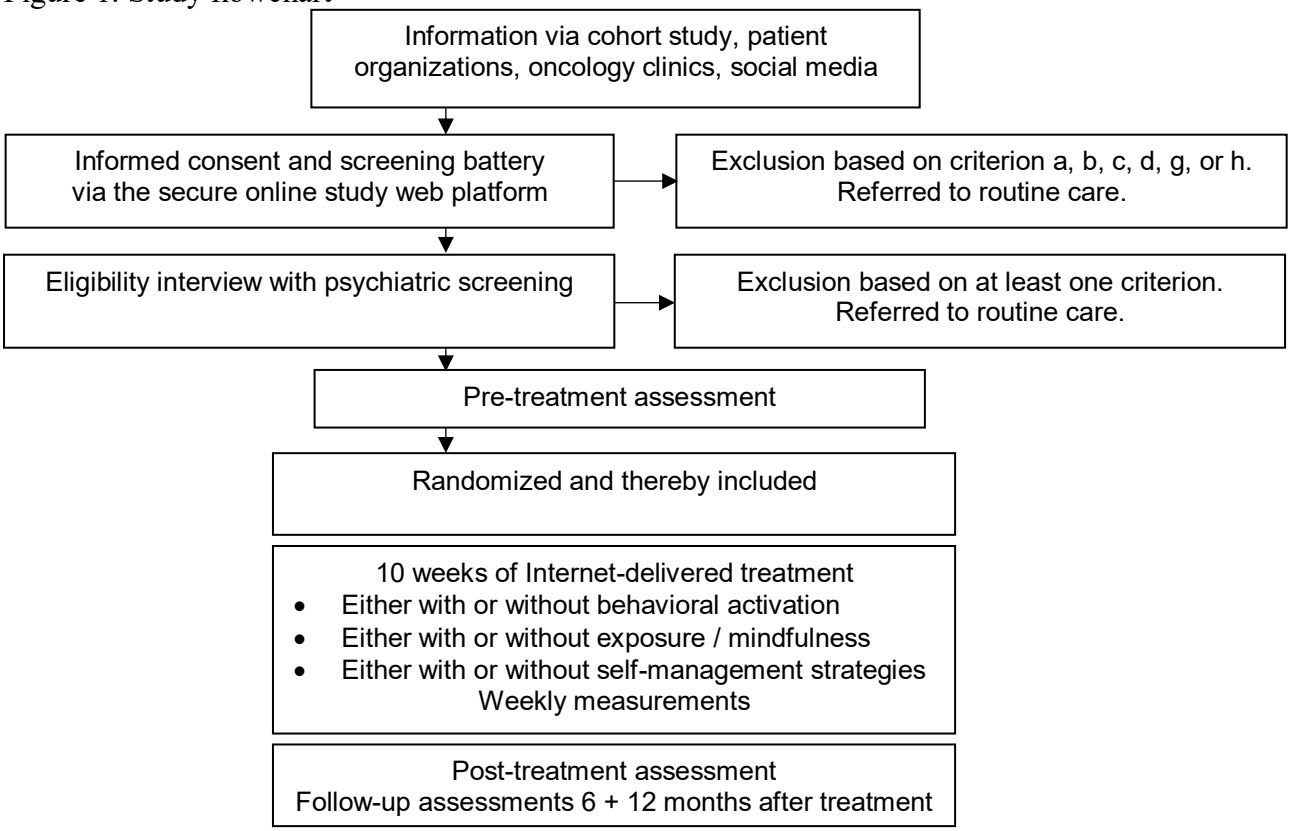
Design

This is a randomized factorial trial (N=400; 2x2x2 with a cell size of 50; for the pilot study: N=48; 2x2x2 with a cell size of 6) of therapist-guided Internet-delivered psychological treatment for cancer survivors with long-term clinically significant anxiety or depression despite a good prognosis. Study site is Karolinska Institutet, Stockholm, Sweden. The sample size allows for two-sided conventional mean tests of small ($d \approx 0.3$) component effects (n=200 vs. 200) with 80% power of, given an alpha of 5% and up to 14% missing data post-treatment. The pilot study will have a feasibility focus, though the sample size will also be sufficient to study average within-group effects with 80% power in two-sided tests of moderate effects ($d \approx 0.45$) on efficacy outcomes measured at two time points, given a 5% alpha and up to 20% missing data post-treatment. The study protocol will be reviewed by the Swedish Ethical Review Authority and preregistered at ClinicalTrials.gov. All procedures will adhere to the declaration of Helsinki and the relevant privacy and data management legislation.

Eligibility criteria

a) Cancer survivor 0.5-20 years after main therapy. For the pilot study: survivor of breast cancer (n=24), testicular cancer (n=12), or thyroid cancer (n=12),
b) Clinically significant anxiety or depression (PHQ-9≥10, or GAD-7≥8) (24, 25)
c) At least 18 years old
d) Resident of Sweden (listed and de facto). For the full trial: Stockholms län, Västra Götalands län, or Skåne län.
e) Sufficient technical knowledge and knowledge of the Swedish language to take part in a text-based online treatment
f) Continuous access to an electronic device that can be used to access the study web platform
g) Not recurrent thoughts of suicide, as based on clinical judgement aided by the structured interview (see below) and the MADRS-S item 9
h) No severe medical condition (e.g., very poor prognosis, stage IV cancer), severe psychiatric disorder (e.g., psychotic disorder, bipolar disorder, or severely debilitating substance use disorder, severe depression), or medical treatment (e.g., chemotherapy, immunotherapy, radiotherapy) that makes the treatment unfeasible
i) No other ongoing psychological treatment
j) Either no continuous psychotropic medication, or continuous psychotropic medication stable for the past 4 weeks, and expected to remain so during the intended treatment period
k) Not planned absence for more than one week of the intended treatment period
l) Complete pre-treatment assessment and subsequently randomized to a condition

Figure 1. Study flowchart



Procedure

Recruitment

The study will be advertised via oncology clinics, patient organizations, and social media. We also aim to inform the participants in an ongoing cohort study of thyroid cancer who previously, as part of that project, indicated that they were interested in psychological treatment (2014/714-31, with a separate amendment that will be submitted for this purpose). On the secure study web platform, self-referred individuals are presented with written information about participation in the study including data management procedures and their right to drop out of the study at any point, and how to get in contact with the research group. Applicants provide informed consent via a secure web form. This procedure for obtaining informed consent is widespread and has been used in several previous online treatment trials (e.g., 2014/1530-31/2, 2020-01740, 2021-01400). After having provided informed consent applicants complete a screening battery which includes validated online questionnaires (Table 2) and standard questions about key demographic and clinical characteristics. Applicants who, based on their replies, are subject for immediate exclusion based on criterion a, b, c, d, g, or h (see above) are informed of this and referred to routine care services by means of a standardized e-mail. The remaining applicants are contacted for a brief psychiatric interview with a psychologist or physician working under the supervision of the principal investigator. This interview establishes eligibility and is based primarily on the Mini-International Neuropsychiatric Interview (26) with a separate module for the assessment of pathological health anxiety (Open Science Framework identifier: t3yvz). Information from the interview and screening battery is also used to describe the final sample in terms of sociodemographic and clinical characteristics.

Measurements

Participants complete validated self-report questionnaires at screening, before treatment, each week during treatment, after treatment, and 3 months after treatment. These are administered online in Swedish (Table 2). In the pilot study, follow-up will take place 3 months after treatment (not at 6 or 12 months).

Table 2. Validated self-report questionnaires administered in the study

Questionnaire	Outcome	Ref	SN	PRE	WK	PST	6MFU	12MFU
Screening and safety only								
Alcohol Use Disorders Identification Test (AUDIT)	Alcohol use	(27)	x					
Drug Use Disorders Identification Test (DUDIT)	Drug use	(28)	x					
Hospital Anxiety and Depression Scale (HADS)	General distress	(29)	x					
Montgomery-Åsberg Depression Rating Scale item 9	Suicidal ideation[a]	(30)	x	x	x	x		
Symptom domains and similar								
36-Item Short Form Health Survey (SF-36)	Health-related quality of life	(31)		x		x		
7-item general anxiety questionnaire (GAD-7)	General anxiety	(32)	x	x[b]	x[b]	x[b]	x[b]	x[b]
9-item Patient Health Questionnaire (PHQ-9)	Depression symptoms	(33)	x	x[b]	x[b]	x[b]	x[b]	x[b]
9-item Fear of Cancer Recurrence Inventory (FCRI-9)	Fear of cancer recurrence	(34)		x	x	x	x	x
14-item Health Anxiety Inventory (HAI-14)	Health anxiety	(11)		x		x	x	x
Somatic Symptom Scale 8 (SSS-8)	Somatic symptom burden	(35)		x		x	x	x
Body Image Scale (BIS)	Body image	(36)	x			x		
12-item WHO Disability Assessment Schedule 2.0 (WD2-12)	Disability	(37)	x	x		x	x	x
Process and target variables								
3-item Behavioral Activation for Depression Scale – Activation (BADS-AC-3)	Behavioral activation	(38)		x	x	x	x	x
Symptom preoccupation scale (SYMPS)	Symptom preoccupation	Not yet published		x	x	x	x	x
Godin-Shephard Leisure-Time Physical Activity Questionnaire (GSLTPAQ)	Physical activity	(39)		x	x	x	x	x
Adapted self-efficacy scale	Self-efficacy	(40)		x	x	x	x	x
Credibility/Expectancy scale (C/E scale)	Credibility and expectancy	(21)			w. 2			
Working Alliance Inventory (WAI)	Relationship with the therapist	(41)			w. 2			
Explicit evaluation of therapy								
8-item Client satisfaction questionnaire (CSQ-8)	Satisfaction with treamtent	(22)				x		
20-item Negative Effects Questionnaire (NEQ-20)	Negative effects of treamtent	(23)				x		
Cost-effectiveness outcomes								
EuroQol 5D (EQ5D)	Utility score	(42)		x		x	x	x
Trimbos questionnaire (TIC-P)	Resource use	(43)		x		x	x	x

SN = screening, PRE = pre-treatment, WK = weekly, PST = post-treatment, 6/12MFU = 6/12-months follow-up

a) Patients with heightened scores are assessed by a clinician, and referred to routine care services if necessary

b) For the weekly (non-screening) measurements, rephrased to concern the past week.

Treatment conditions

General format of Internet-delivered treatment

Therapist-guided online treatment is delivered over 10 weeks, which is proven format (18) recommended for cancer survivors (20). The patient regularly logs in to the encrypted web platform ("BASS", as provided via the Karolinska Institutet eHealth core facility). Most of the treatment content is conveyed via an illustrated text divided into modules, equivalent of book chapters. Each modules contains an educational text, homework assignments, and questions for reflection. Participants communicate with their therapist via a system reminiscent of email, and receive a reply within about two weekdays. Homework exercises are tailored to the individual needs of the patient. In total, eight modules are completed at a pace of about one module per week. Participants gain access to new models contingent on progress. Therapists receive continuous supervision from the principal investigator.

Open access publication of treatment content

In order to promote transparency and contribute to the research field as well as clinical practice, the treatment content from this pilot study will be transferred to the public domain and published open access online, tentatively via the Open Science Framework (OSF).

Randomized allocation of treatment components

The following randomization procedure will be piloted: Each cohort size is a multiplier of the number of unique combinations of treatment components (i.e., 8). After completion of the pre-treatment assessment, and separately for each cohort, randomization is achieved using a true random number service (www.random.org), managed by an individual otherwise not involved in the trial. Tentatively, based on the outcome of the 2023 pilot trial and feasibility outcomes, interventions will be built using the following components derived from existing protocols: (a) behavioral activation with existential themes and emphasis on values (44, 45) and relationships, (b) systematic exposure with mindfulness training with a focus on anxiety about health and/or death (46), body image, and cancer-related trauma, and (c) an overview of self-management techniques in terms of physical exercise, dietary advice, and strategies for improved sleep. Fifty patients are randomized to each combination of treatment components: a, b, c, a+b, a+c, b+c, a+b+c, and also a null group where support and rudimentary clinical information is given to control for the effect of attention from a clinician and enrollment in the structured online format, resulting in the total sample size of 400. The point of administering all these combinations is to make it possible to model the simple effect (added contribution) of each component to the treatment effect, and also all component interactions. After the follow-up phase (see below), for ethical reasons, controls are crossed over to the a+b+c combination though without therapist support. To the extent that this is found feasible in the pilot study, the treatment content for all combinations of components will be developed with similar readability (47), interactivity, and picture content. Importantly, even in the null group attention control, the treatment will involve support from a clinician, information about the negative long-term effects of cancer and will offer participants the possibility of observing their own symptoms in a systematic manner.

Partial blinding of study design

In order for the analysis of treatment components to be valid and helpful in the design of future therapies, it is important that the participants remain blinded to the randomized factorial design throughout the full measurement period. (Full blinding, i.e., where the patient and therapist remain unaware of the treatment condition, is not possible in psychological treatment research (48).) Regardless of condition, participants will be informed that they take

part in an Internet-delivered support program for improved mood in the aftermath of cancer. At the 12-months follow-up (3 months in the pilot study), a written blinding check will then be conducted whereby participants are asked about whether they are aware of which treatment variants that are being compared and why. Participants will then be unblinded (debriefed) and those in the attention control (see above) will be offered the full material from the full factor version of the treatment.

Secondary outcome: registry data on healthcare consumption

If funding is secured for this secondary outcome, registry data on health care consumption will also be collected, pertaining to the 2 years immediately before treatment, and the 2 years immediately following treatment. To ensure access to health consumption data, patients will be recruited exclusively from Stockholms län, Västra Götalands län, and Skåne län for the full trial. This will not be implemented in the pilot study.

Data safety and management

Throughout the project, data management plans and documentation will be maintained and revised in accordance with up-to-date guidelines of Karolinska Institutet. The study web platform will employ encrypted traffic and two-factor authentication. Researchers in the project have access to study data, which is stored and managed in accordance with European Union and Swedish data protection and privacy legislation, and the guidelines of Karolinska Institutet. Personal data are exclusively stored in systems classified and provided specifically for this purpose by Karolinska Institutet. Study results are reported in a manner that does not make it possible to identify individual participants.

Statistical analysis

The main pre-post efficacy outcomes will be analysed by an individual blinded to treatment identity (each component is coded simply as -0.5 vs. 0.5 without labels in the dataset). Hierarchical multiple imputation by chained equations will be employed to manage missing data, and imputation will be conducted separately for each cell so as to maintain interaction effects (49). Efficacy outcomes are analysed using fully factorial linear mixed models, so that the simple effects of the components, and also their interactions, can be quantified and tested. Health economic analyses will focus on comparing the most potent treatment configuration (cells are collapsed if no component shows superiority) to the null group (i.e., rudimentary information and support from a clinician only). Mediation analysis will be conducted within a structural equation modelling framework, based on parallel process growth models. The pilot study will not focus on inferential statistics, but rather the feasibility outcomes (see Table 1).

Ethical considerations

This randomized factorial trial and the pilot study are conducted in accordance with the declaration of Helsinki, current Swedish and European Union privacy and data management legislation, and internal guidelines of Karolinska Institutet. The project will be preregistered online, and results including the treatment content will be published open access so as to ensure transparency and that findings benefit the research field. Applicants will be required to provide informed consent in order to be included as participants.

Psychological treatments can induce unwanted effects for example in terms of deterioration or an increase in symptoms, disappointment with the quality of treatment, dependency on the therapist, stigma associated with enrollment, hopelessness as a consequence of insufficient efficacy, or a sense of failure or reduced self-efficacy (50). Based on the existing evidence base, the negative effects of therapist-guided Internet-delivered psychological treatments

similar to that evaluated here are typically limited (51, 52). In contrast, the beneficial effects for example on anxiety are more likely to be at least moderately sized on average. Adverse events and participants mood is tightly monitored throughout the intervention. Heightened suicidal ideation is automatically flagged and cause for clinical assessment. Participants are referred to routine services if necessary.

Personal data including sensitive information about health outcomes, cognitions, and mood will be collected, stored, managed as part of the study. This imposes requirements on the online treatment format. Applicants and participants are given a personal account to the study web platform, access to which requires two-factor authentication. Traffic with the study web platform is encrypted. Data are stored on servers classed as secure and suitable for personal data by Karolinska Institutet.

Another ethical dilemma relevant to most randomized clinical trial is that of fairness. There is reason to suspect that not all variations on the treatment evaluated in this study will eventually be found to have equal effects. This said, knowledge about which combinations that will do best is so far lacking. This important research question will be addressed by the study, and findings can benefit a large number of patients in the population at large. In summary, we consider the potential scientific value of the trial combined with the potential gains for individual participants to clearly outweigh the expected harms associated with participation.

Research group and previous experience

The research group has experience of several clinical trials of psychological interventions delivered via the Internet, and are well familiar with the patient group and key psychological outcomes. The principal investigator, Erland Axelsson, lic. psychologist, PhD, Liljeholmen Primary Care Center and Karolinska Institutet has published extensively in the field of eHealth and health anxiety in the past 10 years, and has been involved in 14 randomized controlled trials of psychological treatment, focusing primarily on distress related to somatic symptoms, functional somatic syndromes, chronic stress, anxiety and depression. He has certification in good clinical practice (GCP), has led the largest published direct comparison of Internet-delivered and face-to-face treatment for any psychiatric condition (52), and has experience in evaluating interventions, supervising clinicians, developing research methods, and overseeing the management of clinical trials.

The pilot study for this trial will be conducted within the context of the PhD studies of Julia Winter, physician (Karolinska Institutet), who will play an active role in the development of procedures, in recruitment, and in treatment, under the supervision of CH (main supervisor), EA, and LBB. Nils Gasslander, lic. psychologist (Uppsala university), expected to defend his thesis around the summer of 2023 will also make substantial contributions to the development of procedures, to recruitment and to treatment. Nils has previous experience of online therapy for chronic health conditions, and the design and management of randomized clinical trials.

Christel Hedman, lic. physician and PhD at the Department of Molecular Medicine and Surgery, KI, and affiliated with research at Karolinska university hospital Solna has extensive experience of research on psychological outcomes in cancer survivors with particular emphasis on patient's long-term health-related quality of life in differentiated thyroid cancer.

Linda Björkhem-Bergman, lic. physician and PhD, has extensive experience of palliative care and chronic cancer forms, and is an expert in fatigue: one of the most common long-term

somatic symptoms in long-term cancer survivors (53). She also has experience of working with randomized clinical trials, and developing guidelines for the management of distress.

In summary, the collaboration between EA, CH, and LBB (plus MSc JW, and MSc NG) ensures that several perspectives on psychological distress in cancer survivors are represented in the research group. EA will lead the project, and continuous meetings will involve all researchers. Results will be communicated in open access peer-reviewed journal articles. EA also has a broad informal national network in psychotherapy research that will be used to spread knowledge about the treatment content and findings of this randomized factorial trial.

Time schedule as of February 2023

Preparatory work in terms of writing protocols, producing content, and submitting the work for ethical review will take place in May-September 2023. We plan to involve patient representatives in the treatment drafting process. Hands-on procedures are first evaluated, and recruitment is initiated, in September 2023. Recruitment for the pilot trial is complete around the end of 2023. The finalization of all routines for the full-scale trial, including the recruitment of additional psychologists interested in contributing to the project by serving as therapists in exchange for co-authorship, will be completed during the January-June period. Recruitment of participants for the full-scale randomized factorial trial will begin in August 2024. From then on, approximately 80 participants will be recruited each semester until the end of 2026. We expect the last 12-month follow-up assessment to be completed in December 2027. Manuscripts will be submitted for publication throughout 2028 to 2030.

Significance

This project can lead to substantial societal gains. The population of cancer survivors who experience long-term distress is substantial, and access to structured treatment is insufficient. Internet-delivered psychological treatment is relatively easy to scale up and disseminate, for example in the primary care context, and the development of a free-to-use treatment protocol based on rigorous evaluation in clinical trials could potentially have pervasive effects on suffering and health care utilization. Though the project will proceed in accordance with this research plan, the outcome of the pilot study can also inform the precise design of the full-sized clinical trial and sufficient amendments will be submitted for ethical review as deemed necessary. Experiences from the randomized factorial trial can inform clinical practice in that we will arrive at an evidence-based Internet-delivered psychological treatment for cancer survivors with clinically significant psychiatric symptoms.

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