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-"Protocol for a pilot randomised controlled trial of an online intervention for post-treatment cancer survivors with persistent fatigue

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Abstract

Introduction: Many post-treatment cancer survivors experience persistent fatigue that can interfere with the transition from patient to survivor of cancer. Theoretical models that aim to explain contributory factors that initiate and sustain fatigue symptoms, or that influence the efficacy of interventions for CrF require testing. Adjustment to fatigue is likely to be influenced by coping behaviours that are guided by the representations of the symptom.
Objectives: This paper describes the protocol for a pilot trial of a systematically and theoretically designed online intervention to enable self-management of cancer-related fatigue after cancer treatment.
Methods and Analysis: This 2-armed randomized controlled pilot trial will study the feasibility and potential effectiveness of an online intervention. Participants will be allocated to either the online intervention (REFRESH (Recovery from Cancer-Related Fatigue)), or a leaflet comparator.
Participants: 80 post-treatment cancer survivors will be recruited for the study.
Interventions: An 8-week online intervention based on cognitive behavioural therapy.
Primary and secondary outcome measures: The primary outcome is a change in fatigue as measured by the Piper Fatigue Scale (revised). Quality of Life will be measured using the Quality of Life in Adult Survivors of Cancer Scale. Outcome measures will be collected at baseline and at completion of intervention.
Results: The feasibility of trial procedures will be tested, as well as the effect of the intervention on the outcomes.
Conclusions: This study may lead to the development of a supportive resource to target representations and coping strategies of cancer survivors with CrF post-treatment.
Setting: Recruitment from general public in Ireland

Ethics and Dissemination: This trial was approved by the Research Ethics Committee at National University of Ireland Galway in January 2013. Trial results will be communicated in a peer reviewed journal.
Trial registration: REFRESH (Recovery from Cancer-Related Fatigue) is listed on the ISRCTN registry with study ID ISRCTN55763085.

Strengths and limitations of this study

- The development of the intervention was informed by the Medical Research Council's guidelines on developing complex interventions and was developed through the systematic application of theory, evidence, and user-testing.
- Despite being a complex and multifaceted intervention, transparency was sought by detailing the components of the intervention, the proposed mechanisms of change.
- The complementary strengths of the quantitative and qualitative data collection methods employed here provide a comprehensive understanding of the needs of the target user group.
- This evidence-based online programme is the first intervention of its kind based on the Self-Regulation Model of Health and Illness theory, with the primary aim of targeting the representations of fatigue and enhancing self-management of CrF specifically. It also provides the first systematic coding of a CBT intervention using the BCT taxonomy (v1).
- Self-selection bias into study conditions may influence the outcomes, understating the actual effectiveness of the intervention. Self-reported information obtained from questionnaires may be inaccurate or incomplete.
- Due to resource constraints, a longer-term follow-up will not be included in the initial pilot trial.

Introduction

This paper describes the protocol of a 2-armed randomized controlled pilot trial that is designed to study the feasibility and potential effectiveness of an online intervention that aims to reduce fatigue in post-treatment cancer survivors(1). Up to 75% of post-treatment cancer survivors experience negative health-related consequences (2). Cancer-related fatigue (CrF) is the most common and disruptive symptom reported. CrF is a persistent, subjective sense of physical, emotional and/or cognitive tiredness related to cancer or cancer treatment (3). It is not proportional to recent activity, and interferes with usual functioning (4). It impacts the physical, emotional, and/or cognitive functioning of the survivor. Guidelines recommend that if there is no evidence of a somatic condition causing the fatigue, behavioural interventions should also be considered (5). There is no recommended standard nonpharmacological treatment of CrF in those with cancer (6), highlighting a need for effective and accessible treatments.

CrF persists for months and even years following completion of treatment in about one third of those with cancer (7). Fatigue that persists for 3 months or longer after cancer treatment completion is unlikely to decrease of its own accord (8). The cause of fatigue after cancer is unclear.

Theoretical models that aim to explain contributory factors that initiate and sustain fatigue symptoms, or that influence the efficacy of interventions for CrF require testing (6). In a Cochrane review of psychosocial interventions for reducing fatigue during cancer treatment, the effectiveness of interventions specifically designed for fatigue was significantly higher compared to interventions not specifically for fatigue (9).

In planning the intervention, Bradbury, Watts (10) note that deductive approaches (including reviews of the existing literature) are useful to ascertain what is already known about changing a behaviour and inform intervention design. A systematic review of the literature (11) revealed that the most commonly used intervention strategies were CBT, mindfulness-based interventions and psycho-education. No single intervention type emerged as superior in this review, and a decision was made to base the current intervention on CBT. This decision was based on the quality and quantity of existing literature, as well as clinical expertise. The National Comprehensive Cancer Net-work has published guidance on supporting patients with CrF following treatment. Recommendations include the use of CBT. (Berger, Abernethy, & Atkinson, 2012). CBT is also recommended by the American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guidelines (Runowicz et al., 2016).

Qualitative focus group research was carried out to explore the experience of cancer-related fatigue in post-treatment cancer survivors. Findings suggested that using the participants' descriptions mapped onto the Self-regulation Model of Health and Illness (SRM) (12). The study will incorporate Leventhal's self-regulation theory as a framework for conceptualising the process of adjustment (13). This theory proposes that the representation of a symptom such as fatigue involves a cognitive pathway (i.e. the creation of a knowledge-based conceptualisation of CrF) and an emotional pathway (i.e. emotional response to CrF). Coping behaviours are guided by the representations of the symptom (14). This is an iterative feedback process of developing and analysing coping efforts and representations of the problem, leading to further coping attempts.

A Cognitive behavioral therapy (CBT) model of fatigue (15) was used to apply SRM theory in a treatment model. CBT models focus on similar cognitive, emotional and

coping/behavioural factors as those outlined by Leventhal (13). Andrykowski, et al. (16) proposed that biological insults such as the cancer or its treatment may precipitate the initial experience of fatigue during cancer, whereas a cognitive-behavioural model of fatigue may predict the persistence of fatigue in survivorship. Using the SRM to describe fatigue after cancer provides an integrated theoretical model for developing interventions for fatigue based on cognitive–behavioural principles.

INSERT FIGURE 1. HERE

Figure 1. From theory to practice: Applying the self-regulation model to a cognitive-behavioural therapy treatment model.

As CrF is a multidimensional and complex symptom (17), an intervention mode that can incorporate multiple and complex behaviour change techniques was required (10). Chou, Liu (18) encourage using Internet to better serve survivors' needs as it is increasingly being used as a resource by cancer survivors (19). Online interventions have been found to be at least as effective as face-to-face therapies for a wide range of issues (20). This mode of delivery affords the opportunity to reach a wider range of patients compared to face-to-face interventions, especially severely fatigued patients or those with limited mobility. 'LifeGuide' is a set of open-source software that enables researchers to collaboratively create and evaluate interventions (21). This software allows non-programmers to create and easily modify web-based interventions (10). This tool has been used by researchers to create websites which provide tailored long-term support for behaviour change (Michie et al., 2012). Researchers can rapidly test the effects of intervention components. LifeGuide facilitates easily modification and improvement of components at any stage of the intervention (Michie et al., 2012).

The intervention described in this paper will build upon previous studies that have employed internet-based self-management programmes (19, 22, 23). Further, it will employ Roth and Pilling's competence framework for cognitive behavioural therapy for those with persistent physical health conditions (24). Adjustment to fatigue will be a primary focus of the intervention, with cognitive, behavioural, affective and social responses being addressed (25). The goal is to improve functioning, and to enable the participants to make meaningful changes in their daily lives, rather than symptom reduction per se. The aim is to determine the feasibility of the "*REFRESH* (Recovery from Cancer-Related Fatigue)" intervention trial. It

will also assess the overall impact of the intervention on fatigue and proposed mediating factors in cancer survivors. It is hypothesized that an online intervention designed using a theoretical, systematic and person-based approach will be successful in reducing the effects of fatigue in post-treatment cancer survivors.

Specific objectives

1. To conduct an evaluation of the feasibility of the intervention, looking at
    i. Recruitment (number of patients approached about the study, source of referral to the study, number consenting to participate and those eligible to be randomized)
    ii. Adherence and attrition to the intervention
    iii. Drop out from trial (i.e. follow-up questionnaires not completed)
    iv. Evaluation of functionality, acceptability and usability of website
    v. Participant satisfaction with the website.
2. To assess the potential efficacy of the "*REFRESH* programme" in adult survivors of cancer. Changes in fatigue will be assessed by comparing intervention and wait-list control groups at baseline and post-intervention in terms of the following outcome:
    i. Fatigue (primary outcome) - assessed using the Revised Piper Fatigue Scale (PFS-R). ((26)
    ii. Quality of Life (secondary outcome), as measured using the Quality of Life in Adult Cancer Survivors (QLACS) Scale
3. To explore change in potential therapeutic mechanisms of change in relation to fatigue outcomes. Changes will be assessed by comparing intervention and wait-list control groups at baseline and post-intervention in terms of the following outcomes:
    i. Illness perceptions relating to CrF
    ii. Cognitive-behavioral coping strategies used in the management of fatigue
    iii. Appraisal of Coping

Ethical approval

This trial was approved by the Research Ethics Committee at National University of Ireland Galway in January 2013. Full written informed consent will be sought from all participants for both their participation and the publication of the results of the research. Participants will be reminded that they are free to withdraw at any time and that their data will be stored

securely and anonymously. All data will be stored on password protected hard drives in accordance with the Data Protection Act. All data will be anonymised.

Method

The study is designed as an exploratory, parallel-group pilot randomised controlled trial to determine the feasibility, potential effectiveness (as assessed using Piper Fatigue scale (26)) and acceptability of an online CBT intervention for cancer-related fatigue called *REFRESH* (Recovery from Cancer-Related Fatigue). The study will include 2 parallel conditions: experimental conditions (online CBT for fatigue) and a wait-list control condition. Feasibility will be measured by assessing recruitment, willingness to be randomized, attrition, adherence and completion of outcome measurements. Acceptability will be assessed by participant satisfaction with the intervention. Participants will be randomized in a 1:1 ratio to receive either the *REFRESH* online intervention, or a widely available leaflet comparator developed by the Irish Cancer society, called "*Coping with Fatigue"* (27). The intervention group will access 8 online CBT for CrF sessions each week for a 10-week period. Assessments will be conducted at baseline and immediately after intervention (at 10 weeks).

Participants

A total of 80 Irish cancer survivors will be randomized to receive the intervention or usual care. The intervention group will receive an 8-session interactive intervention (*REFRESH*) and the control group will receive an online copy of the Irish Cancer Society "*Coping with Fatigue*" booklet at the beginning of the study. This booklet is currently widely available as a source of information about fatigue.

Inclusion and Exclusion Criteria

Participants are eligible for the study if they

1. are over 18 years of age,
2. are experiencing fatigue defined as scoring ≥4 on a unidimensional 11-point numeric rating for fatigue as suggested by the National Comprehensive Cancer Network (3),
3. are able to complete written records in English,
4. have or are willing to create an email account and have access to the internet,
5. have access to, and basic ability to use a computer
6. have completed primary treatment for cancer (patients are eligible for the study if

they are receiving maintenance therapy such as hormone therapies) at least 3 months prior to baseline assessment (8)

Patients will be excluded if they

1. Do not provide informed consent or refuse to be randomized.
2. have history of cancer recurrence
3. do not confirm that they have received medical clearance for participation
4. are currently participating in any other psychosocial intervention

Recruitment process

It is intended to recruit 60 participants who have completed primary treatment with curative intent for non-metastatic cancer at least 3 months prior to baseline assessments. Recruitment will take place from October 2015- April 2016.

Online Recruitment

An online recruitment strategy will run separately and concurrently with the rest of the research recruitment campaign in order to broaden exposure (28). Social media sites will be used to target cancer survivors engaged in online activity. Use of popular existing social network sites are expected to address issues of reach, engagement, and retention (29). Online social networks have been found to typically achieve high levels of user engagement and retention. Social media enables the researcher to actively generate engaging and novel content, which is likely to be more influential than traditional static and passive websites (30). They are a cost-effective means of recruitment, that may engage potentially difficult-to-reach groups, providing participants a more accessible method by which to participate in health research (30). These websites will inform potential participants of the study and provide a link to the survey.

I. WordPress® will be used to develop a host website for the study. Participants will be able to access the participant information sheet and links to the online questionnaire on this site. Another page will give description of the study investigators. Pictures and engaging content will be posted to build rapport and credibility with the audience (28).

II. Facebook® is the world's largest social networking website and has 1.1 billion users each month). A Facebook fan page will be created to recruit participants and raise awareness of the study (28). Posts will include study announcements, links to the WordPress® website, pictures, and videos featuring the primary researcher discussing the project. Posts will be scheduled in advance, with about a new post per day during the recruitment period. Other Facebook fan pages with similar purpose or interest will be interacted with, by "liking" these

organizations' pages, which were found using keyword searches for cancer, oncology and health care. "Facebook Adverts ©" will be used to advertise the study to a large number of social media users.

III. Twitter® will be used to target individuals using short messages (tweets) to share online material including links to the *REFRESH* WordPress® website. Users will be encouraged to share (i.e. 'retweet') these messages with their own followers (30). Stakeholders and key influencers will be targeted in particular. These include patient advocates and healthcare professionals. Organisations affiliated with cancer survivorship will be followed. Hashtags (#) related to cancer, fatigue and related topics will be used to reach a large audience of potential participants (28).

IV. LinkedIn® groups that included content related to cancer survivorship will be used to reach potential participants. Again, these messages will target those people living with CrF, cancer survivorship advocates, healthcare professionals working in oncology and psycho-oncology, and other researchers. Group members will be asked to share the survey link with other potentially interested groups or individuals (28).

Offline Recruitment.

The offline recruitment strategy will centre on interaction with community organizations and leaders(31). Cancer support groups and national cancer charities and organizations will be contacted and asked to promote the study. Researchers will also recruit in-person at the Irish National Cancer Survivorship Conference in September 2015.

Media outlets will be contacted via press releases, with information about the study being promoted nationally in press and on the radio. Printed advertisements (such as leaflets) will be distributed in local pharmacies and coffee shops.

Health system recruitment will also be employed, given the importance of physician referrals as gatekeepers to patient research recruitment(31). General practitioners and health care professionals will be informed about the study. They will be encouraged to share the information with any patients who may benefit from partaking in the research.

Trial procedures

Interested participants will be invited to access a recruitment website hosted on WordPress®. An information sheet about the study will be provided. This will include the rationale for the study and will explain that participants can opt out of the programme at any point without penalty. This website will also include details about the inclusion/exclusion criteria for the study. A link to the baseline assessment will be posted on this website during the recruitment

period. Eligible and willing participants, after reading the documentation, will be invited to complete these baseline assessments using an online survey tool (Survey Monkey®). Before progressing to the baseline questionnaire, participants will be required to provide informed consent outlining their awareness of the trial protocol and inclusion criteria. Participants will be screened for inclusion after the completion of the baseline questionnaire, prior to randomization. Only those who meet the eligibility criteria gain access to the website.

Randomization and blinding

Participants will be randomized in a 1:1 ratio to receive either the *REFRESH* intervention, or a leaflet comparator developed by the Irish Cancer Society, *Coping with Fatigue*. Upon completion of the baseline questionnaire, participants will be randomized to either the waitlist control or intervention group. Participants will randomized in blocks of six, using a computer-generated number sequence that was created apriori using Random.org (32). An independent research assistant will email participants to inform them of their group allocation. The research team will be made aware of group allocation in advance of the half-way contact point with participants. The nature of the trial is such that blinding of participants cannot be achieved. No changes in assignment will be possible until after the trial period. Figure 2 shows the flow of participants through the trial.

INSERT FIGURE 2. HERE

Figure 2. Planned flow of participants through the *REFRESH* randomized controlled trial.

Control group/usual care

The control group will receive an online copy of a booklet with brief general recommendations about fatigue management that was designed by the Irish Cancer Society (27). This will contain some general information about CrF. After completion of this study, control participants will be given the opportunity to access the *REFRESH* program. Data gathered during this period will be analysed to evaluate user processes such as engagement, and dose of intervention received (33).

Intervention

The *REFRESH* online intervention was developed using LifeGuide, open source software (34). The intervention is a web-based online program that can be accessed from any location or device with Internet access (21). The purpose of this intervention is to target individuals'

illness representations and coping strategies in order to facilitate coping with CRF. Table 1 summarizes the intervention and the association of the components with the SRM model and CBT. In order to describe intervention content and avoid the problems of lack of consistency across interventions, The Behavior Change Technique Taxonomy (v1) was employed (35). A behaviour change technique (BCT) is an observable, replicable, and irreducible component of an intervention designed to alter or redirect causal processes that regulate behaviour (35). To our awareness, this is the first instance of the BCT taxonomy being used to specify components of a CBT intervention.

Content

The information provided in this website was developed based on the Medical Research Council guidance (36). It draws on the findings of a systematic review of the literature relating to psychological interventions for CrF. The content is also based on qualitative research conducted with cancer survivors suffering with persistent fatigue after the completion of curative treatment. The structure and layout has been designed in line with previous CBT interventions, in particular, the "*Understanding and Managing Persistent Cancer-Related Fatigue manual*" (37) and the *MSInvigor8* trial (23) (38). Aspects of the intervention relating to thoughts and emotions also draws on the principles of CBT as outlined in the "Feeling Better" manual(39). An expert design team supported the development of *REFRESH.* These included Health Psychologists and Clinical Psychologists. A nurse, cancer care staff and a cancer survivor also contributed to the design of the programme. The CBT intervention techniques used in this intervention are based upon those outlined in the competence framework for psychological interventions with people with persistent physical health conditions developed by Roth and Pilling (24). These are presented in Table 1. Further information and specific components of the intervention were also informed by the available evidence on symptom focusing (40); activity scheduling, insomnia management (41) (42) (43) ; and stress management (44) in cancer patients.

The *REFRESH* intervention was created with the goal of providing participants with a user-friendly, engaging and effective online environment while affording them the opportunity to learn more about their fatigue symptoms and management. Figure 2 shows the basic structure of the program. Given online security concerns, all user data is protected.

INSERT TABLE 1. HERE

Procedure of the intervention

Participants in the intervention group will be asked to sign-up for the *REFRESH* programme with their email and unique password. New users will receive instructions on the "About *REFRESH*" page before logging in. The page includes an introduction to the aims of CBT and step-by-step instructions for how to navigate the programme.

The intervention requires 45-60 minutes per week over 8-10 weeks. The online intervention is accessed through the main welcome page. Once logged in, each user is presented with a personalized "Home Page" (see Figure 2) that provides information about the last time the user logged in. The screen allows for easy navigation to each of the main sections of the site: "Useful Content", "Sessions" and "About the programme". The Useful Content contains useful links that are relevant to participants (links to cancer support service websites etc.) the printable elements of the program such as diaries and tips. The Information about the programme tabs offer information about how to contact the research team, a "Frequently Asked Questions" (FAQ) page addressing technical issues, and a "What is *REFRESH*" tab that provides a brief introduction to the system and a "Who made *REFRESH*?" tab that introduces participants to the research team involved in developing the programme. The "Disclaimer" tab reminds users that the information provided is for educational purposes only and should not replace or override a physician's care.

Every session follows a similar structure: objectives and outline, main content, review and to-do list. This can be seen in Table 2. Each of the 8 sessions acts as an online analog for the weekly sessions conducted in traditional in-person CBT. The intervention content incorporates the essential treatment elements of CBT: educational, behavioural, and cognitive techniques (45).

INSERT FIGURE 3. HERE

Figure 3. Basic structure of the *REFRESH* program.

INSERT TABLE 2. HERE

The intervention involves a high degree of interactivity and personalization. In addition to using the individuals name at various stages of the intervention, personalization also occurs in the form of re-showing unique user-information. Participants are asked to identify problems

associated with their fatigue. These problems are later presented as part of goal-setting exercises in order to remind participants to set specific goals that are relevant to them. Participants are also presented with a personalized CBT-model of fatigue, based on answers about their feelings, actions and cognitions pertaining to their fatigue symptoms. Users are free to revisit a session as many times as they choose. Answers will be saved and presented to allow participants to review their progress. Further personalization occurs in the form of in-session exercises in which users are asked to describe the specifics of their experience with CrF.

Participants are encouraged to challenge cognitions and learn to prioritize certain behaviours in order to maintain a healthy energy balance. *REFRESH* includes a range of behaviour change techniques (BCTs) designed to enhance relevant information, motivation and behavioural skills. The programme utilises accessible and engaging delivery methods that are in line with Ritterband's theory of online interventions (46). Table 1 shows each phase of *REFRESH* the change targets, BCTs used and the method and agent of delivery (47).

The hypothesis is that targeting cognitive and emotional representations of symptoms will lead to improvements in coping skills and in turn, reduce fatigue levels. These processes may be moderated by cancer-related factors (e.g. diagnosis, treatment type, time since treatment) and demographic factors (e.g. gender, socioeconomic circumstances, education).

Telephone calls

The effectiveness of Internet-based interventions have been found to be enhanced by the use of additional methods of communicating with participants (47). A semi-structured interview guide will be followed in each of these calls. The structure has been outlined in a manual to enable replication. The calls will be made by the primary researcher who has a background in Health Psychology and experience in working with patient groups. Each group will receive one phone call after 4 weeks of the programme (i.e. half-way). Each phone call will last 15-20 minutes. For the intervention group, the aim of these calls will be to solve any problems with the sessions or content. Also, messages of encouragement will be given to stimulate adherence to the program. The wait-list control group will be called to remind them that they can gain access to the programme in the weeks that follow. Calls will be audio recorded and checked for fidelity. The content of these calls may also be used to guide improvements for future iterations of the website (48).

Intervention fidelity

A content manual has been developed to accompany this intervention. The 'Intervention

Manual' describes and defines the programme components for each module. The website will include features to monitor adherence and completion rates of each module by each user. Individual factors which may affect fatigue and/or energy level (medication-use, comorbidities, physical disability etc.) will be documented for both control and intervention groups.

Follow-up Measurement, Assessment and Outcomes

Follow-up assessments will take place 10 weeks after randomization. Participants (intervention and control group) will continue to have access to the *REFRESH* programme for 2 months following completion of follow-up questionnaires.

Timing of assessments

Participants will be recruited and assessed at baseline from October 2015- March 2016. Follow-up data will be collected upon completion of the trial, 10 weeks post-baseline. Outcomes are self-reported at baseline (T0), post-intervention (T1). Figure 1. shows a schematic summary of the trial design. All participants are invited to fill out short questionnaires at baseline pre-randomisation. After completion of follow up assessments at T1, patients in the control condition are offered the experimental intervention. The protocol allows delay within the 8- week intervention period of a maximum of 1 week. For all participants, the duration of their participation is approximately 10 weeks. Additional qualitative feedback will be obtained through explorative open-ended questions with a subset of participants in the experimental condition shortly after T1.

Methods for dealing with loss to follow-up

This pilot trial aims to assess attrition rates for a future large RCT. In order to reduce loss-to-follow up, the researchers will aim to foster trusting relationships, helping the participants to feel engaged in the research process. All participants will be contacted via telephone in the fourth week of the programme to enhance this relationship. Familiarity with the researchers will be promoted through the use of familiar and consistent voices on the narration of videos used in the online programme. Participants will be able to access a page entitled "About us", which will include photographs and brief biographies of each the researchers.
Participants will be reminded of their commitment to the programme at the outset of the intervention in order to promote a sense of self-responsibility. Participants will be congratulated upon completing a module in order to boost self-esteem and garner a sense of achievement. At the end of each session, participants will select a time to receive one prompt

email to continue to the next session in the week that follows.

Outcome measurements

Assessments will be undertaken online. Assessors of outcomes will be blinded to group allocation until after baseline measures have been completed. Outcomes will be assessed at baseline and at 10 weeks.

1. The primary goal of this study is to assess the feasibility and functionality of an online CBT programme for this sample. Therefore, the following outcomes will be assessed.

I. Recruitment and uptake
II. Adherence and attrition
III. Evaluation of functionality and usability of website
IV. Participant satisfaction with website.

This feasibility trial aims to provide insight into the way *REFRESH* is used by participants. Information on intervention uptake, delivery and experience will be collected. Delivery and uptake will be determined by assessing initial uptake to the programme and participation in each of the sessions. This is outlined in Figure 4.

INSERT FIGURE 4 HERE

Figure 4. Uptake and participation assessment

Adherence to, and engagement with, the programme will also be assessed. In order to determine the 'intensity' of the intervention components delivered; the 'engagement' of participants will be assessed. Data relating to pages visited and time spent on each page will be collected in LifeGuide (21). This data will be used to gain a sense of how participants engaged with the programme. Criteria for assessing engagement for each individual are:

i) active participation in 90% of at least 4 of the *REFRESH* sessions.
ii) completion of exercises within the sessions
iii) level of engagement with course materials.

The Internet Evaluation and Utility Questionnaire measures participants' experiences and perceptions of the intervention. This measure has two main sections – generic and specific. In an earlier and shorter version of this measure (41), good internal reliability was found (alpha = .69). Patients respond to the questions on a 5-point Likert scale from 0 ("not at all") to 4

("very"), with 2 open-ended items requesting patients to identify "most helpful" and "least helpful" parts of the web program.

- The first 15 questions make up the generic section. The constructs measured by items 1-8 include ease of use, convenience, engagement, enjoyment, layout, privacy, satisfaction, and acceptability.
- Items 9 to15 assess perceptions of the web program material in terms of usefulness, comprehension, credibility, likelihood of returning, mode of delivery, and helpfulness.
- Following these 15 items are questions specific to the *REFRESH* intervention.

Open-ended questions will also be asked of all participants at follow-up to obtain further qualitative data on the barriers and facilitators to participation as well as to understand the experience of participating. Those who withdraw from the intervention will be invited to participate in an exit interview/debrief with the principal investigator.

2. To assess the effectiveness of the "*REFRESH* (Recovery from Cancer-Related Fatigue) intervention" in long-term adult survivors of cancer, by comparing intervention and wait-list control groups:

Primary outcome: Fatigue as measured by the Piper Fatigue Scale (revised) (PFS-R) (26). The revised PFS-R consists of 22 items measured on a 10-item numeric rating scale items. Higher mean scores represent greater fatigue. Four open-ended questions are also included as descriptive items. The scale is multidimensional and incorporates key dimensions of the fatigue experience including cognition, behaviours, affect, and sensory symptoms (49). Reported Cronbach alphas have ranged from 0.98 for the total scale and 0.94 for subscales in women with fatigue after cancer treatment (50) indicating good internal consistency. Research has demonstrated good psychometric properties, with high concurrent validity with the FQ (r=.80) and good test–retest reliability results (r=.98) (51). The scale has been validated in a group of cancer survivors (52).

Secondary outcome: Quality of Life as measured by the Quality of Life in Adult Cancer Survivors (QLACS) questionnaire (53)

The QLACS is a multi-dimensional measure with 47 items that assess 12 QOL domains. It includes. negative feelings; positive feelings; cognitive problems; pain, items; sexual interest; energy/fatigue; sexual function; social avoidance; financial problems; benefits; distress-family; appearance; and distress-recurrence. Participants are asked to rate how often they felt a certain way in the past 4 weeks (never, seldom, sometimes, about as often as not,

frequently, very often, always). The scale is validated in a range of cancer types (54) and has good internal consistency reliability, and adequate concurrent and retrospective validity (55).

3. To assess the relationship between therapy process and outcomes

In line with the recommendations of the competence framework for psychological interventions with people with persistent physical health conditions, this trial will also incorporate measures that aim to further explore the relationship between therapy process and outcomes. Therefore, drawing on the theory of the self-regulatory model of illness (13) the following outcomes will also be assessed. This is outlined in Figure 5.

I. **The Illness Perceptions Questionnaire for Cancer-Related Fatigue (CRF)** will be used to assess perceptions relating to CrF Cognitive and Emotional Representations. The IPQ-R for CrF (56) is adapted from the IPQ-R (57). The scale is divided into three sections. Section A assesses CrF identity and asks respondents to report (a) whether they have experienced each of a list of 14 commonly experienced core symptoms and (b) whether they believe each of these symptoms is specifically related to their CrF using a *yes*/*no* response format. The list of symptoms included in the identity dimension is tailored to CrF by including 12 symptoms specifically associated with this condition based on the CrF diagnostic criteria (35).

Section B contains 38 items that assess the timeline acute/chronic, timeline cyclical, consequences, personal control, treatment control, illness coherence, and emotional representation dimensions (35). These items consist of statements that are rated on five-point Likert scales ranging from 1 (*strongly disagree*) to 5 (*strongly agree*). The mean of the subscale items measures that illness dimension. Section C is concerned with the cause dimension. Respondents indicate whether they believe each of a list of items cause or contribute to their fatigue using the same five-point Likert scale. The scale has been validated on cancer patients and survivors (35).

The Cognitive and Behavioural Responses to Symptoms Questionnaire (CBSQ) will be used to assess which cognitions and behaviours mediate the effect of cognitive behavioural therapy on fatigue in this group. The CBSQ consists of two behavioural subscales and five cognitive subscales. These subscales measure aspects of the response to (or coping strategy employed to manage) symptoms. The CBSQ subscales have an acceptable internal reliability. The scale has previously been used in MS patients (58). All items are scored on a five-point frequency scale ranging from never (0) to all the time (4). Item scores are added from each subscale to obtain a total score (58). The scale includes "Cognitive Subscales" which assess

interpretation of the symptoms. These include: fear avoidance catastrophising, damaging beliefs, embarrassment avoidance and symptom focusing. It also includes "Behavioural Subscales" which measure all-or-nothing behavior (tendency of patients to overexert themselves, followed by periods of inactivity) and avoidance/resting behaviour.

II. Appraisal of Coping: The Coping Efficacy Scale (59)

Coping efficacy will be measured to assess respondents' appraisal of coping with fatigue. Participants will be asked "How satisfied are you with how you coped with your fatigue?" referring to the past week. The second item will be, "If you had similar symptoms again, how certain are you that you would be able to adjust well to its negative aspects?" referring to the past week. Participants were asked to indicate on a 5-point Likert scale about how certain they were that they could cope with similar symptoms in the future. The scores of these items will be averaged to produce one composite score of coping efficacy. A score of 1 will indicate low coping efficacy and 10 will indicate high coping efficacy. Evidence for the validity of these measures of coping efficacy is strong (59, 60)

INSERT FIGURE 5 HERE

Figure 5. Proposed assessment of Self-regulation Model theory.

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4. Demographic and cancer-related information

Possible moderating variables (individual demographic factors and medical-related factors) will be taken from baseline data. Demographic (age, gender, marital and employment status) and medical information (cancer type and treatment, time of diagnosis and treatment, comorbid medical conditions) will be obtained.

Sample size

The primary aim of this study is to assess initial uptake of the study and following attrition. Figure 1 shows the flow diagram of the study participants. A process evaluation will investigate how the intervention was delivered, how it might be replicated and improved upon (33).

Mechanisms of impact and effectiveness will only be assessed if a sufficient number of participants are recruited (33). In line with Viechtbauer et al (61), the estimated sample size of 59 cancer survivors would be required to reach a 95% confidence level in a pilot study.

Assuming that intervention improves fatigue in survivors compared to those in the control group differences of at least 5% with a power of 90% and α of 0.05 with two groups (intervention and waitlist control group) could be detected.

Statistical analyses

Where hypothesis tests are carried out, these will be at the 5% level for primary and secondary outcomes. All analyses will be planned *a priori* and reported in full. The reporting and presentation of this trial will be in accordance with the CONSORT guidelines for randomized trials (1), with the primary comparative analysis being conducted on an intention-to-treat basis. Mean and standard deviation will be used to represent the variable scores at baseline and follow-up measurements.

Study population will be characterized using various descriptive statistics parameters. Initially, possible differences between groups at baseline will be assessed using a one-way analysis of variance for continuous data (or equivalent statistical approach in the case of non-parametrical data) and Chi-square for categorical data.

Comparisons of outcome measures will be undertaken at baseline and 10 weeks for all available measures. Between-group comparisons will be made using a 2 (group) x 2 (time) mixed ANOVA.

Although the trial is not powered to detect the influence of mediating and moderating factors on fatigue, we will explore possible interactions in the following secondary analyses: (i) interaction terms will be examined to investigate possible differences in intervention effects on the primary outcome by demographic and cancer-related factors; (ii) engagement with *REFRESH* will be determined and a comparison between those who meet the criteria for engagement versus those who do not will be undertaken to assess 'per protocol' effectiveness; (iii) a mediational analysis exploring whether the effect of the intervention on the primary outcomes is mediated by illness perceptions and cognitive behavioral strategies using the analytic framework recommended for RCTs will also be undertaken.

Data Management and Access

This data management plan has been created using the UCD Data Management Checklist. The data will be saved online through Inquisit (the Sternberg Memory Task) and Surveygizmo (all other tasks and questionnaires). This data is only accessible by the first author. When these data are collated, the second author will also have access to the relevant data files. The data will be saved in both .csv and .sav formats. These files will be stored in encrypted Dropbox folders. A detailed logbook will be created to complement these files. We

do not currently have ethical approval to share these data. In accordance with the NUI Galway data retention policy, these data will be retained for 5 years at the NUI Galway School of Psychology (as well as being backed up on Dropbox) and anonymised by replacing student ID numbers and names with randomly generated subject ID numbers.

Discussion

REFRESH has been developed according to the MRC guidance for developing and evaluating complex interventions(36). The content is based on the SRM which proposes that coping behaviours in response to a symptom such as fatigue are guided by cognitive and emotional representations of that symptom. This approach has guided the linking of theory to specific cognitive-behavioural intervention techniques and mechanism of change targets.

The website has been systematically and theoretically developed in an Irish population, working with cancer care teams, clinical psychologists and cancer survivors suffering with fatigue. This study will provide additional insight into the efficacy of the intervention and allow the researchers to understand the experience of the participants. This will enable any necessary post-trial modifications or remodeling in order to enhance the effectiveness of *REFRESH* prior to the development of a larger scale RCT of the programme.

Throughout the design of this programme, the developers were cognizant of the need to develop interventions that not only incorporate theory but also aim to evaluate the application of specific theoretical frameworks. The systematic theoretical underpinning of '*REFRESH'* will allow the researchers to gain an insight into how some psychological and behavioural variables (mediators) are related to fatigue. However, in the feasibility trial described here, the study will not be powered to assess these potential effects.

The primary outcome measure for *REFRESH* is fatigue as measured by the PFS-R at 10 weeks post-baseline for this pilot trial. An extension of the timing of the main outcome measure in future iterations of the trial will allow for the assessment of any sustained effect on outcomes.

The results from this trial will provide information regarding the potential of a novel theoretical approach to online interventions for cancer related fatigue in post-treatment cancer survivors. The research seeks to create supportive online environments at home to ameliorate fatigue and promote self-management of symptoms in this group. Any amendments or updates to this protocol will be lodged with the journal such that it links them to this protocol document. This will allow all future trial publications and conclusions to be assessed against the extent to which we have adhered to the protocol.

Trial status

The trial and recruitment is ongoing.

List of abbreviations

CrF- Cancer-related Fatigue

CBT- Cognitive Behavioural Therapy

CBSQ- The Cognitive and Behavioural Responses to Symptoms Questionnaire

CONSORT- Consolidated Standards of Reporting Trials

IPQ-R- The Revised Illness Perceptions Questionnaire

ISRCTN- International Standard Randomised Controlled Trials Number

MRC- Medical Research Council

QLACS- Quality of Life in Adult Cancer Survivors

PFS-R- Piper Fatigue Scale (revised)

RCT- Randomised Controlled Trial

REFRESH- *REFRESH* (Recovery from Cancer-Related Fatigue) intervention

SRM- Self-regulation Model

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Competing interests

The authors declare that they have no competing interests.

Authors' contributions

TC conceived of the study, its design and coordination, and drafted the manuscript. JW, AMG and BMG participated in the design of the study and revisions to the manuscript. RMM had input in the conception and design of the paper and has contributed in critically revising

the manuscript for important intellectual content. All authors read and approved the final manuscript.

Communication of Findings: The authors intend to fully communicate trial results in a peer reviewed journal.

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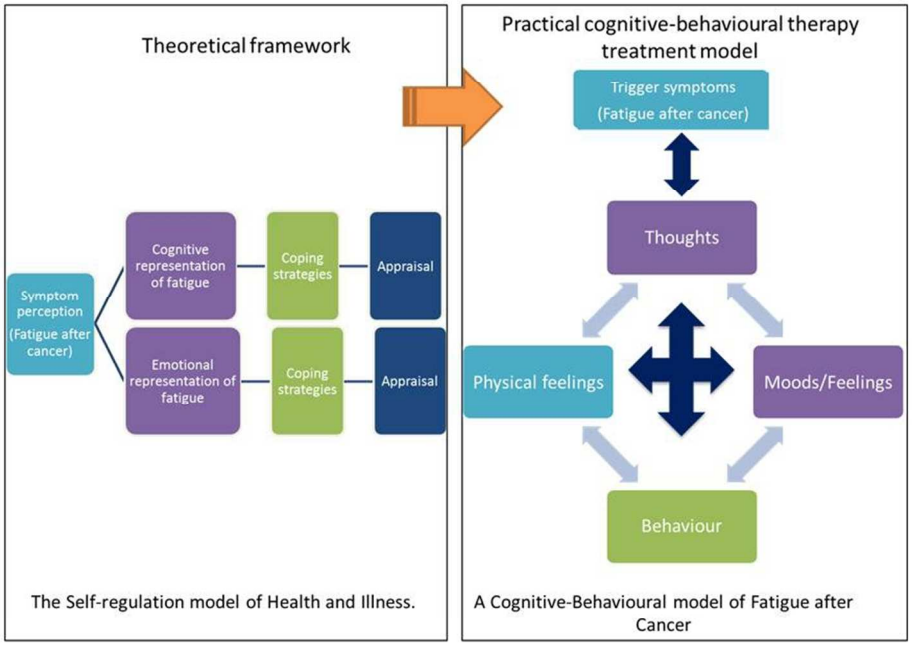

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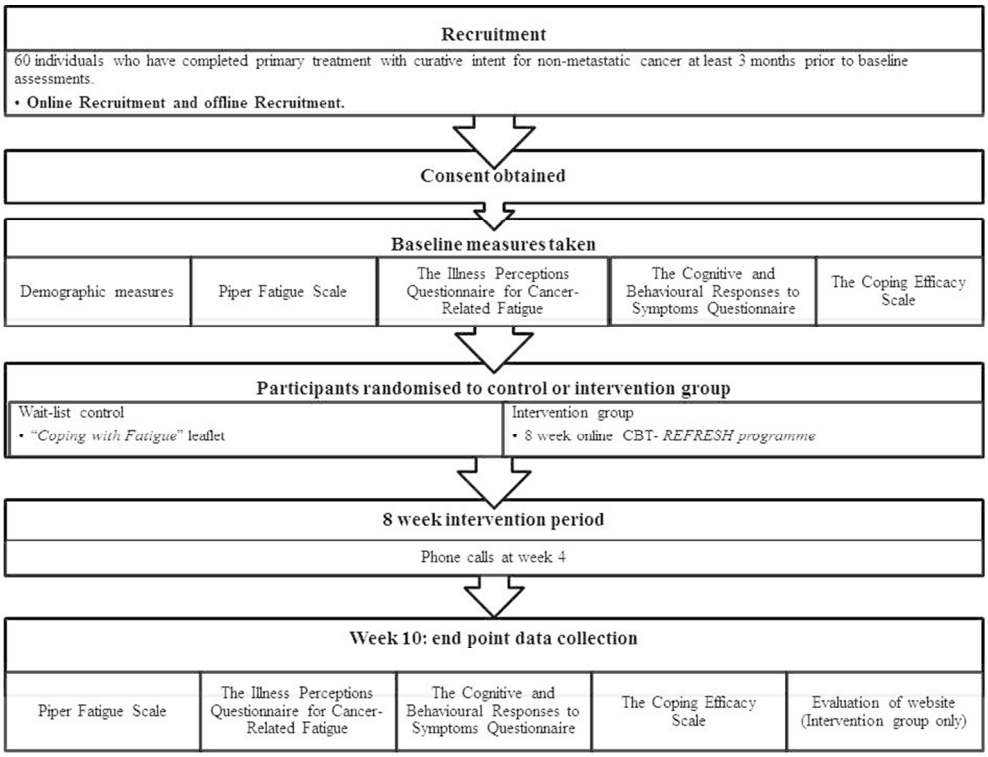

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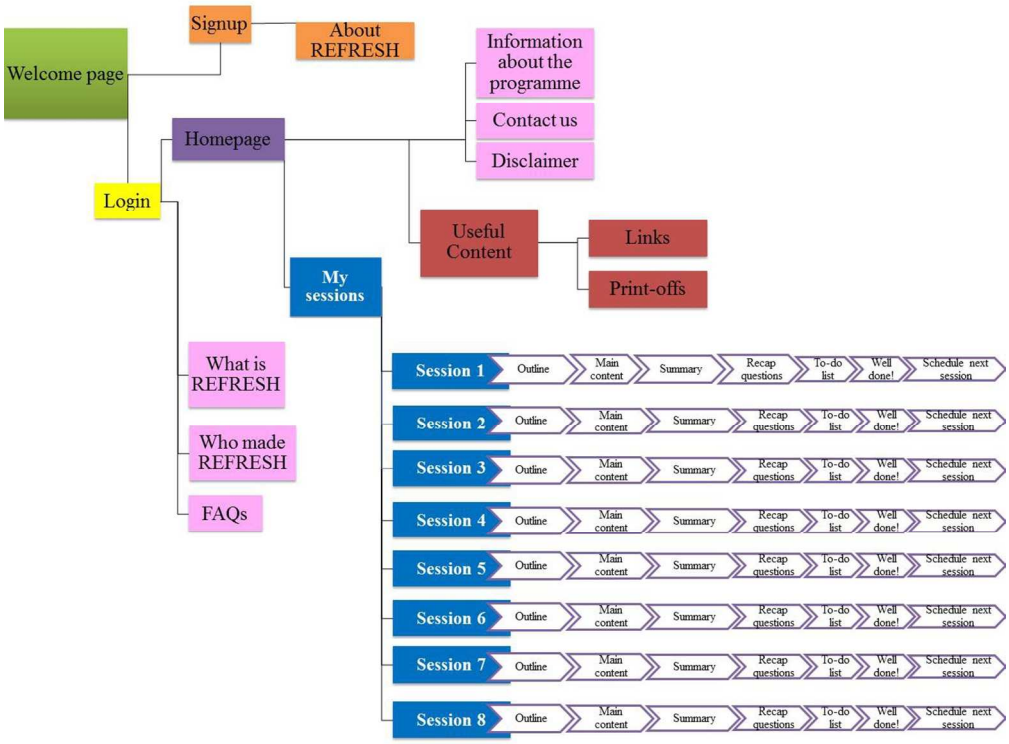

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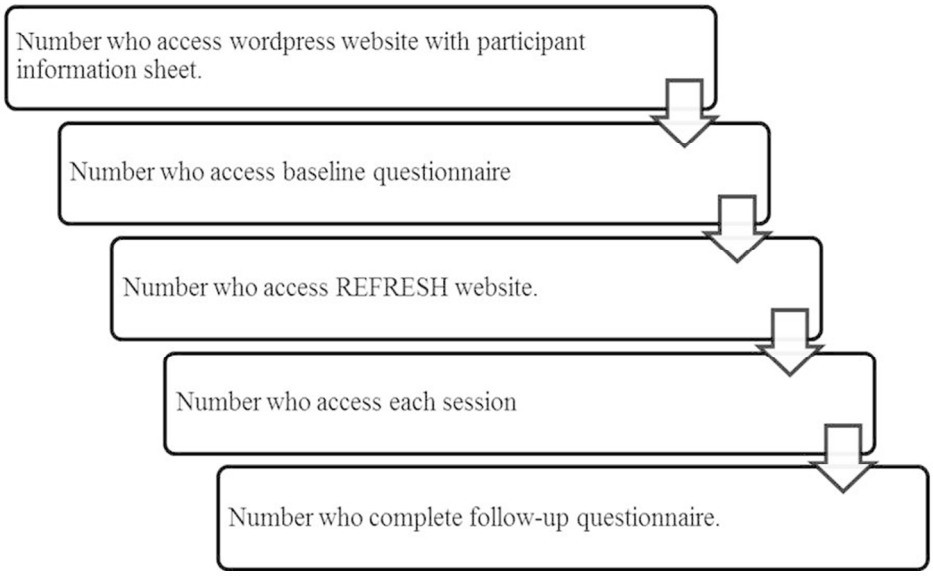

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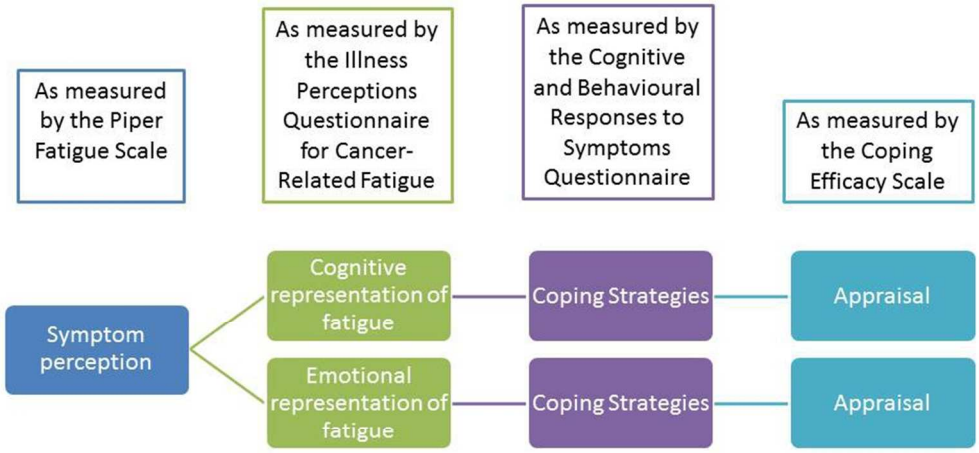

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Table 1. *Intervention phases, CBT intervention techniques, proposed mechanisms of change and theoretical constructs targeted and behavior change techniques employed.*

Session	CBT intervention techniques	Theoretical Construct targeted	Behaviour Change Techniques used
1. Overview of Cancer-related Fatigue.	Elicit from participant their understanding of fatigue - Draw on knowledge about fatigue - Reflect information using patients' own language	• Symptom perceptions • Emotional (mood) • Illness (identity, timeline, consequences, control) representations of symptoms - Inaccurate illness perceptions - Treatment outcome expectancies - Coherence/overall illness understanding	2.4. Self-monitoring of outcome(s) of behaviour 3.1. Social support (unspecified) 4.2. Information about Antecedents 5.1. Information about health consequences 5.2. Salience of consequences 5.3. Information about social and environmental consequences 5.6. Information about emotional consequences 6.2. Social comparison 13.2. Framing/reframing 15.2. Mental rehearsal of successful performance
2. What is Cognitive Behavioral Therapy (CBT)?	Explanation about the CBT model of adjustment - Develop case conceptualisation with participant - Draw on information elicited from participant to describe	• Illness Representations (identity, timeline, consequences, cause, control) • Emotional Representations (mood) - Understanding of poor	1.1. Goal setting (behavior) 1.2. Problem solving 1.3. Goal setting (outcome) 1.4. Action planning 4.1. Instruction on how to perform the behavior 5.2. Salience of consequences

interaction between thoughts, feelings, behaviours and physical symptoms in response to fatigue.

Activity monitoring

- Facilitate process of guided discovery by encouraging participants to record and evaluate behaviour patterns.
- Problem solving encourage participant to identify a specific problem that they are having difficulties with at the moment.

SMART Goal Setting

- Identify a goal they would like to work towards. Action plan how to implement steps defined within SMART goal acronym (Specific, Measurable, adjustment in the context of fatigue

• Coping

- Target specific triggers that the participant is concerned about.

Fatigue management tasks and broader life goals

5.4. Monitoring of emotional consequences
6.1. Demonstration of the behaviour
8.1. Behavioral practice/rehearsal
8.2. Behavior substitution
8.4. Habit reversal
13.2. Framing/reframing
15.1. Verbal persuasion about capability

		Achievable, Realistic, Timely) - Apply chunking: breaking goal down where necessary		
3. Thoughts and Fatigue	Cognitive reappraisal - Patients encouraged to keep a thought record. Thought record used as prompt to identify biased thinking patterns. - Participant guided to identify evidence for and against biased thoughts. - Realistic thought generation, based on objective evidence is encouraged. - Socratic questioning principles implemented.	• Challenging inaccurate illness perceptions (cause, control) • Emotional Representations (mood) • Coping - Identifying and challenging Cognitive biases	1.2. Problem solving 1.6. Discrepancy between current behavior and goal 1.7. Review outcome goal(s) 2.3. Self-monitoring of behaviour 2.4. Self-monitoring of outcome(s) of behaviour 2.5. Monitoring of outcome(s) of behavior without feedback 4.1. Instruction on how to perform the behavior 4.2. Information about Antecedents 4.3. Re-attribution 4.4. Behavioral experiments 5.1. Information about health consequences 5.2. Salience of consequences 5.3. Information about social and environmental consequences 5.4. Monitoring of emotional consequences 5.6. Information about emotional consequences 6.1. Demonstration of the behavior 6.2. Social comparison	

4. Activity Scheduling	Activity monitoring - Facilitate process of guided discovery by encouraging participants to record and evaluate behaviour patterns. Activity scheduling - Rational for activity scheduling outlined in relation to fatigue. - Planning when to implement an activity. Graded exposure - Generate graded exposure hierarchy - Allow exposure and habituation to a feared situation.	• Illness representations (timeline, consequences, cause, control) • Coping - Behavioural disengagement (distress) - All or nothing behaviour (boom and bust cycles) - Behavioural avoidance/social withdrawal in relation to feared situations - Fatigue management tasks and broader life goals	11.2. Reduce negative emotions 12.4. Distraction 13.2. Framing/reframing 1.1. Goal setting (behavior) 1.2. Problem solving 1.3. Goal setting (outcome) 1.4. Action planning 1.5. Review behavior goal(s) 2.3. Self-monitoring of behaviour 2.4. Self-monitoring of outcome(s) of behaviour 4.1. Instruction on how to perform the behavior 4.2. Information about Antecedents 4.3. Re-attribution 5.1. Information about health consequences 5.2. Salience of consequences 5.3. Information about social and environmental consequences 5.4. Monitoring of emotional consequences 5.6. Information about emotional consequences 6.2. Social comparison 7.7. Exposure	

	Exercise - Apply chunking: breaking goal down where necessary. - Encourage participants to implement an exercise routine that fits in with their physical demands and ability.		8.1. Behavioral practice/rehearsal 8.2. Behavior substitution 8.3. Habit formation 8.4. Habit reversal 8.7. Graded tasks 11.2. Reduce negative emotions 13.2. Framing/reframing 13.3. Incompatible beliefs 15.1. Verbal persuasion about capability 15.3. Focus on past success 16.2. Imaginary reward
5. Improving your sleep	Attentional control and cognitive processes Relaxation skills - Rationale for relaxation explained as a way of reducing tension and attentional processes towards threat. - Provide participants with skills to implement relaxing strategies including breathing	• Illness representations (consequences, control) • Coping - Impact of self-management techniques, threat of future complications or worry about fatigue. - Fatigue management tasks and broader life goals - Target increased arousal	1.1. Goal setting (behavior) 1.2. Problem solving 1.3. Goal setting (outcome) 1.4. Action planning 2.3. Self-monitoring of behaviour 3.2. Social support (practical) 3.3. Social support (emotional) 4.1. Instruction on how to perform the behaviour 4.2. Information about Antecedents 4.3. Re-attribution

exercises. Sleep routines - Implement changes to current sleeping patterns. - Manage outcome expectancies about the time it takes to achieve change in sleep patterns.	and “fight/flight response” - Altered sleep	5.1. Information about health consequences 5.3. Information about social and environmental consequences 5.6. Information about emotional consequences 6.1. Demonstration of the behavior 6.2. Social comparison 7.1. Prompts/cues 7.5. Remove aversive stimulus 7.8. Associative learning 8.2. Behavior substitution 8.3. Habit formation 8.4. Habit reversal 8.7. Graded tasks 11.2. Reduce negative emotions 11.3. Conserving mental resources 11.4. Paradoxical instructions 12.1. Restructuring the physical environment 12.3. Avoidance/reducing exposure to cues for the behavior 12.4. Distraction 12.5. Adding objects to the environment 13.2. Framing/reframing 15.1. Verbal persuasion about capability

6. Dealing with low mood and changing your thinking	Cognitive reappraisal - Participant guided to identify evidence for and against biased thoughts. - Realistic thought generation, based on objective evidence is encouraged. - Socratic questioning principles implemented. Acceptance - Alter functional relationship with thoughts. Thoughts experienced without letting thoughts control other aspects of behaviour. - Participants supported with their acceptance using principles of Socratic questioning (e.g. prompting	• Illness representations (identity, timeline, consequences, cause, control) • Emotional representation • Coping - Acceptance used in the context of accurate illness perceptions. - Allows person to maintain levels of functioning with fatigue.	15.2. Mental rehearsal of successful performance 15.3. Focus on past success 1.2. Problem solving 1.6. Discrepancy between current behavior and goal 2.3. Self-monitoring of behaviour 3.2. Social support (practical) 3.3. Social support (emotional) 4.1. Instruction on how to perform the behavior 4.2. Information about Antecedents 4.3. Re-attribution 5.1. Information about health consequences 5.3. Information about social and environmental consequences 5.6. Information about emotional consequences 6.1. Demonstration of the behavior 6.2. Social comparison 8.1. Behavioral practice/rehearsal 8.2. Behavior substitution 8.3. Habit formation 8.4. Habit reversal 9.3. Comparative imagining of future outcomes 11.2. Reduce negative emotions

	self-reflection, stimulate thought and increase awareness. Mindfulness - Mindfulness-based exercises promote present moment awareness. - Attentional control in a constructive non-ruminative manner.		11.3. Conserving mental resources 12.4. Distraction 13.2. Framing/reframing 13.3. Incompatible beliefs 15.4 Self-talk
7. Worries and Anxieties/Stress Management	Problem solving - Pros and cons Relaxation skills - Explain rationale for relaxation exercises. - Provide participants with skills to implement relaxing strategies including breathing exercises. Emotional expression	• Illness representations (identity, timeline, consequences, cause, control) • Emotional representations • Coping - Target increased arousal - Processing emotions in a healthier manner	3.3. Social support (emotional) 4.1. Instruction on how to perform the behavior 4.2. Information about Antecedents 5.1. Information about health consequences 5.3. Information about social and environmental consequences 5.4. Monitoring of emotional consequences 5.6. Information about emotional consequences 6.2. Social comparison 8.2. Behavior substitution 8.3. Habit formation

	- Encourage participants to write about feelings during "worry time"		8.4. Habit reversal 9.1. Credible source 9.2. Pros and cons 9.3. Comparative imagining of future outcomes 11.2. Reduce negative emotions 11.3. Conserving mental resources 12.4. Distraction 12.5. Adding objects to the environment 13.2. Framing/reframing 13.3. Incompatible beliefs 15.4 Self-talk
8. Social Support and Preparing for the future	Assertiveness skills training - Facilitate participant expressing themselves with others. - Explaining about lifestyle restrictions of fatigue. - Practice scenarios of expressing themselves.	• Coping - Behavioural avoidance/social withdrawal in relation to feared situations - Lack of assertion - Increasing degree and type of social support. - Evaluation	1.1. Goal setting (behavior) 1.2. Problem solving 1.3. Goal setting (outcome) 1.4. Action planning 1.5. Review behavior goal(s) 1.6. Discrepancy between current behavior and goal 1.7. Review outcome goal(s) 3.1. Social support (unspecified) 3.2. Social support (practical) 3.3. Social support (emotional)

4.1. Instruction on how to perform the behavior

4.3. Re-attribution

6.1. Demonstration of the behavior

6.2. Social comparison

6.3. Information about others 'approval

8.1. Behavioral practice/rehearsal

8.6. Generalisation of target behavior

9.2. Pros and cons

12.2. Restructuring the social environment

12.3. Avoidance/reducing exposure to cues for the behavior

13.2. Framing/reframing

13.3. Incompatible beliefs

13.4. Valued self-identify

13.5. Identity associated with changed behavior

15.1. Verbal persuasion about capability

15.2. Mental rehearsal of successful performance

15.3. Focus on past success

15.4. Self-talk

16.3. Vicarious consequences

Table 2. *Structure of each session in the REFRESH programme.*

Objectives and outline	The objectives and outline provides a rationale for learning the material from that session by reminding participants what has been covered to date and addressing the questions, "What will I learn in this session?" and "Why is this session important?"
Main content	Each session typically requires 30-45 minutes to complete. The main content screens for each session address a unique aspect of fatigue through a variety of interactive features, including vignettes, images, videos and interactive questions. "Learn more" buttons provide in-depth information about a topic by opening a pop-up window. "Key words" are highlighted in the text and definitions of these new concepts are presented in a box on the side of the page.
Summary	Every session has a summary page that provides a review of the 10 main points presented in the session.
Recap questions	A short recap quiz that prompts participants to reflect on what they learned in each session.
To-do list	Each session ends with a "To-Do List" page that reminds participants about the skills they have learned and how to improve fatigue coping skills in the coming week.
Well done!	Participants are congratulated on their progress to-date
Schedule next session	Participants are asked to schedule a time and date to receive an email reminder for their next session.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Title page
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Title page/abstract
	2b	All items from the World Health Organization Trial Registration Data Set	Abstract
Protocol version	3	Date and version identifier	Title page
Funding	4	Sources and types of financial, material, and other support	19
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Title page/ 19
	5b	Name and contact information for the trial sponsor	19
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	19
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	1
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	10
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	4
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	_12_
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	_10

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	16
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	8
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	_____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	_17__
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13_
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	4
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	__4_____

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_na____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	_4____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	19
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	4_
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20
	31b	Authorship eligibility guidelines and any intended use of professional writers	19_
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	na_
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_appended__
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	__na_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Protocol for a pilot randomised controlled trial of an online intervention for post-treatment cancer survivors with persistent fatigue.

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-"Protocol for a pilot randomised controlled trial of an online intervention for post-treatment cancer survivors with persistent fatigue

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Keywords: Cancer Survivors; Self-Regulation Model; Fatigue; Oncology; Protocol; Psychology; Intervention.

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Abstract

Introduction: Many post-treatment cancer survivors experience persistent fatigue that can disrupt the transition from patient to survivor of cancer.Theoretical models that aim to explain contributory factors that initiate and sustain fatigue symptoms, or that influence the efficacy of interventions for CrF require testing. Adjustment to fatigue is likely to be influenced by coping behaviours that are guided by the representations of the symptom.

Objectives: This paper describes the protocol for a pilot trial of a systematically and theoretically designed online intervention to enable self-management of cancer-related fatigue after cancer treatment.

Methods and Analysis: This 2-armed randomized controlled pilot trial will study the feasibility and potential effectiveness of an online intervention. Participants will be allocated to either the online intervention (REFRESH (Recovery from Cancer-Related Fatigue)), or a leaflet comparator.

Participants: 80 post-treatment cancer survivors will be recruited for the study.

Interventions: An 8-week online intervention based on cognitive behavioural therapy.
Primary and secondary outcome measures: The primary outcome is a change in fatigue as measured by the Piper Fatigue Scale (revised). Quality of Life will be measured using the Quality of Life in Adult Survivors of Cancer Scale. Outcome measures will be collected at baseline and at completion of intervention.
Results: The feasibility of trial procedures will be tested, as well as the effect of the intervention on the outcomes.
Conclusions: This study may lead to the development of a supportive resource to target representations and coping strategies of cancer survivors with CrF post-treatment.
Setting: Recruitment from general public in Ireland
Ethics and Dissemination: This trial was approved by the Research Ethics Committee at National University of Ireland Galway in January 2013. Trial results will be communicated in a peer reviewed journal.
Trial registration: REFRESH (Recovery from Cancer-Related Fatigue) is listed on the ISRCTN registry with study ID ISRCTN55763085.

Strengths and limitations of this study

- The development of the intervention was informed by the Medical Research Council's guidelines on developing complex interventions and was developed through the systematic application of theory, evidence, and user-testing.
- Despite being a complex and multifaceted intervention, transparency was sought by detailing the components of the intervention, the proposed mechanisms of change.
- The complementary strengths of the quantitative and qualitative data collection methods employed here provide a comprehensive understanding of the needs of the target user group.
- This evidence-based online programme is the first intervention of its kind based on the Self-Regulation Model of Health and Illness theory, with the primary aim of targeting the representations of fatigue and enhancing self-management of CrF specifically. It also provides the first systematic coding of a CBT intervention using the BCT taxonomy (v1).
- Self-selection bias into study conditions may influence the outcomes, understating the actual effectiveness of the intervention. Self-reported information obtained from questionnaires may be inaccurate or incomplete.

- Due to resource constraints, a longer-term follow-up will not be included in the initial pilot trial.

Introduction

This paper describes the protocol of a 2-armed randomized controlled pilot trial that is designed to study the feasibility and potential effectiveness of an online intervention that aims to reduce the impact of fatigue in post-treatment cancer survivors(1). Up to 75% of post-treatment cancer survivors experience negative health-related consequences (2). Cancer-related fatigue (CrF) is the most common and disruptive symptom reported. CrF is a persistent, subjective sense of physical, emotional and/or cognitive tiredness related to cancer or cancer treatment (3). It is not proportional to recent activity, and interferes with usual functioning (4). It impacts the physical, emotional, and/or cognitive functioning of the survivor. Guidelines recommend that if there is no evidence of a somatic condition causing the fatigue, behavioural interventions should also be considered (5). There is no recommended standard nonpharmacological treatment of CrF in those with cancer (6), highlighting a need for effective and accessible treatments.

CrF persists for months and even years following completion of treatment in about one third of those with cancer (7). Fatigue that persists for 3 months or longer after cancer treatment completion is unlikely to decrease of its own accord (8). The cause of fatigue after cancer is unclear.

Theoretical models that aim to explain contributory factors that initiate and sustain fatigue symptoms, or that influence the efficacy of interventions for CrF require testing (6). In a Cochrane review of psychosocial interventions for reducing fatigue during cancer treatment, the effectiveness of interventions specifically designed for fatigue was significantly higher compared to interventions not specifically for fatigue (9).

Bradbury et al (10) note that deductive approaches (including reviews of the existing literature) are useful to ascertain what is already known about changing a behaviour and inform intervention design. A systematic review of the literature (11) revealed that the most commonly used intervention strategies were CBT, mindfulness-based interventions and psycho-education. No single intervention type emerged as superior in this review, and a decision was made to base the current intervention on CBT. This decision was based on the quality and quantity of existing literature, as well as clinical expertise. The National Comprehensive Cancer Net-work has published guidance on supporting patients with CrF

following treatment. Recommendations include the use of CBT. (Berger, Abernethy, & Atkinson, 2012). CBT is also recommended by the American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guidelines (Runowicz et al., 2016).

In line with the person-centred approach developed by Yardley et al (12), qualitative focus group research was carried out to explore the experience of cancer-related fatigue in post-treatment cancer survivors. Four focus groups were held with 18 cancer survivors who reported 'significant fatigue or reduced energy.' A theoretical thematic analysis indicated that the participants' descriptions mapped onto the Self-regulation Model of Health and Illness (SRM) (13). This theory proposes that the representation of a symptom such as fatigue involves a cognitive pathway (i.e. the creation of a knowledge-based conceptualisation of CrF) and an emotional pathway (i.e. emotional response to CrF). Coping behaviours are guided by the representations of the symptom (14). This is an iterative feedback process of appraising coping efforts and representations of the problem, leading to further coping attempts. The study demonstrated the complexity of the individuals' meaning-making processes and identified specific factors that were important issues for those with CrF. Participants did not always understand unexpected persistent fatigue after cancer and were left confused, isolated and frustrated as a result. This qualitative research indicated that the SRM could be applied to CrF in post-treatment cancer survivors and provides a theoretical framework for understanding individuals' representations, and coping strategies, and thus identifying targets for intervention (15). The intervention will incorporate Leventhal's self-regulation theory as a framework for conceptualising the process of adjustment (16).

A Cognitive behavioral therapy (CBT) model of fatigue (13) was used to apply SRM theory in a treatment model. CBT models focus on similar cognitive, emotional and coping/behavioural factors as those outlined by Leventhal (14). Andrykowski, et al. (15) proposed that biological insults such as the cancer or its treatment may precipitate the initial experience of fatigue during cancer, whereas a cognitive-behavioural model of fatigue may predict the persistence of fatigue in survivorship. Using the SRM to describe fatigue after cancer provides an integrated theoretical model for developing interventions for fatigue based on cognitive–behavioural principles.

INSERT FIGURE 1. HERE

Figure 1. From theory to practice: Applying the self-regulation model to a cognitive-behavioural therapy treatment model.

As CrF is a multidimensional and complex symptom (16), an intervention mode that can incorporate multiple and complex behaviour change techniques was required (10). Chou, Liu (17) encourage using Internet to better serve survivors' needs as it is increasingly being used as a resource by cancer survivors (18). Online interventions have been found to be at least as effective as face-to-face therapies for a wide range of issues (19). This mode of delivery affords the opportunity to reach a wider range of patients compared to face-to-face interventions, especially severely fatigued patients or those with limited mobility. Although online interventions for fatigue after cancer have been tested elsewhere (e.g. the RESTORE trial in the UK (20), little research has been conducted in regions that do not offer free universal healthcare. In Ireland, while those with a medical card receive free General Practitioner(GP) care, the rest of the population pay at the point of delivery(21). Without a medical card, paying the full cost fee (reported in most cases to be €50 per visit) appears to be a deterrent to seeking primary care (22). The perceived "need" of treatment for fatigue may influence an individual's willingness to pay for a GP consultation (22). Health professionals sometimes fail to appreciate the occurrence, duration and detrimental effects associated with CrF (23). Many fatigued individuals do not discuss their symptoms as they perceive fatigue as an untreatable symptom to be endured as a normal part of cancer (24). Many also believe that interventions for fatigue are not available, and cite this as a barrier to opening a conversation about CrF (24).

An online intervention may be particularly beneficial to Irish participants, given reported inequity in care provision(22). The home-based setting of an online intervention may also allow participants to learn more about their symptoms and possible coping strategies, empowering them to begin a conversation about fatigue with their healthcare professional. Some survivors report wanting to move on with their lives and no longer identify as a cancer patient (25). Therefore, the anonymity and privacy of an online programme may be appealing. Participants can practice and incorporate new skills more readily into their daily lives when the intervention is incorporated into their current routine (19, 26).

An open-source web-development platform, LifeGuide was used to develop the programme (www.lifeguideonline.org) in line with existing interventions of this nature (27, 28). 'LifeGuide' is a set of open-source software that enables researchers to collaboratively create and evaluate interventions (29). This software allows non-programmers to create and easily modify web-based interventions (10). This tool has been used by researchers to create websites which provide tailored long-term support for behaviour change (Michie et al.,

2012). Researchers can rapidly test the effects of intervention components. LifeGuide facilitates easily modification and improvement of components at any stage of the intervention (Michie et al., 2012).

The intervention described in this paper will build upon previous studies that have employed internet-based self-management programmes (18, 30, 31), while applying a novel theoretical approach that addresses both individuals' understanding of, and coping with, CrF. The RESTORE trial focused on self-efficacy to cope with fatigue (18), however our preliminary qualitative research suggested that participants' understanding of CrF needs to be addressed before coping efficacy can be established. Further, the 'Health Navigation' trial byYun et al (30) incorporated the transtheoretic model (TTM) of health behavior change and social cognitive theory as well as cognitive behavioral therapy (CBT). However, this trial did no assess the theoretical framework that was applied. Therefore the mechanisms of the intervention are unclear.

The current study will employ Roth and Pilling's competence framework for cognitive behavioural therapy for those with persistent physical health conditions (32). Adjustment to fatigue will be a primary focus of the intervention, with cognitive, behavioural, affective and social responses being addressed (33). The goal is to improve functioning, and to enable the participants to make meaningful changes in their daily lives, rather than symptom reduction per se. The aim is to determine the feasibility of the "*REFRESH* (Recovery from Cancer-Related Fatigue)" intervention trial. It will also assess the overall impact of the intervention on fatigue and proposed mediating factors in cancer survivors. It is hypothesized that an online intervention designed using a theoretical, systematic and person-based approach will be successful in reducing the effects of fatigue in post-treatment cancer survivors.

Specific objectives

1. To conduct an evaluation of the feasibility of the intervention, looking at
    i. Recruitment (number of patients approached about the study, source of referral to the study, number consenting to participate and those eligible to be randomized)
    ii. Adherence and attrition to the intervention
    iii. Drop out from trial (i.e. follow-up questionnaires not completed)
    iv. Evaluation of functionality, acceptability and usability of website
    v. Participant satisfaction with the website.
2. To assess the potential efficacy of the "*REFRESH* programme" in adult survivors of

cancer. Changes in fatigue will be assessed by comparing intervention and wait-list control groups at baseline and post-intervention in terms of the following outcome:

i. Fatigue (primary outcome) - assessed using the Revised Piper Fatigue Scale (PFS-R). ((34)
ii. Quality of Life (secondary outcome), as measured using the Quality of Life in Adult Cancer Survivors (QLACS) Scale

3. To explore change in potential therapeutic mechanisms of change in relation to fatigue outcomes. Changes will be assessed by comparing intervention and wait-list control groups at baseline and post-intervention in terms of the following outcomes:

i. Illness perceptions relating to CrF
ii. Cognitive-behavioral coping strategies used in the management of fatigue
iii. Appraisal of Coping

Ethical approval

This design and testing of the trial was approved by the Research Ethics Committee at National University of Ireland Galway in January 2013. Full written informed consent will be sought from all participants for both their participation and the publication of the results of the research. Participants will be reminded that they are free to withdraw at any time and that their data will be stored securely and anonymously. All data will be stored on password protected hard drives in accordance with the Data Protection Act. All data will be anonymised. Recruitment is currently ongoing.

Method

The study is designed as an exploratory, parallel-group pilot randomised controlled trial to determine the feasibility, potential effectiveness (as assessed using Piper Fatigue scale (34)) and acceptability of an online CBT intervention for cancer-related fatigue called *REFRESH* (Recovery from Cancer-Related Fatigue). The study will include 2 parallel conditions: experimental conditions (online CBT for fatigue) and a wait-list control condition. Feasibility will be measured by assessing recruitment, willingness to be randomized, attrition, adherence and completion of outcome measurements. Acceptability will be assessed by participant satisfaction with the intervention. Participants will be randomized to receive either the online intervention, or a widely available leaflet comparator developed by the Irish Cancer society, called "*Coping with Fatigue"*(available online as a pdf) (35). This booklet is currently widely available as a source of information about fatigue. The intervention group will access an interactive CBT for CrF intervention (*REFRESH*) Participants will be asked to complete a

session each week for 8 weeks. Assessments will be conducted at baseline and immediately after intervention (at 10 weeks).

Participants

A total of 80 Irish cancer survivors will be randomized to receive the intervention or usual care.

Inclusion and Exclusion Criteria

Participants are eligible for the study if they

1. are over 18 years of age,
2. have completed primary treatment with curative intent for non-metastatic cancer at least 3 months prior to baseline assessments
3. are experiencing fatigue defined as scoring ≥4 on a unidimensional 11-point numeric rating for fatigue as suggested by the National Comprehensive Cancer Network (3),
4. are able to complete written records in English,
5. have or are willing to create an email account and have access to the internet,
6. have access to, and basic ability to use a computer
7. have completed primary treatment for cancer (patients are eligible for the study if they are receiving maintenance therapy such as hormone therapies) at least 3 months prior to baseline assessment (8)

Patients will be excluded if they

1. Do not provide informed consent or refuse to be randomized.
2. have history of cancer recurrence
3. do not confirm that they have received medical clearance for participation
4. are currently participating in any other psychosocial intervention

Recruitment

It is intended to recruit 80 participants who have completed primary treatment with curative intent for non-metastatic cancer at least 3 months prior to baseline assessments. Recruitment will take place from October 2015- April 2016.

Online Recruitment

An online recruitment strategy will run separately and concurrently with the rest of the research recruitment campaign in order to broaden exposure (36). Social media sites will be used to target cancer survivors engaged in online activity. Use of popular existing social

network sites are expected to address issues of reach, engagement, and retention (37). Online social networks have been found to typically achieve high levels of user engagement and retention. Social media enables the researcher to actively generate engaging and novel content, which is likely to be more influential than traditional static and passive websites (38). They are a cost-effective means of recruitment, that may engage potentially difficult-to-reach groups, providing participants a more accessible method by which to participate in health research (38). These websites will inform potential participants of the study and provide a link to the survey.

I. WordPress® will be used to develop a host website for the study. Participants will be able to access the participant information sheet and links to the online questionnaire on this site. Another page will give description of the study investigators. Pictures and engaging content will be posted to build rapport and credibility with the audience (36).

II. A Facebook® fan page will be created to recruit participants and raise awareness of the study (36). Posts will include study announcements, links to the WordPress® website, pictures, and videos featuring the primary researcher discussing the project. Posts will be scheduled in advance, with about a new post per day during the recruitment period. Other Facebook fan pages with similar purpose or interest will be interacted with, by "liking" these organizations' pages, which were found using keyword searches for cancer, oncology and health care. "Facebook Adverts ©" will be used to advertise the study to a large number of social media users.

III. Twitter® will be used to target individuals using short messages (tweets) to share online material including links to the *REFRESH* WordPress® website. Users will be encouraged to share (i.e. 'retweet') these messages with their own followers (38). Stakeholders and key influencers will be targeted in particular. These include patient advocates and healthcare professionals. Organisations affiliated with cancer survivorship will be followed. Hashtags (#) related to cancer, fatigue and related topics will be used to reach a large audience of potential participants (36).

IV. LinkedIn® groups that included content related to cancer survivorship will be used to reach potential participants. Again, these messages will target those people living with CrF, cancer survivorship advocates, healthcare professionals working in oncology and psycho-oncology, and other researchers. Group members will be asked to share the survey link with other potentially interested groups or individuals (36).

Offline Recruitment.

The offline recruitment strategy will centre on interaction with community organizations and leaders(39). Cancer support groups and national cancer charities and organizations will be contacted and asked to promote the study. Researchers will also recruit in-person at the Irish National Cancer Survivorship Conference in September 2015.

Media outlets will be contacted via press releases, with information about the study being promoted nationally in press and on the radio. Printed advertisements (such as leaflets) will be distributed in local pharmacies and coffee shops.

Health system recruitment will also be employed, given the importance of physician referrals as gatekeepers to patient research recruitment(39). General practitioners and health care professionals will be informed about the study. They will be encouraged to share the information with any patients who may benefit from partaking in the research.

Trial procedures

Interested participants will be invited to access a recruitment website hosted on WordPress®. An information sheet about the study will be provided. This will include the rationale for the study and will explain that participants can opt out of the programme at any point without penalty. This website will also include details about the inclusion/exclusion criteria for the study. A link to the baseline assessment will be posted on this website during the recruitment period.

Eligible and willing participants, after reading the documentation, will be invited to complete these baseline assessments using an online survey tool (Survey Monkey®). The method of recruitment is self-selection, and the questionnaire is the initial point of contact for the research team and the participant. Before progressing to the baseline questionnaire, participants will be required to provide informed consent outlining their awareness of the trial protocol and inclusion criteria. Participants will be screened for inclusion after the completion of the baseline questionnaire, prior to randomization. Due to practical constraints, it was decided that retention in the trial would be enhanced if interested participants completed a single initial survey. The aim of this study is to gain an insight into those who may be interested in participating in a trial such as this. Only those who meet the eligibility criteria gain access to the website.

Randomization and blinding

Participants will be randomized in a 1:1 ratio to receive either the *REFRESH* intervention, or a leaflet comparator developed by the Irish Cancer Society, *Coping with Fatigue*. Upon completion of the baseline questionnaire, participants will be randomized to either the waitlist

control or intervention group. Participants will randomized in blocks of six, using a computer-generated number sequence that was created apriori using Random.org (40). An independent research assistant will email participants to inform them of their group allocation. The research team will be made aware of group allocation in advance of the half-way contact point with participants. The nature of the trial is such that blinding of participants cannot be achieved. No changes in assignment will be possible until after the trial period. Figure 2 shows the flow of participants through the trial.

INSERT FIGURE 2. HERE

Figure 2. Planned flow of participants through the *REFRESH* randomized controlled trial.

Control group/usual care

The control group will receive an online copy of a booklet with brief general recommendations about fatigue management that was designed by the Irish Cancer Society (35). This will contain some general information about CrF. After completion of this study, control participants will be given the opportunity to access the *REFRESH* program. Online user data gathered in the post-assessment period will be analysed to evaluate user processes such as engagement, and dose of intervention received (41).

Intervention

The *REFRESH* online intervention was developed using LifeGuide, open source software (42). The intervention is a web-based online program that can be accessed from any location or device with Internet access (29). The purpose of this intervention is to target individuals' illness representations and coping strategies in order to facilitate coping with CRF. Table 1 summarizes the intervention and the association of the components with the SRM model and CBT. In order to describe intervention content and avoid the problems of lack of consistency across interventions, The Behavior Change Technique Taxonomy (v1) was employed (43). A behaviour change technique (BCT) is an observable, replicable, and irreducible component of an intervention designed to alter or redirect causal processes that regulate behaviour (43). To our awareness, this is the first instance of the BCT taxonomy being used to specify components of a CBT intervention.

Content

The information provided in this website was developed based on the Medical Research Council guidance (44). It draws on the findings of a systematic review of the literature relating to psychological interventions for CrF. The content is also based on qualitative research conducted with cancer survivors suffering with persistent fatigue after the completion of curative treatment.

The structure and layout has been designed in line with previous CBT interventions, in particular, the "*Understanding and Managing Persistent Cancer-Related Fatigue manual*" (45) and the *MSInvigor8* trial (31) (46). Aspects of the intervention relating to thoughts and emotions also draws on the principles of CBT as outlined in the "Feeling Better" manual(47). An expert design team supported the development of *REFRESH.* These included Health Psychologists and Clinical Psychologists. A nurse, cancer care staff and a cancer survivor also contributed to the design of the programme. The CBT intervention techniques used in this intervention are based upon those outlined in the competence framework for psychological interventions with people with persistent physical health conditions developed by Roth and Pilling (32). These are presented in Table 1. Further information and specific components of the intervention were also informed by the available evidence on symptom focusing (48); activity scheduling, insomnia management (49) (50) (51) ; and stress management (52) in cancer patients.

The *REFRESH* intervention was created with the goal of providing participants with a user-friendly, engaging and effective online environment while affording them the opportunity to learn more about their fatigue symptoms and management. Figure 2 shows the basic structure of the program. Given online security concerns, all user data is protected.

Table 1. *Intervention phases, CBT intervention techniques, proposed mechanisms of change and theoretical constructs targeted and behavior change techniques employed.*

Session	CBT intervention techniques	Theoretical Construct targeted	Behaviour Change Techniques used
1. Overview of Cancer-related Fatigue.	Elicit from participant their understanding of fatigue - Draw on knowledge about fatigue - Reflect information using patients' own language	• Symptom perceptions • Emotional (mood) • Illness (identity, timeline, consequences, control) representations of symptoms - Inaccurate illness perceptions - Treatment outcome expectancies - Coherence/overall illness understanding	2.4. Self-monitoring of outcome(s) of behaviour 3.1. Social support (unspecified) 4.2. Information about Antecedents 5.1. Information about health consequences 5.2. Salience of consequences 5.3. Information about social and environmental consequences 5.6. Information about emotional consequences 6.2. Social comparison 13.2. Framing/reframing 15.2. Mental rehearsal of successful performance
2. What is Cognitive Behavioral Therapy (CBT)?	Explanation about the CBT model of adjustment - Develop case conceptualisation with participant - Draw on information elicited	• Illness Representations (identity, timeline, consequences, cause, control) • Emotional Representations (mood)	1.1. Goal setting (behavior) 1.2. Problem solving 1.3. Goal setting (outcome) 1.4. Action planning 4.1. Instruction on how to perform the behavior

from participant to describe interaction between thoughts, feelings, behaviours and physical symptoms in response to fatigue.

Activity monitoring

- Facilitate process of guided discovery by encouraging participants to record and evaluate behaviour patterns.
- Problem solving encourage participant to identify a specific problem that they are having difficulties with at the moment.

SMART Goal Setting

- Identify a goal they would like to work towards. Action plan how to implement steps defined within SMART goal acronym
  - Understanding of poor adjustment in the context of fatigue

• Coping
  - Target specific triggers that the participant is concerned about.

Fatigue management tasks and broader life goals

5.2. Salience of consequences
5.4. Monitoring of emotional consequences
6.1. Demonstration of the behaviour
8.1. Behavioral practice/rehearsal
8.2. Behavior substitution
8.4. Habit reversal
13.2. Framing/reframing
15.1. Verbal persuasion about capability

		(Specific, Measurable, Achievable, Realistic, Timely) - Apply chunking: breaking goal down where necessary		
3. Thoughts and Fatigue	Cognitive reappraisal - Patients encouraged to keep a thought record. Thought record used as prompt to identify biased thinking patterns. - Participant guided to identify evidence for and against biased thoughts. - Realistic thought generation, based on objective evidence is encouraged. - Socratic questioning principles implemented.	• Challenging inaccurate illness perceptions (cause, control) • Emotional Representations (mood) • Coping - Identifying and challenging Cognitive biases	1.2. Problem solving 1.6. Discrepancy between current behavior and goal 1.7. Review outcome goal(s) 2.3. Self-monitoring of behaviour 2.4. Self-monitoring of outcome(s) of behaviour 2.5. Monitoring of outcome(s) of behavior without feedback 4.1. Instruction on how to perform the behavior 4.2. Information about Antecedents 4.3. Re-attribution 4.4. Behavioral experiments 5.1. Information about health consequences 5.2. Salience of consequences 5.3. Information about social and environmental consequences 5.4. Monitoring of emotional consequences 5.6. Information about emotional consequences 6.1. Demonstration of the behavior	

4. Activity Scheduling	Activity monitoring - Facilitate process of guided discovery by encouraging participants to record and evaluate behaviour patterns. Activity scheduling - Rational for activity scheduling outlined in relation to fatigue. - Planning when to implement an activity. Graded exposure - Generate graded exposure hierarchy - Allow exposure and habituation to a feared situation.	• Illness representations (timeline, consequences, cause, control) • Coping - Behavioural disengagement (distress) - All or nothing behaviour (boom and bust cycles) - Behavioural avoidance/social withdrawal in relation to feared situations - Fatigue management tasks and broader life goals	6.2. Social comparison 11.2. Reduce negative emotions 12.4. Distraction 13.2. Framing/reframing	1.1. Goal setting (behavior) 1.2. Problem solving 1.3. Goal setting (outcome) 1.4. Action planning 1.5. Review behavior goal(s) 2.3. Self-monitoring of behaviour 2.4. Self-monitoring of outcome(s) of behaviour 4.1. Instruction on how to perform the behavior 4.2. Information about Antecedents 4.3. Re-attribution 5.1. Information about health consequences 5.2. Salience of consequences 5.3. Information about social and environmental consequences 5.4. Monitoring of emotional consequences 5.6. Information about emotional consequences 6.2. Social comparison

	Exercise - Apply chunking: breaking goal down where necessary. - Encourage participants to implement an exercise routine that fits in with their physical demands and ability.		7.7. Exposure 8.1. Behavioral practice/rehearsal 8.2. Behavior substitution 8.3. Habit formation 8.4. Habit reversal 8.7. Graded tasks 11.2. Reduce negative emotions 13.2. Framing/reframing 13.3. Incompatible beliefs 15.1. Verbal persuasion about capability 15.3. Focus on past success 16.2. Imaginary reward
5. Improving your sleep	Attentional control and cognitive processes Relaxation skills - Rationale for relaxation explained as a way of reducing tension and attentional processes towards threat. - Provide participants with skills to implement relaxing	• Illness representations (consequences, control) • Coping - Impact of self-management techniques, threat of future complications or worry about fatigue. - Fatigue management tasks and broader life goals	1.1. Goal setting (behavior) 1.2. Problem solving 1.3. Goal setting (outcome) 1.4. Action planning 2.3. Self-monitoring of behaviour 3.2. Social support (practical) 3.3. Social support (emotional) 4.1. Instruction on how to perform the behaviour 4.2. Information about Antecedents

strategies including breathing exercises.	- Target increased arousal and "fight/flight response"	4.3. Re-attribution
Sleep routines	- Altered sleep	5.1. Information about health consequences
- Implement changes to current sleeping patterns.		5.3. Information about social and environmental consequences
- Manage outcome expectancies about the time it takes to achieve change in sleep patterns.		5.6. Information about emotional consequences
		6.1. Demonstration of the behavior
		6.2. Social comparison
		7.1. Prompts/cues
		7.5. Remove aversive stimulus
		7.8. Associative learning
		8.2. Behavior substitution
		8.3. Habit formation
		8.4. Habit reversal
		8.7. Graded tasks
		11.2. Reduce negative emotions
		11.3. Conserving mental resources
		11.4. Paradoxical instructions
		12.1. Restructuring the physical environment
		12.3. Avoidance/reducing exposure to cues for the behavior
		12.4. Distraction
		12.5. Adding objects to the environment
		13.2. Framing/reframing

6. Dealing with low mood and changing your thinking	Cognitive reappraisal - Participant guided to identify evidence for and against biased thoughts. - Realistic thought generation, based on objective evidence is encouraged. - Socratic questioning principles implemented. Acceptance - Alter functional relationship with thoughts. Thoughts experienced without letting thoughts control other aspects of behaviour. - Participants supported with their acceptance using principles of Socratic	• Illness representations (identity, timeline, consequences, cause, control) • Emotional representation • Coping - Acceptance used in the context of accurate illness perceptions. - Allows person to maintain levels of functioning with fatigue.	15.1. Verbal persuasion about capability 15.2. Mental rehearsal of successful performance 15.3. Focus on past success 1.2. Problem solving 1.6. Discrepancy between current behavior and goal 2.3. Self-monitoring of behaviour 3.2. Social support (practical) 3.3. Social support (emotional) 4.1. Instruction on how to perform the behavior 4.2. Information about Antecedents 4.3. Re-attribution 5.1. Information about health consequences 5.3. Information about social and environmental consequences 5.6. Information about emotional consequences 6.1. Demonstration of the behavior 6.2. Social comparison 8.1. Behavioral practice/rehearsal 8.2. Behavior substitution 8.3. Habit formation 8.4. Habit reversal 9.3. Comparative imagining of future outcomes

	questioning (e.g. prompting self-reflection, stimulate thought and increase awareness. Mindfulness - Mindfulness-based exercises promote present moment awareness. - Attentional control in a constructive non-ruminative manner.		11.2. Reduce negative emotions 11.3. Conserving mental resources 12.4. Distraction 13.2. Framing/reframing 13.3. Incompatible beliefs 15.4 Self-talk
7. Worries and Anxieties/Stress Management	Problem solving - Pros and cons Relaxation skills - Explain rationale for relaxation exercises. - Provide participants with skills to implement relaxing strategies including breathing exercises.	• Illness representations (identity, timeline, consequences, cause, control) • Emotional representations • Coping - Target increased arousal - Processing emotions in a healthier manner	3.3. Social support (emotional) 4.1. Instruction on how to perform the behavior 4.2. Information about Antecedents 5.1. Information about health consequences 5.3. Information about social and environmental consequences 5.4. Monitoring of emotional consequences 5.6. Information about emotional consequences 6.2. Social comparison 8.2. Behavior substitution

	Emotional expression - Encourage participants to write about feelings during "worry time"		8.3. Habit formation 8.4. Habit reversal 9.1. Credible source 9.2. Pros and cons 9.3. Comparative imagining of future outcomes 11.2. Reduce negative emotions 11.3. Conserving mental resources 12.4. Distraction 12.5. Adding objects to the environment 13.2. Framing/reframing 13.3. Incompatible beliefs 15.4 Self-talk
8. Social Support and Preparing for the future	Assertiveness skills training - Facilitate participant expressing themselves with others. - Explaining about lifestyle restrictions of fatigue. - Practice scenarios of expressing themselves.	• Coping - Behavioural avoidance/social withdrawal in relation to feared situations - Lack of assertion - Increasing degree and type of social support. - Evaluation	1.1. Goal setting (behavior) 1.2. Problem solving 1.3. Goal setting (outcome) 1.4. Action planning 1.5. Review behavior goal(s) 1.6. Discrepancy between current behavior and goal 1.7. Review outcome goal(s) 3.1. Social support (unspecified) 3.2. Social support (practical)

3.3. Social support (emotional)

4.1. Instruction on how to perform the behavior

4.3. Re-attribution

6.1. Demonstration of the behavior

6.2. Social comparison

6.3. Information about others 'approval

8.1. Behavioral practice/rehearsal

8.6. Generalisation of target behavior

9.2. Pros and cons

12.2. Restructuring the social environment

12.3. Avoidance/reducing exposure to cues for the behavior

13.2. Framing/reframing

13.3. Incompatible beliefs

13.4. Valued self-identify

13.5. Identity associated with changed behavior

15.1. Verbal persuasion about capability

15.2. Mental rehearsal of successful performance

15.3. Focus on past success

15.4. Self-talk

16.3. Vicarious consequences

Procedure of the intervention

Participants in the intervention group will be asked to sign-up for the *REFRESH* programme with their email and unique password. New users will receive instructions on the "About *REFRESH*" page before logging in. The page includes an introduction to the aims of CBT and step-by-step instructions for how to navigate the programme.

The intervention requires 45-60 minutes per week over 8-10 weeks. The online intervention is accessed through the main welcome page. Once logged in, each user is presented with a personalized "Home Page" (see Figure 3) that provides information about the last time the user logged in. The screen allows for easy navigation to each of the main sections of the site: "Useful Content", "Sessions" and "About the programme". The Useful Content contains useful links that are relevant to participants (links to cancer support service websites etc.) the printable elements of the program such as diaries and tips. The Information about the programme tabs offer information about how to contact the research team, a "Frequently Asked Questions" (FAQ) page addressing technical issues, and a "What is *REFRESH*" tab that provides a brief introduction to the system and a "Who made *REFRESH*?" tab that introduces participants to the research team involved in developing the programme. The "Disclaimer" tab reminds users that the information provided is for educational purposes only and should not replace or override a physician's care.

Every session follows a similar structure: objectives and outline, main content, review and to-do list. This can be seen in Table 2. Each of the 8 sessions acts as an online analog for the weekly sessions conducted in traditional in-person CBT. The intervention content incorporates the essential treatment elements of CBT: educational, behavioural, and cognitive techniques (53).

INSERT FIGURE 3. HERE

Figure 3. Basic structure of the *REFRESH* program.

Table 2. *Structure of each session in the REFRESH programme.*

Objectives and outline	The objectives and outline provides a rationale for learning the material from that session by reminding participants what has been covered to date and addressing the questions, "What will I learn in this session?" and "Why is this session important?"
Main content	Each session typically requires 30-45 minutes to complete. The main content screens for each session address a unique aspect of fatigue through a variety of interactive features, including vignettes, images, videos and interactive questions. "Learn more" buttons provide in-depth information about a topic by opening a pop-up window. "Key words" are highlighted in the text and definitions of these new concepts are presented in a box on the side of the page.
Summary	Every session has a summary page that provides a review of the 10 main points presented in the session.
Recap questions	A short recap quiz that prompts participants to reflect on what they learned in each session.
To-do list	Each session ends with a "To-Do List" page that reminds participants about the skills they have learned and how to improve fatigue coping skills in the coming week.
Well done!	Participants are congratulated on their progress to-date
Schedule next session	Participants are asked to schedule a time and date to receive an email reminder for their next session.

The intervention involves a high degree of interactivity and personalization. In addition to using the individuals name at various stages of the intervention, personalization also occurs in the form of re-showing unique user-information. Participants are asked to identify problems associated with their fatigue. These problems are later presented as part of goal-setting exercises in order to remind participants to set specific goals that are relevant to them. Participants are also presented with a personalized CBT-model of fatigue, based on answers about their feelings, actions and cognitions pertaining to their fatigue symptoms. Users are free to revisit a session as many times as they choose. Answers will be saved and presented to allow participants to review their progress. Further personalization occurs in the form of in-session exercises in which users are asked to describe the specifics of their experience with CrF.

Participants are encouraged to challenge cognitions and learn to prioritize certain behaviours in order to maintain a healthy energy balance. *REFRESH* includes a range of behaviour change techniques (BCTs) designed to enhance relevant information, motivation and behavioural skills. The programme utilises accessible and engaging delivery methods that are in line with Ritterband's theory of online interventions (54). Table 1 shows each phase of *REFRESH* the change targets, BCTs used and the method and agent of delivery (55).
The hypothesis is that targeting cognitive and emotional representations of symptoms will lead to improvements in coping skills and in turn, reduce fatigue levels. These processes may be moderated by cancer-related factors (e.g. diagnosis, treatment type, time since treatment) and demographic factors (e.g. gender, socioeconomic circumstances, education).

Telephone calls

The effectiveness of Internet-based interventions have been found to be enhanced by the use of additional methods of communicating with participants (55). A semi-structured interview guide will be followed in each of these calls. The structure has been outlined in a manual to enable replication. The calls will be made by the primary researcher who has a background in Health Psychology and experience in working with patient groups. Each group will receive one phone call after 4 weeks of the programme (i.e. half-way). Each phone call will last 15-20 minutes. For the intervention group, the aim of these calls will be to solve any problems with the sessions or content. Also, messages of encouragement will be given to stimulate adherence to the program. The wait-list control group will be called to remind them that they can gain access to the programme in the weeks that follow. Calls will be audio recorded and checked for fidelity. The content of these calls may also be used to guide improvements for future iterations of the website (12).

Intervention fidelity

A content manual has been developed to accompany this intervention. The 'Intervention Manual' describes and defines the programme components for each module. The website will include features to monitor adherence and completion rates of each module by each user. Individual factors which may affect fatigue and/or energy level (medication-use, comorbidities, physical disability etc.) will be documented for both control and intervention groups.

Follow-up Measurement, Assessment and Outcomes

Timing of assessments

Participants will be recruited and assessed at baseline from October 2015- September 2016. Outcomes are self-reported at baseline (T0), post-intervention (T1). Figure 1. shows a schematic summary of the trial design. All participants are invited to fill out short questionnaires at baseline pre-randomisation. Participants are expected to complete one session per week for 8 weeks.Follow-up data will be collected upon completion of the trial, 10 weeks post-baseline. Additional qualitative feedback will be obtained through explorative open-ended questions at T1 for participants in the experimental condition . After completion of follow up assessments at T1, participants in the control condition will be offered the experimental intervention. Participants (intervention and control group) will continue to have access to the *REFRESH* programme for 2 months following completion of follow-up questionnaires.

Methods for dealing with loss to follow-up

This pilot trial aims to assess attrition rates for a future large RCT. In order to reduce loss-to-follow up, the researchers will aim to foster trusting relationships, helping the participants to feel engaged in the research process. All participants will be contacted via telephone in the fourth week of the programme to enhance this relationship. Familiarity with the researchers will be promoted through the use of familiar and consistent voices on the narration of videos used in the online programme. Participants will be able to access a page entitled "About us", which will include photographs and brief biographies of each the researchers.
Participants will be reminded of their commitment to the programme at the outset of the intervention in order to promote a sense of self-responsibility. Participants will be congratulated upon completing a module in order to boost self-esteem and garner a sense of achievement. At the end of each session, participants will select a time to receive one prompt email to continue to the next session in the week that follows.

Outcome measurements

Assessments will be undertaken online. Assessors of outcomes will be blinded to group allocation until after baseline measures have been completed.

1. The primary goal of this study is to assess the feasibility and functionality of an online CBT programme for this sample. Therefore, the following outcomes will be assessed.

I. Recruitment and uptake

II. Adherence and attrition

III. Evaluation of functionality and usability of website

IV. Participant satisfaction with website.

This feasibility trial aims to provide insight into the way *REFRESH* is used by participants. Information on intervention uptake, delivery and experience will be collected. Delivery and uptake will be determined by assessing initial uptake to the programme and participation in each of the sessions. This is outlined in Figure 4.

INSERT FIGURE 4 HERE

Figure 4. Uptake and participation assessment

Adherence to, and engagement with, the programme will also be assessed. In order to determine the 'intensity' of the intervention components delivered; the 'engagement' of participants will be assessed. Data relating to pages visited and time spent on each page will be collected in LifeGuide (29). This data will be used to gain a sense of how participants engaged with the programme. Criteria for assessing engagement for each individual are:

i) active participation in 90% of at least 4 of the *REFRESH* sessions.

ii) completion of exercises within the sessions

iii) level of engagement with course materials.

The Internet Evaluation and Utility Questionnaire measures participants' experiences and perceptions of the intervention. This measure has two main sections – generic and specific. In an earlier and shorter version of this measure (49), good internal reliability was found (alpha = .69). Patients respond to the questions on a 5-point Likert scale from 0 ("not at all") to 4 ("very"), with 2 open-ended items requesting patients to identify "most helpful" and "least helpful" parts of the web program.

- The first 15 questions make up the generic section. The constructs measured by items 1-8 include ease of use, convenience, engagement, enjoyment, layout, privacy, satisfaction, and acceptability.
- Items 9 to15 assess perceptions of the web program material in terms of usefulness, comprehension, credibility, likelihood of returning, mode of delivery, and helpfulness.
- Following these 15 items are questions specific to the *REFRESH* intervention.

Open-ended questions will also be asked of all participants at follow-up to obtain further

qualitative data on the barriers and facilitators to participation as well as to understand the experience of participating. These questions will be included at the end of the follow-up questionnaire. Those who withdraw from the intervention will be invited to participate in an exit interview/debrief with the principal investigator.

2. To assess the effectiveness of the "*REFRESH* (Recovery from Cancer-Related Fatigue) intervention" in long-term adult survivors of cancer, by comparing intervention and wait-list control groups:

Primary outcome: Fatigue as measured by the Piper Fatigue Scale (revised) (PFS-R) (34). The revised PFS-R consists of 22 items measured on a 10-item numeric rating scale items. Higher mean scores represent greater fatigue. Four open-ended questions are also included as descriptive items. The scale is multidimensional and incorporates key dimensions of the fatigue experience including cognition, behaviours, affect, and sensory symptoms (56). Reported Cronbach alphas have ranged from 0.98 for the total scale and 0.94 for subscales in women with fatigue after cancer treatment (57) indicating good internal consistency. Research has demonstrated good psychometric properties, with high concurrent validity with the FQ (r=.80) and good test–retest reliability results (r=.98) (58). The scale has been validated in a group of cancer survivors (59). This multidimensional measurement model is in keeping with the theoretical framework being assessed in the intervention, as well as reflecting the complex nature of the fatigue experience(5). The scale is cited by the NCCN guidelines for the management of CrF as a commonly used scale(3).

Secondary outcome: Quality of Life as measured by the Quality of Life in Adult Cancer Survivors (QLACS) questionnaire (60)

The QLACS is a multi-dimensional measure with 47 items that assess 12 QOL domains. It includes. negative feelings; positive feelings; cognitive problems; pain, items; sexual interest; energy/fatigue; sexual function; social avoidance; financial problems; benefits; distress-family; appearance; and distress-recurrence. Participants are asked to rate how often they felt a certain way in the past 4 weeks (never, seldom, sometimes, about as often as not, frequently, very often, always). The scale is validated in a range of cancer types (61) and has good internal consistency reliability, and adequate concurrent and retrospective validity (62). Sohl et al (63)concluded that the QLACS is consistent with other widely accepted measures in capturing QoL, while also assessing specific issues relevant to post-treatment cancer survivors.

3. To assess the relationship between therapy process and outcomes

In line with the recommendations of the competence framework for psychological interventions with people with persistent physical health conditions, this trial will also incorporate measures that aim to further explore the relationship between therapy process and outcomes. Therefore, drawing on the theory of the self-regulatory model of illness (14) the following outcomes will also be assessed. This is outlined in Figure 5.

I. **The Illness Perceptions Questionnaire for Cancer-Related Fatigue (CRF)** will be used to assess perceptions relating to CrF Cognitive and Emotional Representations. The IPQ-R for CrF (64) is adapted from the IPQ-R (65). The scale is divided into three sections. Section A assesses CrF identity and asks respondents to report (a) whether they have experienced each of a list of 14 commonly experienced core symptoms and (b) whether they believe each of these symptoms is specifically related to their CrF using a *yes*/*no* response format. The list of symptoms included in the identity dimension is tailored to CrF by including 12 symptoms specifically associated with this condition based on the CrF diagnostic criteria (35).

Section B contains 38 items that assess the timeline acute/chronic, timeline cyclical, consequences, personal control, treatment control, illness coherence, and emotional representation dimensions (35). These items consist of statements that are rated on five-point Likert scales ranging from 1 (*strongly disagree*) to 5 (*strongly agree*). The mean of the subscale items measures that illness dimension. Section C is concerned with the cause dimension. Respondents indicate whether they believe each of a list of items cause or contribute to their fatigue using the same five-point Likert scale. The scale has been validated on cancer patients and survivors (35).

The Cognitive and Behavioural Responses to Symptoms Questionnaire (CBSQ) will be used to assess which cognitions and behaviours mediate the effect of cognitive behavioural therapy on fatigue in this group. The CBSQ consists of two behavioural subscales and five cognitive subscales. These subscales measure aspects of the response to (or coping strategy employed to manage) symptoms. The CBSQ subscales have an acceptable internal reliability. The scale has previously been used in MS patients (66). All items are scored on a five-point frequency scale ranging from never (0) to all the time (4). Item scores are added from each subscale to obtain a total score (66). The scale includes "Cognitive Subscales" which assess interpretation of the symptoms. These include: fear avoidance catastrophising, damaging beliefs, embarrassment avoidance and symptom focusing. It also includes "Behavioural

Subscales" which measure all-or-nothing behavior (tendency of patients to overexert themselves, followed by periods of inactivity) and avoidance/resting behaviour.

II. Appraisal of Coping: The Coping Efficacy Scale (67)

Coping efficacy will be measured to assess respondents' appraisal of coping with fatigue. Participants will be asked "How satisfied are you with how you coped with your fatigue?" referring to the past week. The second item will be, "If you had similar symptoms again, how certain are you that you would be able to adjust well to its negative aspects?" referring to the past week. Participants were asked to indicate on a 5-point Likert scale about how certain they were that they could cope with similar symptoms in the future. The scores of these items will be averaged to produce one composite score of coping efficacy. A score of 1 will indicate low coping efficacy and 10 will indicate high coping efficacy. Evidence for the validity of these measures of coping efficacy is strong (67, 68)

INSERT FIGURE 5 HERE

Figure 5. Proposed assessment of Self-regulation Model theory.

4. Demographic and cancer-related information

Possible moderating variables (individual demographic factors and medical-related factors) will be taken from baseline data. Demographic (age, gender, marital and employment status) and medical information (cancer type and treatment, time of diagnosis and treatment, comorbid medical conditions) will be obtained via self-report.

Sample size

The primary aim of this study is to assess initial uptake of the study and following attrition. Figure 1 shows the flow diagram of the study participants. A process evaluation will investigate how the intervention was delivered, how it might be replicated and improved upon (41).

Mechanisms of impact and effectiveness will only be assessed if a sufficient number of participants are recruited (41). In line with guidelines for the calculation of sample size in pilot studies by Viechtbauer et al (69), the estimated sample size of 59 cancer survivors would be required to reach a 95% confidence level. Assuming that intervention improves fatigue in survivors compared to those in the control group differences of at least 5% with a

power of 90% and α of 0.05 with two groups (intervention and waitlist control group) could be detected.

Statistical analyses

Where hypothesis tests are carried out, these will be at the 5% level for primary and secondary outcomes. All analyses will be planned *a priori* and reported in full. The reporting and presentation of this trial will be in accordance with the CONSORT guidelines for randomized trials (1), with the primary comparative analysis being conducted on an intention-to-treat basis. Mean and standard deviation will be used to represent the variable scores at baseline and follow-up measurements.

Study population will be characterized using various descriptive statistics parameters. Initially, possible differences between groups at baseline will be assessed using a one-way analysis of variance for continuous data (or equivalent statistical approach in the case of non-parametrical data) and Chi-square for categorical data.

Comparisons of outcome measures will be undertaken at baseline and 10 weeks for all available measures. Between-group comparisons will be made using a 2 (group) x 2 (time) mixed ANOVA.

Although the trial is not powered to detect the influence of mediating and moderating factors on fatigue, we will explore possible interactions in the following secondary analyses: (i) interaction terms will be examined to investigate possible differences in intervention effects on the primary outcome by demographic and cancer-related factors; (ii) engagement with *REFRESH* will be determined and a comparison between those who meet the criteria for engagement versus those who do not will be undertaken to assess 'per protocol' effectiveness; (iii) a mediational analysis exploring whether the effect of the intervention on the primary outcomes is mediated by illness perceptions and cognitive behavioral strategies using the analytic framework recommended for RCTs will also be undertaken.

Data Management and Access

This data management plan has been created using the UCD Data Management Checklist. The data will be saved online through Inquisit (the Sternberg Memory Task) and Surveygizmo (all other tasks and questionnaires). This data is only accessible by the first author. When these data are collated, the second author will also have access to the relevant data files. The data will be saved in both .csv and .sav formats. These files will be stored in encrypted Dropbox folders. A detailed logbook will be created to complement these files. We do not currently have ethical approval to share these data. In accordance with the NUI

Galway data retention policy, these data will be retained for 5 years at the NUI Galway School of Psychology (as well as being backed up on Dropbox) and anonymised by replacing student ID numbers and names with randomly generated subject ID numbers.

Discussion

REFRESH has been developed according to the MRC guidance for developing and evaluating complex interventions(44). The content is based on the SRM which proposes that coping behaviours in response to a symptom such as fatigue are guided by cognitive and emotional representations of that symptom. This approach has guided the linking of theory to specific cognitive-behavioural intervention techniques and mechanism of change targets. This evidence-based online programme is the first intervention of its kind based on SRM theory, with the primary aim of understanding individuals' lay-representations of a commonly misunderstood symptom and enhancing self-management of CrF specifically. It also provides the first systematic coding of a CBT intervention using the BCT taxonomy (v1). In line with the TIDieR checklist and guide (70), the aim is to provide sufficient details to allow replication, including how innovative recruitment modalities can be harnessed to engage those who are already active online(71).

The website has been systematically and theoretically developed in an Irish population, working with cancer care teams, clinical psychologists and cancer survivors suffering with fatigue. This study will provide additional insight into the efficacy of the intervention and allow the researchers to understand the experience of the participants. This will enable any necessary post-trial modifications or remodeling in order to enhance the effectiveness of *REFRESH* prior to the development of a larger scale RCT of the programme.

Throughout the design of this programme, the developers were cognizant of the need to develop interventions that not only incorporate theory but also aim to evaluate the application of specific theoretical frameworks. The systematic theoretical underpinning of '*REFRESH'* will allow the researchers to gain an insight into how some psychological and behavioural variables (mediators) are related to fatigue. However, in the feasibility trial described here, the study will not be powered to assess these potential effects.

The primary outcome measure for *REFRESH* is fatigue as measured by the PFS-R at 10 weeks post-baseline for this pilot trial. An extension of the timing of the main outcome measure in future iterations of the trial will allow for the assessment of any sustained effect on outcomes.

The results from this trial will provide information regarding the potential of a novel theoretical approach to online interventions for cancer related fatigue in post-treatment cancer

survivors. The research seeks to create supportive online environments at home to ameliorate fatigue and promote self-management of symptoms in this group. Any amendments or updates to this protocol will be lodged with the journal such that it links them to this protocol document. This will allow all future trial publications and conclusions to be assessed against the extent to which we have adhered to the protocol.

Trial status

The trial and recruitment is ongoing.

List of abbreviations

CrF- Cancer-related Fatigue

CBT- Cognitive Behavioural Therapy

CBSQ- The Cognitive and Behavioural Responses to Symptoms Questionnaire

CONSORT- Consolidated Standards of Reporting Trials

IPQ-R- The Revised Illness Perceptions Questionnaire

ISRCTN- International Standard Randomised Controlled Trials Number

MRC- Medical Research Council

QLACS- Quality of Life in Adult Cancer Survivors

PFS-R- Piper Fatigue Scale (revised)

RCT- Randomised Controlled Trial

REFRESH- *REFRESH* (Recovery from Cancer-Related Fatigue) intervention

SRM- Self-regulation Model

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Competing interests

The authors declare that they have no competing interests.

Authors' contributions

TC conceived of the study, its design and coordination, and drafted the manuscript. JW, AMG, RMM and BMG participated in the design of the study and revisions to the manuscript. All authors read and approved the final manuscript.

Communication of Findings: The authors intend to fully communicate trial results in a peer reviewed journal.

Future studies planned:

The findings of this feasibility/pilot study will inform any future iterations of the trial. This includes an assessment of the practicality of any proposed future projects. Future trials will only be conducted if the current pilot trial demonstrates potential to be efficacious.

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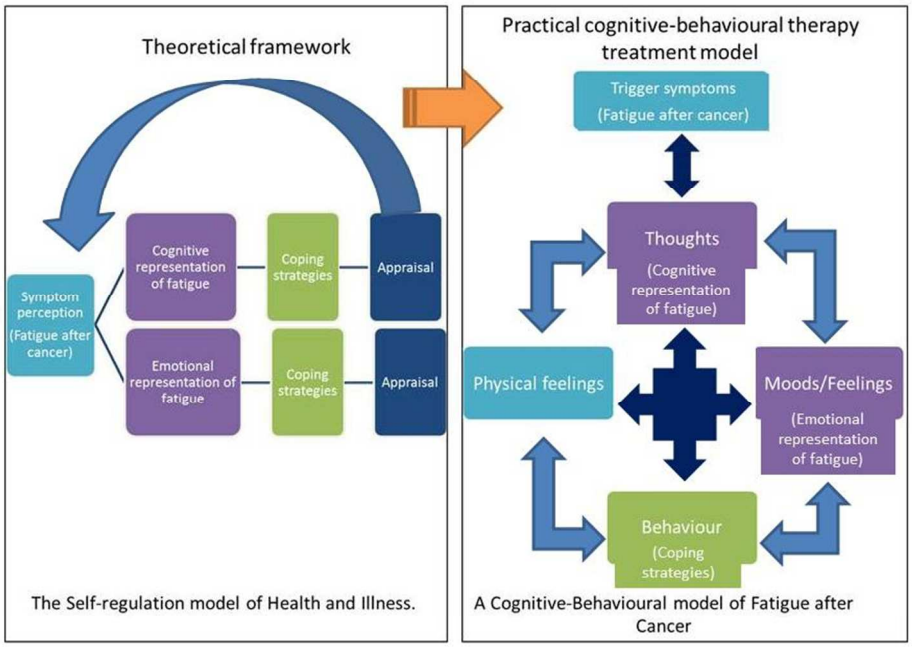

Figure 1. From theory to practice: Applying the self-regulation model to a cognitive-behavioural therapy treatment model.
81x60mm (300 x 300 DPI)

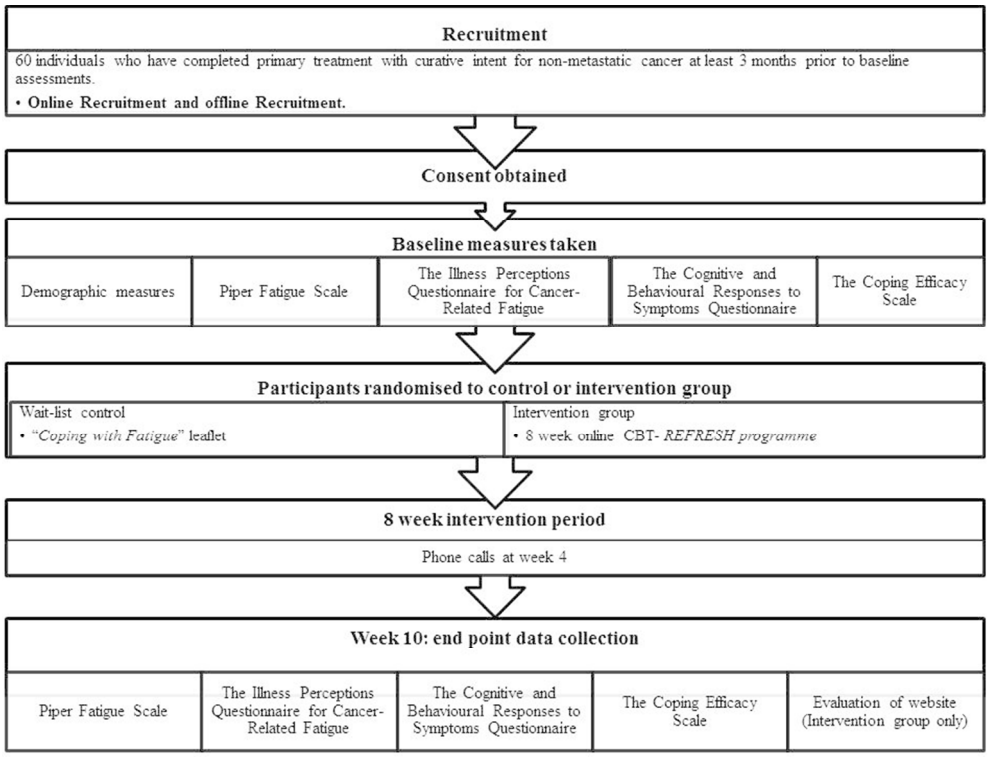

Figure 2. Planned flow of participants through the REFRESH randomized controlled trial.
81x60mm (300 x 300 DPI)

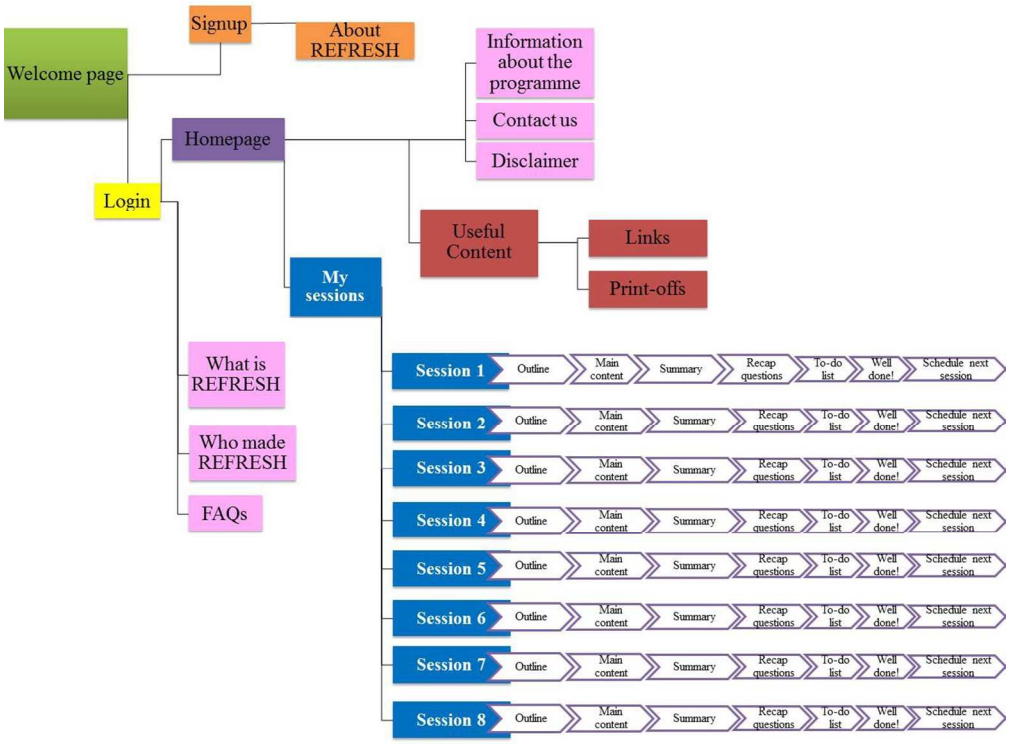

Figure 3. Basic structure of the REFRESH program.
113x85mm (300 x 300 DPI)

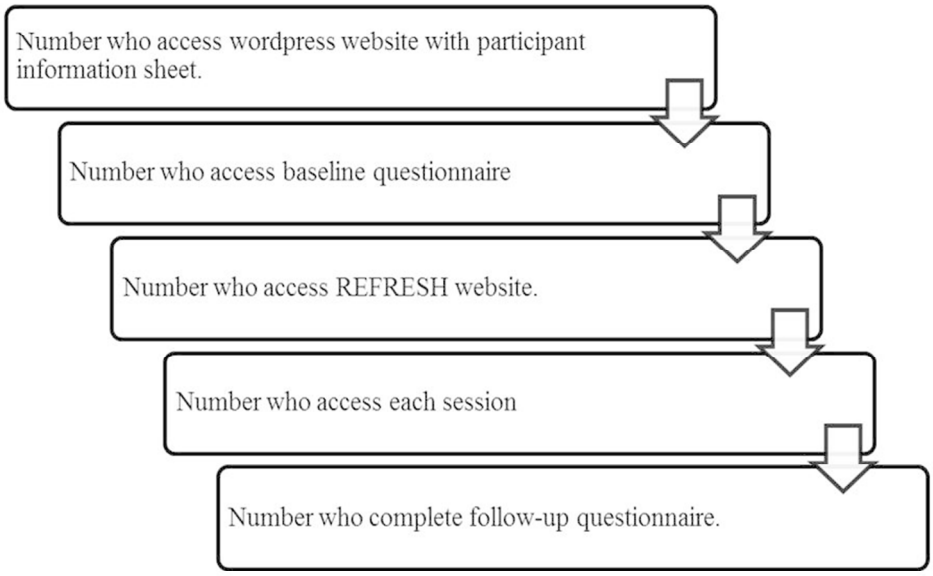

Figure 4. Uptake and participation assessment
81x60mm (300 x 300 DPI)

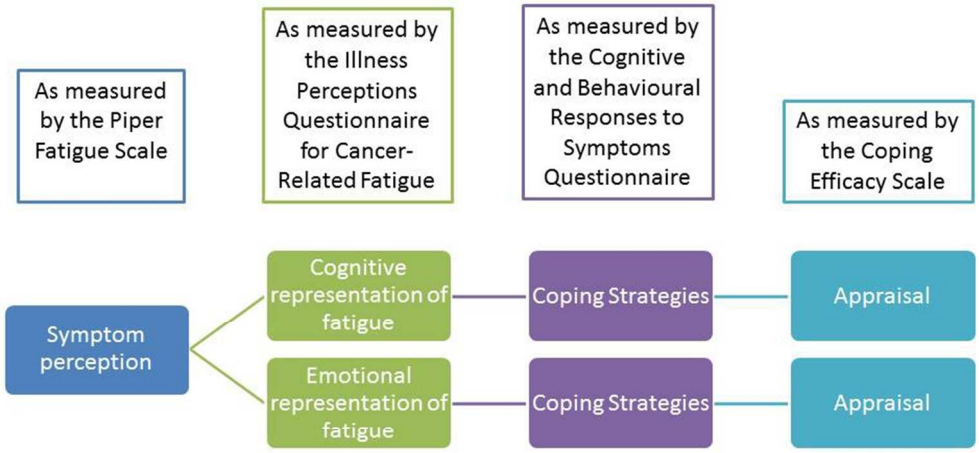

Figure 5. Proposed assessment of Self-regulation Model theory.
81x60mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Title page
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Title page/abstract
	2b	All items from the World Health Organization Trial Registration Data Set	Abstract
Protocol version	3	Date and version identifier	Title page
Funding	4	Sources and types of financial, material, and other support	19
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Title page/ 19
	5b	Name and contact information for the trial sponsor	19
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	19
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	1
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	10
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	4
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	_12_
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	_10

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	16
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	8
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	_____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	_17__
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13_
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	4
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	__4_____

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_na____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	_4____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	19
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	4_
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20
	31b	Authorship eligibility guidelines and any intended use of professional writers	19_
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	na_
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_appended__
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	__na_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Protocol for a pilot randomised controlled trial of an online intervention for post-treatment cancer survivors with persistent fatigue.

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Primary Subject Heading:	Public health
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Keywords:	Cancer survivors, self-regulation model, fatigue, Adult oncology < ONCOLOGY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

-"Protocol for a pilot randomised controlled trial of an online intervention for post-treatment cancer survivors with persistent fatigue

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Abstract

Introduction: Many post-treatment cancer survivors experience persistent fatigue that can disrupt attempts to resume normal everyday activities after treatment. Theoretical models that aim to explain contributory factors that initiate and sustain fatigue symptoms, or that influence the efficacy of interventions for CrF require testing. Adjustment to fatigue is likely to be influenced by coping behaviours that are guided by the representations of the symptom.

Objectives: This paper describes the protocol for a pilot trial of a systematically and theoretically designed online intervention to enable self-management of cancer-related fatigue after cancer treatment.

Methods and Analysis: This 2-armed randomized controlled pilot trial will study the feasibility and potential effectiveness of an online intervention. Participants will be allocated to either the online intervention (REFRESH (Recovery from Cancer-Related Fatigue)), or a leaflet comparator.

Participants: 80 post-treatment cancer survivors will be recruited for the study.

Interventions: An 8-week online intervention based on cognitive behavioural therapy.

Primary and secondary outcome measures: The primary outcome is a change in fatigue as measured by the Piper Fatigue Scale (revised). Quality of Life will be measured using the Quality of Life in Adult Survivors of Cancer Scale. Outcome measures will be collected at baseline and at completion of intervention.

Results: The feasibility of trial procedures will be tested, as well as the effect of the intervention on the outcomes.

Conclusions: This study may lead to the development of a supportive resource to target representations and coping strategies of cancer survivors with CrF post-treatment.

Setting: Recruitment from general public in Ireland

Ethics and Dissemination: This trial was approved by the Research Ethics Committee at National University of Ireland Galway in January 2013. Trial results will be communicated in a peer reviewed journal.

Trial registration: REFRESH (Recovery from Cancer-Related Fatigue) is listed on the ISRCTN registry with study ID ISRCTN55763085.

Strengths and limitations of this study

- The development of the intervention was informed by the Medical Research Council's guidelines on developing complex interventions and was developed through the systematic application of theory, evidence, and user-testing.
- Despite being a complex and multifaceted intervention, transparency was sought by detailing the components of the intervention, the proposed mechanisms of change.
- The complementary strengths of the quantitative and qualitative data collection methods employed here provide a comprehensive understanding of the needs of the target user group.
- This evidence-based online programme is the first intervention of its kind based on the Self-Regulation Model of Health and Illness theory, with the primary aim of targeting the representations of fatigue and enhancing self-management of CrF specifically. It also provides the first systematic coding of a CBT intervention using the BCT taxonomy (v1).
- Self-selection bias into study conditions may influence the outcomes, understating the actual effectiveness of the intervention. Self-reported information obtained from questionnaires may be inaccurate or incomplete.
- Due to resource constraints, a longer-term follow-up will not be included in the initial pilot trial.

Introduction

This paper describes the protocol of a 2-armed randomized controlled pilot trial that is designed to study the feasibility and potential effectiveness of an online intervention that aims to reduce the impact of fatigue in post-treatment cancer survivors(1). Up to 75% of post-treatment cancer survivors experience negative health-related consequences (2). Cancer-related fatigue (CrF) is the most common and disruptive symptom reported. CrF is a

persistent, subjective sense of physical, emotional and/or cognitive tiredness related to cancer or cancer treatment (3). It is not proportional to recent activity, and interferes with usual functioning (4). It impacts the physical, emotional, and/or cognitive functioning of the survivor. Guidelines recommend that if there is no evidence of a somatic condition causing the fatigue, behavioural interventions should also be considered (5). There is no recommended standard nonpharmacological treatment of CrF in those with cancer (6), highlighting a need for effective and accessible treatments.

CrF persists for months and even years following completion of treatment in about one third of those with cancer (7). Fatigue that persists for 3 months or longer after cancer treatment completion is unlikely to decrease of its own accord (8). The cause of fatigue after cancer is unclear.

Theoretical models that aim to explain contributory factors that initiate and sustain fatigue symptoms, or that influence the efficacy of interventions for CrF require testing (6). In a Cochrane review of psychosocial interventions for reducing fatigue during cancer treatment, the effectiveness of interventions specifically designed for fatigue was significantly higher compared to interventions not specifically for fatigue (9).

Bradbury et al (10) note that deductive approaches (including reviews of the existing literature) are useful to ascertain what is already known about changing a behaviour and inform intervention design. A systematic review of the literature (11) revealed that the most commonly used intervention strategies were CBT, mindfulness-based interventions and psycho-education. No single intervention type emerged as superior in this review, and a decision was made to base the current intervention on CBT. This decision was based on the quality and quantity of existing literature, as well as clinical expertise. The National Comprehensive Cancer Net-work has published guidance on supporting patients with CrF following treatment. Recommendations include the use of CBT. (Berger, Abernethy, &

Atkinson, 2012). CBT is also recommended by the American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guidelines (Runowicz et al., 2016).

In line with the person-centred approach developed by Yardley et al (12), qualitative focus group research was carried out to explore the experience of cancer-related fatigue in post-treatment cancer survivors. Four focus groups were held with 18 cancer survivors who reported 'significant fatigue or reduced energy.' A theoretical thematic analysis indicated that the participants' descriptions mapped onto the Self-regulation Model of Health and Illness (SRM) (13). This theory proposes that the representation of a symptom such as fatigue involves a cognitive pathway (i.e. the creation of a knowledge-based conceptualisation of CrF) and an emotional pathway (i.e. emotional response to CrF). Coping behaviours are guided by the representations of the symptom (14). This is an iterative feedback process of appraising coping efforts and representations of the problem, leading to further coping attempts. The study demonstrated the complexity of the individuals' meaning-making processes and identified specific factors that were important issues for those with CrF. Participants did not always understand unexpected persistent fatigue after cancer and were left confused, isolated and frustrated as a result. This qualitative research indicated that the SRM could be applied to CrF in post-treatment cancer survivors and provides a theoretical framework for understanding individuals' representations, and coping strategies, and thus identifying targets for intervention (15). The intervention will incorporate Leventhal's self-regulation theory as a framework for conceptualising the process of adjustment (16).

A Cognitive behavioral therapy (CBT) model of fatigue (13) was used to apply SRM theory in a treatment model. CBT models focus on similar cognitive, emotional and coping/behavioural factors as those outlined by Leventhal (14). Andrykowski, et al. (15) proposed that biological insults such as the cancer or its treatment may precipitate the initial

experience of fatigue during cancer, whereas a cognitive-behavioural model of fatigue may predict the persistence of fatigue in survivorship. Using the SRM to describe fatigue after cancer provides an integrated theoretical model for developing interventions for fatigue based on cognitive–behavioural principles.

INSERT FIGURE 1. HERE

Figure 1. From theory to practice: Applying the self-regulation model to a cognitive-behavioural therapy treatment model.

As CrF is a multidimensional and complex symptom (16), an intervention mode that can incorporate multiple and complex behaviour change techniques was required (10). Chou, Liu (17) encourage using Internet to better serve survivors' needs as it is increasingly being used as a resource by cancer survivors (18). Online interventions have been found to be at least as effective as face-to-face therapies for a wide range of issues (19). This mode of delivery affords the opportunity to reach a wider range of patients compared to face-to-face interventions, especially severely fatigued patients or those with limited mobility. Although online interventions for fatigue after cancer have been tested elsewhere (e.g. the RESTORE trial in the UK (20), little research has been conducted in regions that do not offer free universal healthcare. Due to the lack of universal healthcare provision in Ireland, many individuals pay at the point of delivery(21). The cost of seeking care (reported in most cases to be €50 per visit) may be a deterrent to seeking primary care (22). The perceived "need" of treatment for fatigue may influence an individual's willingness to pay for a GP consultation (22).

Many fatigued individuals do not discuss their symptoms as they perceive fatigue as an untreatable symptom to be endured as a normal part of cancer (23). Many also believe that

interventions for fatigue are not available, and cite this as a barrier to opening a conversation about CrF (23).

The home-based setting of an online intervention may be particularly beneficial to Irish participants, given reported inequity in care provision(22). Some survivors report wanting to move on with their lives and no longer identify as a cancer patient (24). Therefore, the anonymity and privacy of an online programme may be appealing. Participants can practice and incorporate new skills more readily into their daily lives when the intervention is incorporated into their current routine (19, 25).

An open-source web-development platform, LifeGuide was used to develop the programme (www.lifeguideonline.org) in line with existing interventions of this nature (26, 27). 'LifeGuide' is a set of open-source software that enables researchers to collaboratively create and evaluate interventions (28). This software allows non-programmers to create and easily modify web-based interventions (10). This tool has been used by researchers to create websites which provide tailored long-term support for behaviour change (Michie et al., 2012). Researchers can rapidly test the effects of intervention components. LifeGuide facilitates easily modification and improvement of components at any stage of the intervention (Michie et al., 2012).

The intervention described in this paper will build upon previous studies that have employed internet-based self-management programmes (18, 29, 30), while applying a novel theoretical approach that addresses both individuals' understanding of, and coping with, CrF. The 'Health Navigation' trial by Yun et al (29) incorporated the transtheoretic model (TTM) of health behavior change and social cognitive theory as well as cognitive behavioral therapy (CBT). However, this trial did no assess the theoretical framework that was applied.

Therefore the mechanisms of the intervention are unclear.The current study will employ Roth and Pilling's competence framework for cognitive behavioural therapy for those with persistent physical health conditions (31). Adjustment to fatigue will be a primary focus of the intervention, with cognitive, behavioural, affective and social responses being addressed (32). This evidence-based online programme is the first intervention of its kind based on the self-regulation model (SRM), with the primary aim of targeting the representations of fatigue and enhancing self-management of CrF specifically. The study also provides the first systematic coding of a CBT intervention using the BCT taxonomy (v1)(33). This was to reduce the 'black box' criticism of complex interventions (33) by providing a transparent description of the intended intervention, and how it is expected to work (34).

The goal is to improve functioning, and to enable the participants to make meaningful changes in their daily lives, rather than symptom reduction per se. The aim is to determine the feasibility of the "*REFRESH* (Recovery from Cancer-Related Fatigue)" intervention trial. It will also assess the overall impact of the intervention on fatigue and proposed mediating factors in cancer survivors. It is hypothesized that an online intervention designed using a theoretical, systematic and person-based approach will be successful in reducing the effects of fatigue in post-treatment cancer survivors.

Specific objectives

1. To conduct an evaluation of the feasibility of the intervention, looking at
    i. Recruitment (number of patients approached about the study, source of referral to the study, number consenting to participate and those eligible to be randomized)
    ii. Adherence and attrition to the intervention
    iii. Drop out from trial (i.e. follow-up questionnaires not completed)
    iv. Evaluation of functionality, acceptability and usability of website

v. Participant satisfaction with the website.

2. To assess the potential efficacy of the "*REFRESH* programme" in adult survivors of cancer. Changes in fatigue will be assessed by comparing intervention and wait-list control groups at baseline and post-intervention in terms of the following outcome:

i. Fatigue (primary outcome) - assessed using the Revised Piper Fatigue Scale (PFS-R). ((35)

ii. Quality of Life (secondary outcome), as measured using the Quality of Life in Adult Cancer Survivors (QLACS) Scale

3. To explore change in potential therapeutic mechanisms of change in relation to fatigue outcomes. Changes will be assessed by comparing intervention and wait-list control groups at baseline and post-intervention in terms of the following outcomes:

i. Illness perceptions relating to CrF

ii. Cognitive-behavioral coping strategies used in the management of fatigue

iii. Appraisal of Coping

Ethical approval

This design and testing of the trial was approved by the Research Ethics Committee at National University of Ireland Galway in January 2013. Full written informed consent will be sought from all participants for both their participation and the publication of the results of the research. Participants will be reminded that they are free to withdraw at any time and that their data will be stored securely and anonymously. All data will be stored on password protected hard drives in accordance with the Data Protection Act. All data will be anonymised. Recruitment is currently ongoing.

Method

The study is designed as an exploratory, parallel-group pilot randomised controlled trial to

determine the feasibility, potential effectiveness (as assessed using Piper Fatigue scale (35)) and acceptability of an online CBT intervention for cancer-related fatigue called *REFRESH* (Recovery from Cancer-Related Fatigue). The study will include 2 parallel conditions: experimental conditions (online CBT for fatigue) and a wait-list control condition. Feasibility will be measured by assessing recruitment, willingness to be randomized, attrition, adherence and completion of outcome measurements. Acceptability will be assessed by participant satisfaction with the intervention. Participants will be randomized to receive either the online intervention, or a widely available leaflet comparator developed by the Irish Cancer society, called "*Coping with Fatigue"*(available online as a pdf) (36). This booklet is currently widely available as a source of information about fatigue. The intervention group will access an interactive CBT for CrF intervention (*REFRESH*) Participants will be asked to complete a session each week for 8 weeks. Assessments will be conducted at baseline and immediately after intervention (at 10 weeks).

Participants

A total of 80 Irish cancer survivors will be randomized to receive the intervention or usual care.

Inclusion and Exclusion Criteria

Participants are eligible for the study if they

1. are over 18 years of age,
2. have completed primary treatment with curative intent for non-metastatic cancer at least 3 months prior to baseline assessments
3. are experiencing fatigue defined as scoring ≥4 on a unidimensional 11-point numeric rating for fatigue as suggested by the National Comprehensive Cancer Network (3),
4. are able to complete written records in English,

5. have or are willing to create an email account and have access to the internet,
6. have access to, and basic ability to use a computer
7. have completed primary treatment for cancer (patients are eligible for the study if they are receiving maintenance therapy such as hormone therapies) at least 3 months prior to baseline assessment (8)

Patients will be excluded if they

1. Do not provide informed consent or refuse to be randomized.
2. have history of cancer recurrence
3. do not confirm that they have received medical clearance for participation
4. are currently participating in any other psychosocial intervention

Recruitment

It is intended to recruit 80 participants who have completed primary treatment with curative intent for non-metastatic cancer at least 3 months prior to baseline assessments. Recruitment will take place from October 2015- April 2016.

Online Recruitment

An online recruitment strategy will run separately and concurrently with the rest of the research recruitment campaign in order to broaden exposure (37). Social media sites will be used to target cancer survivors engaged in online activity. Use of popular existing social network sites are expected to address issues of reach, engagement, and retention (38). Online social networks have been found to typically achieve high levels of user engagement and retention. Social media enables the researcher to actively generate engaging and novel content, which is likely to be more influential than traditional static and passive websites (39). They are a cost-effective means of recruitment, that may engage potentially difficult-to-reach groups, providing participants a more accessible method by which to participate in health research (39). These websites will inform potential participants of the study and

provide a link to the survey.

I. WordPress® will be used to develop a host website for the study. Participants will be able to access the participant information sheet and links to the online questionnaire on this site. Another page will give description of the study investigators. Pictures and engaging content will be posted to build rapport and credibility with the audience (37).

II. A Facebook® fan page will be created to recruit participants and raise awareness of the study (37). Posts will include study announcements, links to the WordPress® website, pictures, and videos featuring the primary researcher discussing the project. Posts will be scheduled in advance, with about a new post per day during the recruitment period. Other Facebook fan pages with similar purpose or interest will be interacted with, by "liking" these organizations' pages, which were found using keyword searches for cancer, oncology and health care. "Facebook Adverts ©" will be used to advertise the study to a large number of social media users.

III. Twitter® will be used to target individuals using short messages (tweets) to share online material including links to the *REFRESH* WordPress® website. Users will be encouraged to share (i.e. 'retweet') these messages with their own followers (39). Stakeholders and key influencers will be targeted in particular. These include patient advocates and healthcare professionals. Organisations affiliated with cancer survivorship will be followed. Hashtags (#) related to cancer, fatigue and related topics will be used to reach a large audience of potential participants (37).

IV. LinkedIn® groups that included content related to cancer survivorship will be used to reach potential participants. Again, these messages will target those people living with CrF, cancer survivorship advocates, healthcare professionals working in oncology and psycho-oncology, and other researchers. Group members will be asked to share the survey link with other potentially interested groups or individuals (37).

Offline Recruitment.

The offline recruitment strategy will centre on interaction with community organizations and leaders(40). Cancer support groups and national cancer charities and organizations will be contacted and asked to promote the study. Researchers will also recruit in-person at the Irish National Cancer Survivorship Conference in September 2015.

Media outlets will be contacted via press releases, with information about the study being promoted nationally in press and on the radio. Printed advertisements (such as leaflets) will be distributed in local pharmacies and coffee shops.

Health system recruitment will also be employed, given the importance of physician referrals as gatekeepers to patient research recruitment(40). General practitioners and health care professionals will be informed about the study. They will be encouraged to share the information with any patients who may benefit from partaking in the research.

Trial procedures

Interested participants will be invited to access a recruitment website hosted on WordPress®. This website which details study procedures and inclusion/exclusion criteria. After reading this information, participants will be invited to complete baseline assessments using an online survey tool (Survey Monkey®). Participants will then be required to provide informed consent outlining their awareness of the trial protocol. Any participants who do not meet the inclusion/exclusion criteria following baseline assessment were excluded from the study.

Randomization and blinding

Participants will be randomized in a 1:1 ratio to receive either the *REFRESH* intervention, or a leaflet comparator developed by the Irish Cancer Society, *Coping with Fatigue*. Upon completion of the baseline questionnaire, participants will be randomized to either the waitlist control or intervention group. Participants will randomized in blocks of six, using a

computer-generated number sequence that was created apriori using Random.org (41). An independent research assistant will email participants to inform them of their group allocation. The research team will be made aware of group allocation in advance of the half-way contact point with participants. The nature of the trial is such that blinding of participants cannot be achieved. No changes in assignment will be possible until after the trial period. Figure 2 shows the flow of participants through the trial.

INSERT FIGURE 2. HERE

Figure 2. Planned flow of participants through the *REFRESH* randomized controlled trial.

Control group/usual care

The control group will receive an online copy of a booklet with brief general recommendations about fatigue management that was designed by the Irish Cancer Society (36). This will contain some general information about CrF. After completion of this study, control participants will be given the opportunity to access the *REFRESH* program. Online user data gathered in the post-assessment period will be analysed to evaluate user processes such as engagement, and dose of intervention received (34).

Intervention

The *REFRESH* online intervention was developed using LifeGuide, open source software (42). The intervention is a web-based online program that can be accessed from any location or device with Internet access (28). The purpose of this intervention is to target individuals' illness representations and coping strategies in order to facilitate coping with CRF. Table 1 summarizes the intervention and the association of the components with the SRM model and CBT. In order to describe intervention content and avoid the problems of lack of consistency across interventions, The Behavior Change Technique Taxonomy (v1) was employed (43). A

behaviour change technique (BCT) is an observable, replicable, and irreducible component of an intervention designed to alter or redirect causal processes that regulate behaviour (43). To our awareness, this is the first instance of the BCT taxonomy being used to specify components of a CBT intervention.

Content

The information provided in this website was developed based on the Medical Research Council guidance (33). It draws on the findings of a systematic review of the literature relating to psychological interventions for CrF. The content is also based on qualitative research conducted with cancer survivors suffering with persistent fatigue after the completion of curative treatment.

The structure and layout has been designed in line with previous CBT interventions, in particular, the "*Understanding and Managing Persistent Cancer-Related Fatigue manual*" (44) and the *MSInvigor8* trial (30) (45). Aspects of the intervention relating to thoughts and emotions also draws on the principles of CBT as outlined in the "Feeling Better" manual(46).

An expert design team supported the development of *REFRESH.* These included Health Psychologists and Clinical Psychologists. A nurse, cancer care staff and a cancer survivor also contributed to the design of the programme. The CBT intervention techniques used in this intervention are based upon those outlined in the competence framework for psychological interventions with people with persistent physical health conditions developed by Roth and Pilling (31). These are presented in Table 1. Further information and specific components of the intervention were also informed by the available evidence on symptom focusing (47); activity scheduling, insomnia management (48) (49) (50) ; and stress management (51) in cancer patients.

The *REFRESH* intervention was created with the goal of providing participants with a user-friendly, engaging and effective online environment while affording them the opportunity to

learn more about their fatigue symptoms and management. Figure 2 shows the basic structure of the program. Given online security concerns, all user data is protected.

INSERT TABLE 1. HERE

Procedure of the intervention

Participants in the intervention group will be asked to sign-up for the *REFRESH* programme with their email and unique password. New users will receive instructions on the "About *REFRESH*" page before logging in. The page includes an introduction to the aims of CBT and step-by-step instructions for how to navigate the programme.

The intervention requires 45-60 minutes per week over 8-10 weeks. The online intervention is accessed through the main welcome page. Once logged in, each user is presented with a personalized "Home Page" (see Figure 3) that provides information about the last time the user logged in. The screen allows for easy navigation to each of the main sections of the site: "Useful Content", "Sessions" and "About the programme". The Useful Content contains useful links that are relevant to participants (links to cancer support service websites etc.) the printable elements of the program such as diaries and tips. The Information about the programme tabs offer information about how to contact the research team, a "Frequently Asked Questions" (FAQ) page addressing technical issues, and a "What is *REFRESH*" tab that provides a brief introduction to the system and a "Who made *REFRESH*?" tab that introduces participants to the research team involved in developing the programme. The "Disclaimer" tab reminds users that the information provided is for educational purposes only and should not replace or override a physician's care.

Every session follows a similar structure: objectives and outline, main content, review and to-do list. This can be seen in Table 2. Each of the 8 sessions acts as an online analog for the

weekly sessions conducted in traditional in-person CBT. The intervention content incorporates the essential treatment elements of CBT: educational, behavioural, and cognitive techniques (52).

INSERT FIGURE 3. HERE

Figure 3. Basic structure of the *REFRESH* program.

INSERT TABLE 2. HERE

The intervention involves a high degree of interactivity and personalization. In addition to using the individuals name at various stages of the intervention, personalization also occurs in the form of re-showing unique user-information. Participants are asked to identify problems associated with their fatigue. These problems are later presented as part of goal-setting exercises in order to remind participants to set specific goals that are relevant to them. Participants are also presented with a personalized CBT-model of fatigue, based on answers about their feelings, actions and cognitions pertaining to their fatigue symptoms. Users are free to revisit a session as many times as they choose. Answers will be saved and presented to allow participants to review their progress. Further personalization occurs in the form of in-session exercises in which users are asked to describe the specifics of their experience with CrF.

Participants are encouraged to challenge cognitions and learn to prioritize certain behaviours in order to maintain a healthy energy balance. *REFRESH* includes a range of behaviour change techniques (BCTs) designed to enhance relevant information, motivation and behavioural skills. The programme utilises accessible and engaging delivery methods that are

in line with Ritterband's theory of online interventions (53). Table 1 shows each phase of *REFRESH* the change targets, BCTs used and the method and agent of delivery (54).

The hypothesis is that targeting cognitive and emotional representations of symptoms will lead to improvements in coping skills and in turn, reduce fatigue levels. These processes may be moderated by cancer-related factors (e.g. diagnosis, treatment type, time since treatment) and demographic factors (e.g. gender, socioeconomic circumstances, education).

Telephone calls

The effectiveness of Internet-based interventions have been found to be enhanced by the use of additional methods of communicating with participants (54). A semi-structured interview guide will be followed in each of these calls. The structure has been outlined in a manual to enable replication. The calls will be made by the primary researcher who has a background in Health Psychology and experience in working with patient groups. Each group will receive one phone call after 4 weeks of the programme (i.e. half-way). Each phone call will last 15-20 minutes. For the intervention group, the aim of these calls will be to solve any problems with the sessions or content. Also, messages of encouragement will be given to stimulate adherence to the program. The wait-list control group will be called to remind them that they can gain access to the programme in the weeks that follow. Calls will be audio recorded and checked for fidelity. The content of these calls may also be used to guide improvements for future iterations of the website (12).

Intervention fidelity

A content manual has been developed to accompany this intervention. The 'Intervention Manual' describes and defines the programme components for each module. The website will include features to monitor adherence and completion rates of each module by each user. Individual factors which may affect fatigue and/or energy level (medication-use, comorbidities, physical disability etc.) will be documented for both control and intervention

groups.

Follow-up Measurement, Assessment and Outcomes

Timing of assessments

Participants will be recruited and assessed at baseline from October 2015- September 2016. Outcomes are self-reported at baseline (T0), post-intervention (T1). Figure 1. shows a schematic summary of the trial design. Participants are expected to complete one session per week for 8 weeks.Follow-up data will be collected upon completion of the trial, 10 weeks post-baseline. Additional qualitative feedback will be obtained through explorative open-ended questions at T1 for participants in the experimental condition . After completion of follow up assessments at T1, participants in the control condition will be offered the experimental intervention. Participants (intervention and control group) will continue to have access to the *REFRESH* programme for 2 months following completion of follow-up questionnaires.

Methods for dealing with loss to follow-up

This pilot trial aims to assess attrition rates for a future large RCT. In order to reduce loss-to-follow up, the researchers will aim to foster trusting relationships, helping the participants to feel engaged in the research process. All participants will be contacted via telephone in the fourth week of the programme to enhance this relationship. Familiarity with the researchers will be promoted through the use of familiar and consistent voices on the narration of videos used in the online programme. Participants will be able to access a page entitled “About us”, which will include photographs and brief biographies of each the researchers.

Participants will be reminded of their commitment to the programme at the outset of the intervention in order to promote a sense of self-responsibility. Participants will be

congratulated upon completing a module in order to boost self-esteem and garner a sense of achievement. At the end of each session, participants will select a time to receive one prompt email to continue to the next session in the week that follows.

Outcome measurements

Assessments will be undertaken online. Assessors of outcomes will be blinded to group allocation until after baseline measures have been completed.

1. The primary goal of this study is to assess the feasibility and functionality of an online CBT programme for this sample. Therefore, the following outcomes will be assessed.

I. Recruitment and uptake

II. Adherence and attrition

III. Evaluation of functionality and usability of website

IV. Participant satisfaction with website.

This feasibility trial aims to provide insight into the way *REFRESH* is used by participants. Information on intervention uptake, delivery and experience will be collected. Delivery and uptake will be determined by assessing initial uptake to the programme and participation in each of the sessions. This is outlined in Figure 4.

INSERT FIGURE 4 HERE

Figure 4. Uptake and participation assessment

Adherence to, and engagement with, the programme will also be assessed. In order to determine the 'intensity' of the intervention components delivered; the 'engagement' of participants will be assessed. Data relating to pages visited and time spent on each page will

be collected in LifeGuide (28). This data will be used to gain a sense of how participants engaged with the programme. Criteria for assessing engagement for each individual are:

i) active participation in 90% of at least 4 of the *REFRESH* sessions.

ii) completion of exercises within the sessions

iii) level of engagement with course materials.

The Internet Evaluation and Utility Questionnaire measures participants' experiences and perceptions of the intervention. This measure has two main sections – generic and specific. In an earlier and shorter version of this measure (48), good internal reliability was found (alpha = .69). Patients respond to the questions on a 5-point Likert scale from 0 ("not at all") to 4 ("very"), with 2 open-ended items requesting patients to identify "most helpful" and "least helpful" parts of the web program.

- The first 15 questions make up the generic section. The constructs measured by items 1-8 include ease of use, convenience, engagement, enjoyment, layout, privacy, satisfaction, and acceptability.
- Items 9 to15 assess perceptions of the web program material in terms of usefulness, comprehension, credibility, likelihood of returning, mode of delivery, and helpfulness.
- Following these 15 items are questions specific to the *REFRESH* intervention.

Open-ended questions will also be asked of all participants at follow-up to obtain further qualitative data on the barriers and facilitators to participation as well as to understand the experience of participating. These questions will be included at the end of the follow-up questionnaire. Those who withdraw from the intervention will be invited to participate in an exit interview/debrief with the principal investigator.

2. To assess the effectiveness of the "*REFRESH* (Recovery from Cancer-Related Fatigue) intervention" in long-term adult survivors of cancer, by comparing intervention and wait-list control groups:

Primary outcome: Fatigue as measured by the Piper Fatigue Scale (revised) (PFS-R) (35). This scale assesses adjustment and interference of fatigue. The scale is multidimensional and incorporates key dimensions of the fatigue experience including cognition, behaviours, affect, and sensory symptoms (55).

The revised PFS-R consists of 22 items measured on a 10-item numeric rating scale items. Higher mean scores represent greater fatigue. Four open-ended questions are also included as descriptive items. Reported Cronbach alphas have ranged from 0.98 for the total scale and 0.94 for subscales in women with fatigue after cancer treatment (56) indicating good internal consistency. Research has demonstrated good psychometric properties, with high concurrent validity with the FQ (r=.80) and good test–retest reliability results (r=.98) (57). The scale has been validated in a group of cancer survivors (58). This multidimensional measurement model is in keeping with the theoretical framework being assessed in the intervention, as well as reflecting the complex nature of the fatigue experience(5). The scale is cited by the NCCN guidelines for the management of CrF as a commonly used scale(3).

Secondary outcome: Quality of Life as measured by the Quality of Life in Adult Cancer Survivors (QLACS) questionnaire (59)

The QLACS is a multi-dimensional measure with 47 items that assess 12 QOL domains. It includes. negative feelings; positive feelings; cognitive problems; pain, items; sexual interest; energy/fatigue; sexual function; social avoidance; financial problems; benefits; distress-family; appearance; and distress-recurrence. Participants are asked to rate how often they felt a certain way in the past 4 weeks (never, seldom, sometimes, about as often as not,

frequently, very often, always). The scale is validated in a range of cancer types (60) and has good internal consistency reliability, and adequate concurrent and retrospective validity (61). Sohl et al (62)concluded that the QLACS is consistent with other widely accepted measures in capturing QoL, while also assessing specific issues relevant to post-treatment cancer survivors.

3. To assess the relationship between therapy process and outcomes

In line with the recommendations of the competence framework for psychological interventions with people with persistent physical health conditions, this trial will also incorporate measures that aim to further explore the relationship between therapy process and outcomes. Therefore, drawing on the theory of the self-regulatory model of illness (14) the following outcomes will also be assessed. This is outlined in Figure 5.

I. **The Illness Perceptions Questionnaire for Cancer-Related Fatigue (CRF)** will be used to assess perceptions relating to CrF Cognitive and Emotional Representations. The IPQ-R for CrF (63) is adapted from the IPQ-R (64). The scale is divided into three sections. Section A assesses CrF identity and asks respondents to report (a) whether they have experienced each of a list of 14 commonly experienced core symptoms and (b) whether they believe each of these symptoms is specifically related to their CrF using a *yes*/*no* response format. The list of symptoms included in the identity dimension is tailored to CrF by including 12 symptoms specifically associated with this condition based on the CrF diagnostic criteria (35).

Section B contains 38 items that assess the timeline acute/chronic, timeline cyclical, consequences, personal control, treatment control, illness coherence, and emotional representation dimensions (35). These items consist of statements that are rated on five-point Likert scales ranging from 1 (*strongly disagree*) to 5 (*strongly agree*). The mean of the subscale items measures that illness dimension. Section C is concerned with the cause

dimension. Respondents indicate whether they believe each of a list of items cause or contribute to their fatigue using the same five-point Likert scale. The scale has been validated on cancer patients and survivors (35).

The Cognitive and Behavioural Responses to Symptoms Questionnaire (CBSQ) will be used to assess which cognitions and behaviours mediate the effect of cognitive behavioural therapy on fatigue in this group. The CBSQ consists of two behavioural subscales and five cognitive subscales. These subscales measure aspects of the response to (or coping strategy employed to manage) symptoms. The CBSQ subscales have an acceptable internal reliability. The scale has previously been used in MS patients (65). All items are scored on a five-point frequency scale ranging from never (0) to all the time (4). Item scores are added from each subscale to obtain a total score (65). The scale includes "Cognitive Subscales" which assess interpretation of the symptoms. These include: fear avoidance catastrophising, damaging beliefs, embarrassment avoidance and symptom focusing. It also includes "Behavioural Subscales" which measure all-or-nothing behavior (tendency of patients to overexert themselves, followed by periods of inactivity) and avoidance/resting behaviour.

II. Appraisal of Coping: The Coping Efficacy Scale (66)

Coping efficacy will be measured to assess respondents' appraisal of coping with fatigue. Participants will be asked "How satisfied are you with how you coped with your fatigue?" referring to the past week. The second item will be, "If you had similar symptoms again, how certain are you that you would be able to adjust well to its negative aspects?" referring to the past week. Participants were asked to indicate on a 5-point Likert scale about how certain they were that they could cope with similar symptoms in the future. The scores of these items will be averaged to produce one composite score of coping efficacy. A score of 1 will indicate low coping efficacy and 10 will indicate high coping efficacy. Evidence for the validity of these measures of coping efficacy is strong (66, 67)

INSERT FIGURE 5 HERE

Figure 5. Proposed assessment of Self-regulation Model theory.

4. Demographic and cancer-related information

Possible moderating variables (individual demographic factors and medical-related factors) will be taken from baseline data. Demographic (age, gender, marital and employment status) and medical information (cancer type and treatment, time of diagnosis and treatment, comorbid medical conditions) will be obtained via self-report.

Sample size

The primary aim of this study is to assess initial uptake of the study and following attrition. Figure 1 shows the flow diagram of the study participants. A process evaluation will investigate how the intervention was delivered, how it might be replicated and improved upon (34).

In line with guidelines for the calculation of sample size in pilot studies by Viechtbauer et al (68), an estimated sample size of 59 cancer survivors would be required. The calculation allows for the identification of unforeseen problems, such as ambiguities in description of the trial or eligibility criteria, or misinterpretations of questionnaire items. If a problem is likely to occur with 5% probability in a participant, the issue would be identified (with 95% confidence) in a pilot study including 59 participants (68).

Mechanisms of impact and effectiveness will only be assessed if a sufficient number of participants are recruited (34). According to G*power (69) 54 participants would be required to demonstrate statistically significant group differences over time at the .05 level (d=.25).

Statistical analyses

Where hypothesis tests are carried out, these will be at the 5% level for primary and secondary outcomes. All analyses will be planned *a priori* and reported in full. The reporting and presentation of this trial will be in accordance with the CONSORT guidelines for randomized trials (1), with the primary comparative analysis being conducted on an intention-to-treat basis. Mean and standard deviation will be used to represent the variable scores at baseline and follow-up measurements.

Study population will be characterized using various descriptive statistics parameters. Initially, possible differences between groups at baseline will be assessed using a one-way analysis of variance for continuous data (or equivalent statistical approach in the case of non-parametrical data) and Chi-square for categorical data.

Comparisons of outcome measures will be undertaken at baseline and 10 weeks for all available measures. Between-group comparisons will be made using a 2 (group) x 2 (time) mixed ANOVA.

Although the trial is not powered to detect the influence of mediating and moderating factors on fatigue, we will explore possible interactions in the following secondary analyses: (i) interaction terms will be examined to investigate possible differences in intervention effects on the primary outcome by demographic and cancer-related factors; (ii) engagement with *REFRESH* will be determined and a comparison between those who meet the criteria for engagement versus those who do not will be undertaken to assess 'per protocol' effectiveness; (iii) a mediational analysis exploring whether the effect of the intervention on the primary outcomes is mediated by illness perceptions and cognitive behavioral strategies using the analytic framework recommended for RCTs will also be undertaken.

Data Management and Access

This data management plan has been created using the UCD Data Management Checklist. The data will be saved online through Inquisit (the Sternberg Memory Task) and Surveygizmo (all other tasks and questionnaires). This data is only accessible by the first author. When these data are collated, the second author will also have access to the relevant data files. The data will be saved in both .csv and .sav formats. These files will be stored in encrypted Dropbox folders. A detailed logbook will be created to complement these files. We do not currently have ethical approval to share these data. In accordance with the NUI Galway data retention policy, these data will be retained for 5 years at the NUI Galway School of Psychology (as well as being backed up on Dropbox) and anonymised by replacing student ID numbers and names with randomly generated subject ID numbers.

Discussion

REFRESH has been developed according to the MRC guidance for developing and evaluating complex interventions(33). The content is based on the SRM which proposes that coping behaviours in response to a symptom such as fatigue are guided by cognitive and emotional representations of that symptom. This approach has guided the linking of theory to specific cognitive-behavioural intervention techniques and mechanism of change targets. This evidence-based online programme is novel in its approach as it is based on SRM theory. The primary aim is to understand individuals' lay-representations of a commonly misunderstood symptom and enhancing self-management of CrF specifically. It also provides the first systematic coding of a CBT intervention using the BCT taxonomy (v1). In line with the TIDieR checklist and guide (69), the aim is to provide sufficient details to allow replication, including how innovative recruitment modalities can be harnessed to engage those who are already active online(70).

The website has been systematically and theoretically developed in an Irish population, working with cancer care teams, clinical psychologists and cancer survivors suffering with

fatigue. This study will provide additional insight into the efficacy of the intervention and allow the researchers to understand the experience of the participants. This will enable any necessary post-trial modifications or remodeling in order to enhance the effectiveness of *REFRESH* prior to the development of a larger scale RCT of the programme.

Throughout the design of this programme, the developers were cognizant of the need to develop interventions that not only incorporate theory but also aim to evaluate the application of specific theoretical frameworks. The systematic theoretical underpinning of '*REFRESH'* will allow the researchers to gain an insight into how some psychological and behavioural variables (mediators) are related to fatigue. However, in the feasibility trial described here, the study will not be powered to assess these potential effects.

The primary outcome measure for *REFRESH* is fatigue as measured by the PFS-R at 10 weeks post-baseline for this pilot trial. An extension of the timing of the main outcome measure in future iterations of the trial will allow for the assessment of any sustained effect on outcomes.

The results from this trial will provide information regarding the potential of a novel theoretical approach to online interventions for cancer related fatigue in post-treatment cancer survivors. The research seeks to create supportive online environments at home to ameliorate fatigue and promote self-management of symptoms in this group. Any amendments or updates to this protocol will be lodged with the journal such that it links them to this protocol document. This will allow all future trial publications and conclusions to be assessed against the extent to which we have adhered to the protocol.

Trial status

The trial and recruitment is ongoing.

List of abbreviations

CrF- Cancer-related Fatigue

CBT- Cognitive Behavioural Therapy

CBSQ- The Cognitive and Behavioural Responses to Symptoms Questionnaire

CONSORT- Consolidated Standards of Reporting Trials

IPQ-R- The Revised Illness Perceptions Questionnaire

ISRCTN- International Standard Randomised Controlled Trials Number

MRC- Medical Research Council

QLACS- Quality of Life in Adult Cancer Survivors

PFS-R- Piper Fatigue Scale (revised)

RCT- Randomised Controlled Trial

REFRESH- *REFRESH* (Recovery from Cancer-Related Fatigue) intervention

SRM- Self-regulation Model

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Competing interests

The authors declare that they have no competing interests.

Authors' contributions

TC conceived of the study, its design and coordination, and drafted the manuscript. JW, AMG, RMM and BMG participated in the design of the study and revisions to the manuscript. All authors read and approved the final manuscript.

Communication of Findings: The authors intend to fully communicate trial results in a peer reviewed journal.

Future studies planned:

The findings of this feasibility/pilot study will inform any future iterations of the trial. This includes an assessment of the practicality of any proposed future projects. Future trials will only be conducted if the current pilot trial demonstrates potential to be feasible based on the findings regarding:

I. Recruitment and uptake

II. Adherence and attrition

III. Evaluation of functionality and usability of website

IV. Participant satisfaction with website

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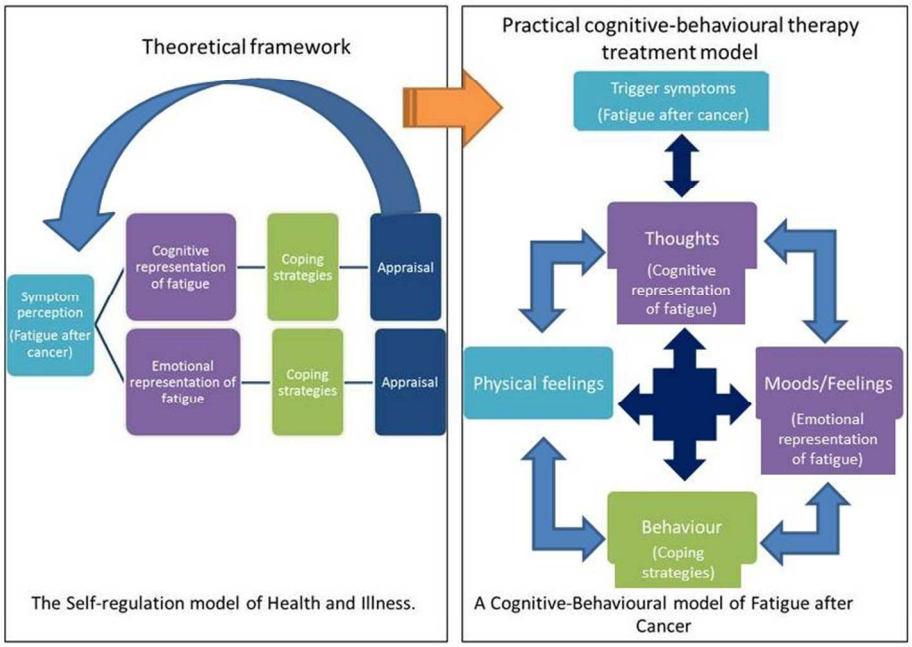

Figure 1. From theory to practice: Applying the self-regulation model to a cognitive-behavioural therapy treatment model.
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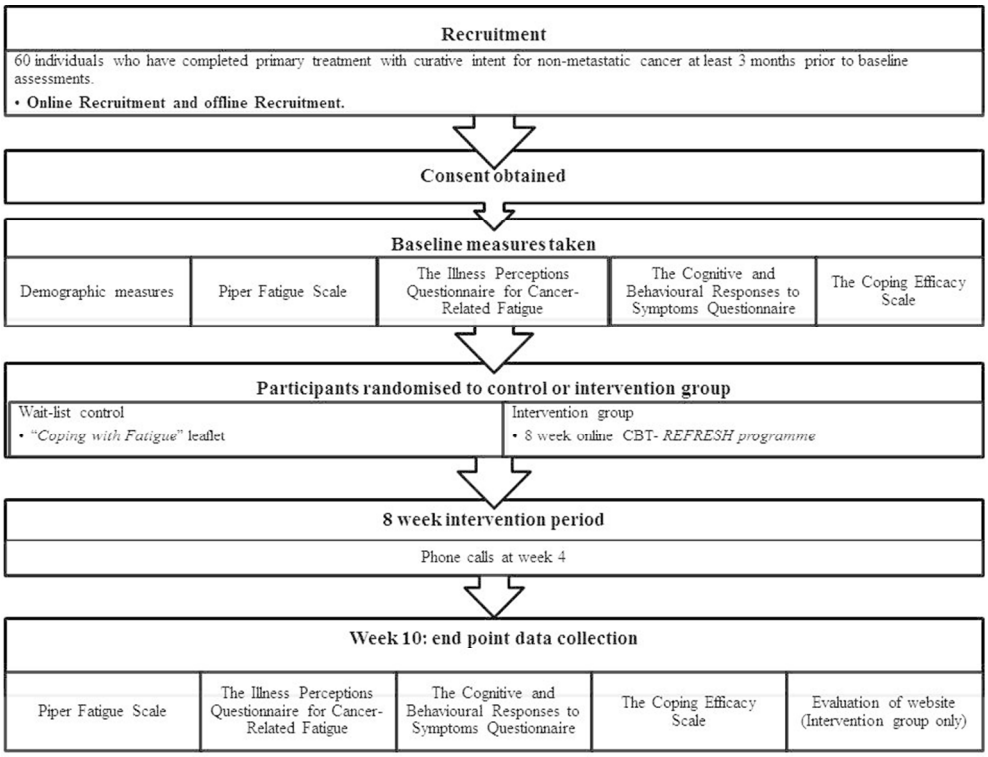

Figure 2. Planned flow of participants through the REFRESH randomized controlled trial.
81x60mm (300 x 300 DPI)

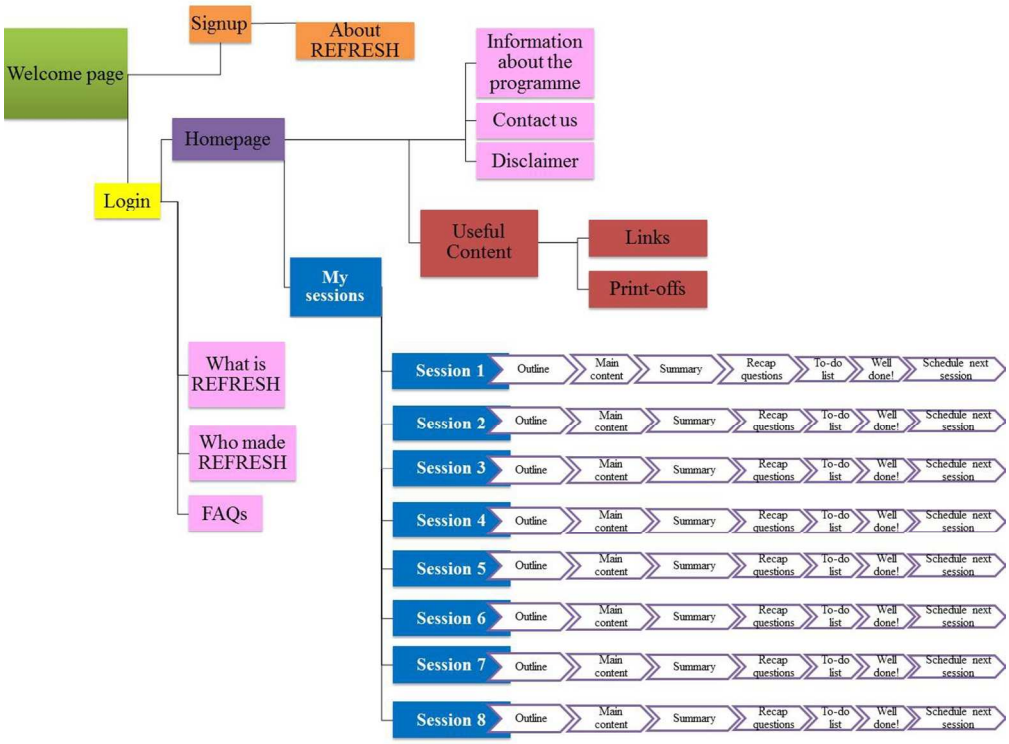

Figure 3. Basic structure of the REFRESH program.
113x85mm (300 x 300 DPI)

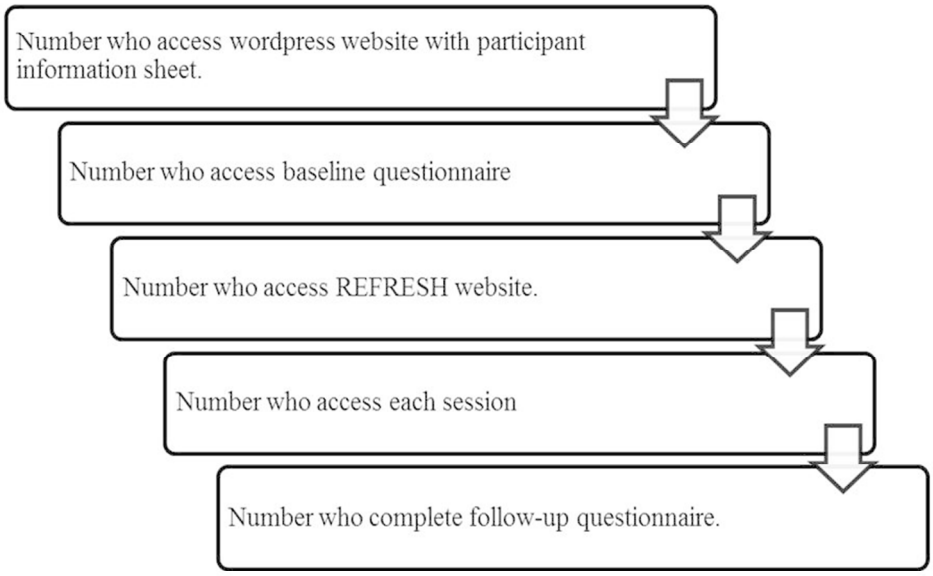

Figure 4. Uptake and participation assessment
81x60mm (300 x 300 DPI)

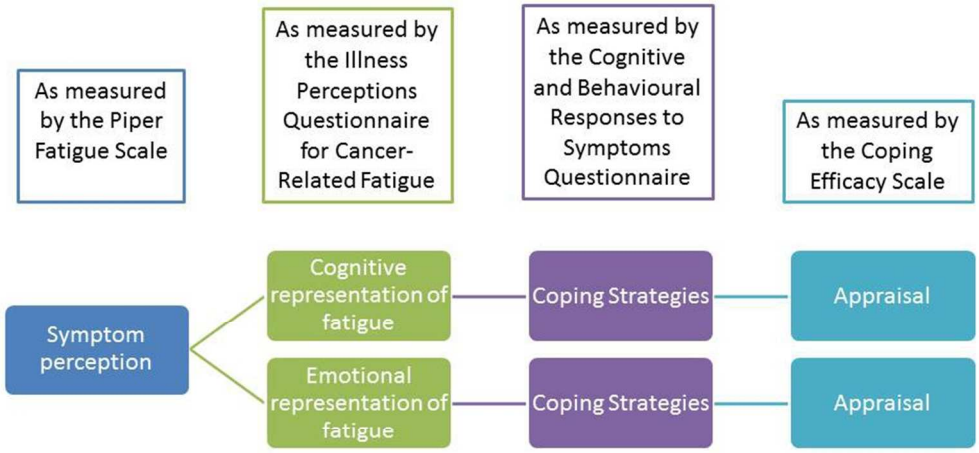

Figure 5. Proposed assessment of Self-regulation Model theory.
81x60mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Title page
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Title page/abstract
	2b	All items from the World Health Organization Trial Registration Data Set	Abstract
Protocol version	3	Date and version identifier	Title page
Funding	4	Sources and types of financial, material, and other support	19
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Title page/ 19
	5b	Name and contact information for the trial sponsor	19
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	19
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	1
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	10
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	4
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	_12_
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	_10

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	16
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	8
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	_____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	_17__
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13_
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	4
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	__4_____

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_na____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	_4____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	19
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	4_
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20
	31b	Authorship eligibility guidelines and any intended use of professional writers	19_
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	na_
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_appended__
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	__na_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.