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Efficacy and cost-effectiveness of an online mindfulness program (MindOnLine) to reduce fear of recurrence among people with cancer: study protocol for a randomized controlled trial

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Title

Efficacy and cost-effectiveness of an online mindfulness program (MindOnLine) to reduce fear of recurrence among people with cancer: study protocol for a randomized controlled trial

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Abstract

Introduction: Fear of cancer recurrence (FCR) is a common condition among cancer survivors that can lead to significant levels of distress, anxiety and depression. Online mindfulness programs may provide the mechanism to support cancer survivors manage FCR and distress, and improve people's wellbeing over the short, medium and long term. The primary aim of this study is to determine the potential efficacy of MindOnLine, a 9 session mindfulness-based program for survivors of breast, prostate and colorectal cancer. A formal economic program will also be conducted.

Methods and analysis: A single-blind randomized controlled trial to determine the efficacy and cost-efficacy of a MindOnLine program for cancer survivors. A total of 400 people living with cancer will be recruited via online advertisements on social media platforms, peak consumer advocacy groups, or through outpatient services at healthcare providers across Victoria. People will be randomly allocated to either the MindOnLine program (n=200) or waitlist control (n=200). Participant assessments will occur at baseline, at 9 weeks and 9-month follow up. The primary outcome is change in Fear of Recurrence Index Score total score between baseline and 9 weeks; secondary outcomes include changes in depression and anxiety, quality of life and mindfulness. The economic analysis comprises a cost-consequences analysis where all outcomes will be compared to costs.

Ethics and dissemination: Ethics approval was obtained from the Peter MacCallum Cancer Centre (20-53) and Deakin University (2020-284). Findings will be disseminated in peer reviewed journals and among key stakeholder organisations including hospitals, cancer and community organisations and Government. If successful the project will be rolled out nationally with a formal implementation plan.

Australian New Zealand Clinical Trials Registry: 12620000645954p. Registered 06 June 2020, https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=379520&isReview=true

Keywords: mindfulness, cancer, fear of cancer recurrence, online; economics of cancer; supportive care; web-based platforms

Article Summary

Strengths and limitations of this study

- Development of the intervention through a literature review, findings from a pilot study, involvement of consumer advocacy groups and Government bodies are the study's strengths. This will ensure translation of the program into policy and practice if shown to be efficacious.
- Involvement of consumer advocacy groups to support recruitment.
- This study will employ a single-blind randomized controlled trial to determine the efficacy and cost-efficacy of MindOnLine.
- Advances in social platforms, smartphone technology and web-based programming can change substantially in a short period and while this may affect the actual online platform used, we do not consider this will influence the program content or delivery mechanisms.

Introduction

Over one million Australians are cancer survivors, and this population is expected to grow substantially over the next 20 years due to an ageing population and improved community-based screening programs and treatments.[1] A cancer diagnosis can cause people to confront their own mortality, often for the first time,[2] so it may be unsurprising that three quarters of cancer survivors experience fear of cancer recurrence (FCR) and 49% report moderate to high levels of fear,[3] as well as high levels of clinical depression [3]and anxiety.[4]

FCR is a highly prevalent and persistent condition that can result in significant levels of anxiety and depression across the disease trajectory.[5] It is imperative to address this issue and our recent work into early psychosocial support indicates it may be possible to significantly reduce FCR through an online mindfulness program.[6] Mindfulness is a state of mind in which one pays attention to the present experience in a nonjudgmental, curious, and accepting way. Some studies have shown mindfulness is associated with improved mental health outcomes and management of the emotional consequences of cancer, [7, 8] while other have found no effect.[9]

Mindfulness-based interventions consist of regular informal and formal mindfulness meditation practices and are supported by educational principles that are person and relationship-centred.[10] Research into the use of mindfulness has mostly evaluated face-to-face programs which are time-intensive, of limited accessibility and costly.[11] Online mindfulness programs represent a potentially cost-effective mechanism to help cancer survivors manage FCR and distress, and improve mental wellbeing over the short, medium and long term.[2] While an online mindfulness-based cognitive therapy (MBCT) intervention was found to be as effective as a face-to-face MBCT in reducing psychological distress and

FCR in cancer patients [12] there is a lack of robust evidence assessing the effectiveness of a general online mindfulness program for cancer survivors, limiting capacity for implementation and dissemination.[13, 14]

The aim of this study is to conduct a randomised controlled trial of *MindOnLine,* an online 9 session mindfulness-based intervention, for survivors of breast, prostate and colorectal cancer, to determine the effectiveness and cost-effectiveness of the program.

Preliminary work

To inform the development of *MindOnLine*, we undertook a systematic review of methodologies for internet based mindfulness interventions.[15] This review showed a dearth of studies with long-term follow up periods. Our team also conducted an exploratory study on the knowledge of, attitudes toward and behaviours regarding meditation among patients with melanoma.[16] Our study of 291 cancer survivors recruited at a single tertiary cancer hospital found that a key barrier to engaging with meditation was a lack of knowledge about its practice. Findings also indicated interest in an online meditation-based intervention once informed about possible benefits of meditation for people with cancer. Those interested in an online meditation-based program reported higher perceived stress, indicating a need for such a program.

We conducted a pilot 6-week RCT [6] to determine the feasibility and acceptability of *MindOnLine*, The secondary aims were to explore intervention impacts on FCR, worry, and perceived stress compared to usual care. Overall, 69 melanoma survivors agreed to participate, and 46 participants were randomised into the intervention group (2:1). Scores on all FCR Inventory (FCRI) subscales reduced in the intervention group, with the severity subscale decreasing significantly compared to the control group (-2.6, 95% CI=(-4.4, -0.7); p=0.008)

after 6 weeks. The total FCRI score also showed a decrease albeit non-significant (−6.2, 95% CI=(−13.12, 0.68), p=0.07). Previous studies have indicated that a 4.1 points decrease on the severity scale is a clinically important change.[17]

Based on participant feedback regarding the benefits of mindfulness practice and the suggestion of a maintenance period to enhance sustainability of the effects, *MindOnLine* was expanded to a 9-week program with the last 3 weeks revisiting concepts already explored in the program and supporting regular practice.

Methods and analysis

Aims and Hypotheses

The aims of this study are to determine the effect of *MindOnLine* on FCR, anxiety and depression in cancer survivors. The specific aims are:

Aim 1: To evaluate the impact of the *MindOnLine* intervention on the primary outcome (FCR), measured using the FCRI total score [18] at the end of the 9-week intervention period. *HYPOTHESIS 1:* Participants receiving the intervention will report lower average FCRI total scores at 9 weeks, compared to the waitlist group.

Aim 2: To evaluate the impact of *MindOnLine* on secondary outcomes at nine weeks: 1) Anxiety and Depression, using the Patient Health Questionnaire (PHQ-9) [19] and Generalised Anxiety Disorder (GAD-7) Scale;[20] 2) Quality of Life (QoL) measured by AQOL-4D;[21] and 3) Mindfulness, using Cognitive and Affective Mindfulness Scale-Revised (CAMS-R).[22] *HYPOTHESIS 2*: Compared to the waitlist group, participants in the intervention group will report improvement in all of the secondary outcomes at nine weeks.

Aim 3: To assess if the intervention effects on the primary and secondary outcomes are sustained at the nine-month follow-up. *HYPOTHESIS 3*: Compared to the waitlist group,

participants in the intervention group will report sustained improvement in primary and secondary outcomes at nine months.

Aim 4: To assess, from a health sector and broader societal perspective, the cost-effectiveness of *MindOnLine. HYPOTHESIS 4*: Compared to the waitlist group, *MindOnLine* will be cost-effective with an incremental cost-effectiveness ratio likely to fall below the commonly used threshold of $28,000 - $50,000/Quality of Life Year (QALY).

Study Design

This study is a randomised controlled trial, to test the effectiveness and cost-effectiveness of MindOnLine compared to usual care on FCR, anxiety, depression and QoL among people diagnosed with breast, prostate or colorectal cancer. Overall, 400 patients will be recruited with 200 patients randomly allocated to the intervention group and 200 to the waitlist group (usual care only). The intervention group will receive usual care and the online mindfulness program. Primary and secondary outcomes will be collected at baseline, nine weeks and nine months post randomisation. Nine months corresponds to approximately six months following the end of the intervention period. Following completion of the study (9 months), participants in the waitlist group will be offered the *MindOnLine* intervention (Figure 1).

Participants

People with a diagnosis of breast, prostate or colorectal cancer will be recruited via online advertisements on social media platforms, peak consumer advocacy groups for each cancer Breast Cancer Network Australia (BCNA), or Prostate Cancer Foundation Australia (PCFA), Bowel Cancer Australia social media platforms and colorectal cancer support groups, or through outpatient services at healthcare providers across Victoria, see Figure 1.

Figure 1. Study flowchart

(Insert Figue 1 here)

FCRI (Fear of Cancer Recurrence Inventory); GAD-7 (General Anxiety and Distress scale; PHQ-9 (Patient Health Questionnaire); CAMS-R (Cognitive and Affective Mindfulness Scale – Revised); AQoL-4D (Assessment of Quality of Life – 4 Dimensions)

Inclusion criteria

Adults, aged 18 year of older, living in Australia, who completed active treatment for Stage 1-3 breast, prostate or colorectal cancer (CRC), (trastuzumab/similar, and hormone treatment exempt) within the past 5 years; have internet access and a FCRI severity score ≥13, indicating clinically significant FCR.[18] Our pilot study showed 74% of participants with melanoma were identified as having clinically significant FCR.[6]

Exclusion criteria

Insufficient English language skills to understand videos presented in English, complete surveys in English or living with advanced cancer (Stage IV or metastatic disease).

Recruitment procedures

Multiple methods will be applied to recruit people to the study:

1) online through *MindOnLine* social media pages including Facebook, Instagram, Twitter, Reddit and LinkedIn

2) sharing recruitment flyers through BCNA and PCFA social media platforms, and Australian based cancer groups

3) email invitations sent to BCNA and PCFA supporters (and colorectal cancer support groups) and cancer registries

4) paid Facebook and Instagram advertising

5) through outpatient clinics, chemotherapy and radiotherapy units and rooms of oncologists and surgeons at cancer treatment centres.

Online recruitment procedure

1) The *MindOnLine* social media pages will be shared among social networks and will allow people to post questions about the project. 2) A recruitment flyer will be distributed by BCNA, PCFA, Bowel Cancer Australia and colorectal cancer Facebook support groups using their

existing social media platforms. 3) Study invitations will be sent to supporters registered with BCNA and PCFA who have indicated an interest in learning about research projects. 4) Paid advertisements will run throughout the recruitment period on Facebook, Instagram and Twitter to distribute the project details to a wider audience. The use of paid advertisements in health research is becoming popular and a systematic review has shown this to be an effective recruitment strategy.[23]

In all online recruitment methods, people will have access to the recruitment flyer, which will provide a brief overview of the study, the link to the *MindOnLine* registration page and the contact number of the project manager.

Health service recruitment procedures

If recruitment across social media platforms, advertisements and peak consumer advocacy groups does not generate sufficient participation levels, participating health services oncologists or surgeons involved in the project, will support the recruitment process. The research assistant (RA) at each site will screen patients and confirm eligibility of patients with treating clinicians or with nurses working in the outpatient units. RAs will then contact patients by phone and interested patients will be emailed the study details with a link to the study webpage and registration page). If there is no response from patients, a message will be left on their phone. Two further attempts to reach patients will be made (a week apart), and after a third unsuccessful attempt no further contact will be made. If patients have not enrolled in the study within two weeks, one follow-up phone call will be made to answer any queries patients may have about the study and to assist with registration. We have used similar screening and recruitment approaches in previous studies and they were found them to be acceptable and successful.[6] We anticipate a recruitment period of 18-months.

Consent and screening

Once directed to the *MindOnLine* registration page, participants will be presented with the plain language statement and then asked to provide consent. Potential participants will be asked to provide basic demographic and disease information allowing screening to ensure they meet study eligibility criteria. Potential participants will also complete the severity subscale of the FCRI to allow those with scores ≥13 to be screening into the study. Those screened into the study will provide their email address and contact number, and directed to the baseline questionnaires. People who are not eligible will receive an online message thanking them for their interest in the study and referring them to local support services provided by leading cancer charities should they require support.

Randomisation

Eligible participants will be allocated to treatment groups using random sequences embedded in the online survey platform Qualtrics, ensuring allocation concealment. Randomisation (using stratified random permuted blocks) will be conducted in blocks of size 2, stratified by cancer type (breast, prostate, CRC) and age (<60; ≥60 years old). Participants will be unblinded to group assignment, while researchers and data analysts will be blinded to the group condition.

Control group

Participants allocated to the waitlist group will receive usual care. Following randomisation, they will receive an email with a list of services they may contact for information and support. They will be informed that they will be granted access to *MindOnLine* intervention in 9-month's time.

Intervention group – MindOnLine program

Participants allocated to the intervention will be provided with the link to *MindOnLine,* which comprises three main components:

(1) an educational component to increase participants' knowledge about the science and practice of mindfulness and how it may benefit them in everyday life;

(2) a formal mindfulness meditation practice to improve awareness and emotion regulation; and

(3) an informal practice to teach participants how to bring mindfulness to daily activities.

A new theme is introduced each week, with a new meditation practice which participants will be encouraged to undertake every day *The MindOnLine* program is detailed in Table 1.

Table 1- Weekly content of the *MindOnLine* Program

Week	Theme	Meditation	Daily practice
1	Introduction to mindfulness	Breath	Being present with the experience
2	Reducing stress	Body Scan	Notice how the body responds to stress
3	Relating to emotions	Working mindfully with emotions	Noticing the cycle of emotions
4	Self-compassion	Self-compassion	Notice self-criticism
5	Communicating mindfully	Listening/ Sound meditations	Bringing attention back to the conversation
6	Living mindfully	Practising with gentleness and patience	Pause throughout the day
7	Reducing worries	Mindfully working with worries and fears	Notice when caught up overthinking

8	Reducing worries mindfully	Loving Kindness meditation	Notice acts of kindness
9	Maintaining mindfulness	Silence with bells	Notice when distracted from being present

Each module's theme will be explained through a short 5-10 minute video. At the end of each week, participants will receive an email with a link to the video introducing the theme for the upcoming week. The script for the videos will be available for downloading and saving or printing in a pdf format so that participants can keep a copy for later reference. At the end of each module, participants will receive an automatically generated email reminding them to continue daily meditation practice (formal practice) and given specific everyday mindfulness exercises to apply during daily activities (informal practice).

To enhance adherence and retention to the 9-week program and deepen their mindfulness experience, participants will have access to additional program features. The features are guided by a framework proposed by Abraham and Michie [24] to facilitate behaviour change in interventions:

1) Twice daily reminders to complete mindfulness practice. Adapted from the pilot study, emails containing a link to a short, guided meditation audio file will be sent to participants twice daily. These emails will serve as reminders to meditate and will provide easy access to the meditation practice of the week.
2) Progress tracking. Participants will be able to monitor their own mindfulness practice each day by reviewing how many times they have used each section of the program, and the duration of use. Embedded usage data tracking systems records each login and provides real time representation of program use.

3) Goal setting. When enrolled in the program, participants will have the opportunity to set goals for their mindfulness practice (Figure 2). Goals are linked to usage data tracking to provide participants with feedback about whether they are reaching their goals. Goals may be practice orientated e.g. to practise mindfulness for five minutes each day, or may be specific to each person's situation e.g. I would like to manage my worries leading up to my oncologist appointment.

4) Reflective journaling. Participants will have the opportunity to journal their experiences during the mindfulness program by using the "My Journal" functionality (Figure 3). Each week's content will have a journal section, which will include prompts related to mindfulness program content, participants will be able to enter and save their responses within the program for future review. Prompts will be developed specifically for the study.

The mindfulness program can be accessed at any time via direct login to the website or via the hyperlink sent to participants in the daily e-mails.

Figure 2. My Goal functionality in MindOnLine

(Insert Figure 2 here)

Figure 3. My Journal guided self-reflection practise in MindOnLine

(Insert Figure 3 here)

Data collection

Table 2 illustrates the overall schedule for trial participants in both groups. All assessments will be performed online. The questionnaires at baseline, at nine weeks including the

satisfaction survey for those in the intervention group and at nine months, will be sent via Qualtrics through an automatically generated schedule. Participants who do not complete questionnaires will be followed up by telephone at each data collection point. At baseline, participants' demographic information (i.e., gender, age, marital status, current employment status, highest level of education, postcode, type of cancer, date of diagnosis, time since end of last treatment, type of treatment and previous meditation experience) will be collected.

Table 2. Schedule of enrolment, interventions, and assessments

	STUDY PERIOD										
	Enrolment	**Allocation**	**Post-allocation**								**Post-Intervention**
TIMEPOINT			***Week 1***	***Week 2***	***Week 3***	***Week 4***	***Week 5***	***Week 6***	***Week 7***	***Week 8***	***Week 9***	***9-months***
ENROLMENT:												
Eligibility screen	X											
Informed consent	X											
Allocation		X										
INTERVENTIONS:												
Immediate access to MindOnLine			←	—	—	—	—	—	—	—	→	
Waitlist group												
ASSESSMENTS (Both groups):												
Demographic characteristics	X											
FCRI [18]	X										X	X
GAD-7 [20]	X										X	X
PHQ-9 [19]	X										X	X
CAMS-R [22]	X										X	X
AQoL-4D [21]	X										X	X
Mindfulness experience	X										X	X
Resource use	X										X	X

COVID-19 measures	X									X	X
ASSESSMENTS (Intervention group only):											
Adherence tracking and meditation log			X	X	X	X	X	X	X	X	X	X
Program satisfaction										X	X

Outcome measures

Fear of cancer recurrence Inventory (FCRI)

The 42-item Fear of Cancer Recurrence Inventory (FCRI) is a multidimensional FCR scale intended for use with all cancer patients. Items were developed on the basis of a cognitive–behavioural formulation of FCR (range:0-168).[18] The FCRI consists of seven domains: triggers, severity, psychological distress, functional impairment, reassurance, insight and coping strategies (scoring range:0-36). It has shown high internal consistency, good construct and criterion validity in adults with different cancer types.[18]

Anxiety and Depression

The *Generalized Anxiety Disorder-7 scale (GAD-7)* [20] is a valid and efficient tool for assessing generalised anxiety symptoms and assessing severity in clinical practice and research. The seven items assess the frequency of core symptoms of generalised anxiety disorder within the past 2 weeks (scoring range:0-21).[20]

The *Patient Health Questionnaire-9 (PHQ-9)* [19] parallels the nine diagnostic symptom criteria that define DSM-IV major depressive disorder. At only 9 items (scoring range:0-27), the PHQ-9 is shorter than most depression tools. Unlike most other measures of depression, the PHQ-9 was developed, tested and refined for use with medical patients.[19]

The PHQ-9 and GAD-7 are recommended for use among cancer survivors in the American Society of Clinical Oncology Guidelines.[25]

Mindfulness

Trait mindfulness is measured using the Cognitive and Affective Mindfulness Scale-Revised (CAMS-R),[22] a 10-item self-report questionnaire. This scale uses everyday language appropriate for those with little meditation experience and is designed to capture mindfulness as a general daily experience. The questionnaire comprises four domains of mindfulness (attention, present-focus, awareness, and acceptance/non-judgment). Participants are asked to rate on a four-point Likert scale how much they relate to each statement (scoring range:4-40). Compared to other measures of mindfulness, the CAMS-R is unique in that it is related to psychological distress,[26] which is highly relevant to the current study population.[27]

Mindfulness experience

In order to control for access to external mindfulness-based programs particularly in the waitlist group, all participants will be asked whether they have enrolled in a mindfulness-based program in the period between surveys and/or used other supportive care services (e.g. peer support, psychologists, psychotherapy, counsellors, yoga and meditation).

Program satisfaction

Participants in the intervention group will be asked to provide feedback about the *MindOnLine* program. Quantitative and qualitative data using open ended questions will be collected in relation to satisfaction with program content, the helpfulness of the program, usability, and areas for improvement. The satisfaction questionnaire has been adapted from the satisfaction questionnaire used in the pilot study.[6]

Economic outcomes

Assessment of Quality of Life (*AQoL 4D*) [21] is a health-related quality of life utility measure. It is generally used in economic evaluations. The *Resource Use Questionnaire* covers general

health care services usage (self-reported), use of other welfare services, and impacts on work force participation. The questionnaire has been successfully used in cancer psychosocial intervention studies.[28]

Adherence tracking and meditation log

The software package used to run *MindOnLine* was developed at Deakin University and has inbuilt functionality to collect and clean usage data. Google Analytics has been incorporated into the platform to allow for validation of findings. Both software will track participants' online activity, including login date/times, navigation patterns, page views and duration, and features used (video, audio, goals and reflective journaling).

Impact of COVID-19

To control for potential environmental impacts on mental wellbeing outcomes, participants will be asked whether COVID-19 has had an impact on their mental wellbeing in the two weeks prior to baseline, 9-weeks and 9-month assessments.

Sample size calculations

Power calculations are conservative, i.e. the detectable differences reported below are possibly larger than the true detectable differences, because they are based on two-group comparison of change while the main analysis (see Analysis Plan) will adjust for baseline values of the outcome and for factors used in the stratified randomisation.[29] The statistical software PASS version 14.0.9 (NCSS, LLC) was used for all calculations (α=0.05; two-sided tests).

Primary outcome

Change in FCRI total score between baseline and 9 weeks. The target sample size (200 participants per arm) achieves 94% (80%) power to detect a mean difference between arms of

10 points (8 points) change in FCRI score or 80% power to detect a difference of 8 points [standard deviation (SD): 23.5;[30]). SD estimate obtained from Butow et al., [30] as their study included a heterogenous sample of cancer patients while our pilot study only included patients with melanoma Stage 2-3. The selected effect sizes correspond to Cohen's d of 0.43 (moderate/large) and 0.34 (small/moderate) respectively. Currently, there is no definition of a clinically significant improvement for FCRI score, however, the proposed effect size is comparable to that described in other studies.[30]

Secondary outcomes

The target sample size (200 participants per arm) achieves 80% power to detect an intervention effect of size 0.34 (Cohen's f, small/moderate) at 9 weeks for any of the outcomes. This effect size corresponds to mean differences between groups of: a) 1.5 point in PHQ-9 depression score (SD = 4.5, maximum SD reported in patients with breast, colorectal and prostate cancer;[31] PHQ-9 minimal clinically important difference (MCID) for cancer patients: 2.6 to 5);[32] b) 1.4 point in GAD-7 anxiety score (SD=4.1, maximum SD reported in patients with breast, colorectal and prostate cancer;[33] MCID=1.95);[32] and mean differences between group in change from baseline to 9 weeks of: c) 1.2 points in FCRI severity score (SD=3.6, pilot study effect: 2.6);[6] d) 1.1 points in CAMS-R score (SD=3.4); e) 2.5 points in Worry score [SD=7.3]; f) 3.0 points in PSS score [SD=8.9]; the last 3 reflecting moderate Cohen's *d* effect sizes (<0.35).

To meet the sample size needs of our desired statistical power, we will recruit 400 participants. In our pilot study, six participants (13%) withdrew in the intervention group and none in the control group. Assuming a conservative 30% attrition rate at nine months, we expect to have complete data for approximately 280 participants (140 per group).

Analysis plan

All statistical analysis will be conducted on an intention-to-treat basis whereby all randomised participants with at least one post-baseline measurement will be analysed by original treatment assignment regardless of adherence. Baseline characteristics will be described using summary measures selected based on variable distribution. The main analysis will adjust for baseline values of the outcome and for factors used in the stratified randomisation.[29]

Aims 1 and 2. The effect of the intervention on each of the outcomes, defined as change from baseline to nine weeks, will be assessed using linear models including group and the stratification factors. *Aim 3.* The effect of the intervention across the three measurement times will be estimated using linear mixed models, including study group, time (categorical: 9 weeks, 9 months) interaction group×time and the stratification factors as fixed effects and participant as a random effect. If there is a positive intervention effect on mental health outcomes, exploratory mediation analyses will be conducted to determine whether improvements are mediated by increases in mindfulness.[34] For outcomes where it is a plausible assumption that missing data are completely at random, we will use complete case analysis; if not plausible, we will use multiple imputation. *Subgroup analysis*: We will explore whether age or gender modify the effect of the intervention on FCR, depression and anxiety at 9 weeks.

Aim 4. This study will also comprise a cost-consequences analysis where incremental costs of the intervention will be compared with the full spectrum of outcomes included in the study. A series of cost-effectiveness ratios can be determined which have been shown to be useful for decision-makers. Inclusion of the AQoL 4D will also enable a cost-utility analysis to be undertaken, thereby allowing practical judgements to be made regarding value for money

credentials of the intervention. Nevertheless, the economic analysis will be primarily from the perspective of the health care sector and a secondary analysis from the broader societal perspective will also be undertaken. A detailed costing of the intervention will be undertaken and the evaluation will first measure and value any change to the use of health care resources over the period of the study between the two arms of the trial and then compare any additional costs to the additional outcomes achieved. Standardised economic evaluation techniques will be used including incremental analysis of mean differences and bootstrapping to determine confidence intervals along with a net monetary analysis to determine the cost-effectiveness of the intervention for different value for money threshold criteria. The costs of routine roll-out will be estimated.

MindOnLine usage data by the intervention group will be reported using descriptive statistics. Linear mixed models, with random intercept and slope for each person, will be fitted to estimate time trends in usage.

Data management

Data will be exported from Qualtrics on a monthly basis and crossed checked during exportation to ensure accuracy in results. All identifying participant information will be removed from data sets. Documents containing sensitive information will be saved as password protected files and stored within the Deakin University One Drive.

Monitoring

Data

The adherence data will be monitored by the program developer. The program developer does not have any competing interests. Other project data will be monitored by the project steering committee with regular meetings and progress updates. No interim analysis will be performed during the trial.

Patient and Public Involvement

Representatives from three consumer organisations have been involved in the design and implementation of the project since its inception. Their contribution has included development of the intervention and its content, wording on recruitment material, and provided advice on recruitment strategies. Representatives from each consumer organisation has contributed to project steering meetings.

Ethics and Dissemination

Harms

In the event that a participant reports distress to the project manager they will be advised to seek assistance from the regular medical professionals and provided with additional referrals to lifeline.org.au. Ethics approval was obtained from the Peter MacCallum Cancer Centre (20-53) and Deakin University (2020-284). Any adverse events will be reported to the ethics committees.

Auditing

The trial may be audited by the governing Human Research Ethics Committees.

Protocol amendments

Protocol amendments will be approved by the governing Human Research Ethics Committees. Any relevant changes will be submitted as a modification to the Australian and New Zealand Clinical Trial Registry.

Dissemination

The findings of this study will be written by study authors and published in peer reviewed journals project steering committee. Access to full datasets will be made available upon reasonable request. All identifying participant information will be removed prior to publication.

Discussion

One of the most significant changes across society is the use of web-based technology. Online mindfulness-based interventions circumvent problems with traditional face-to-face delivery of

the program, impacted by work commitments, caring responsibilities and geographic isolation.[2]

This study will rigorously evaluate the efficacy of a self-directed online mindfulness program in reducing FCR in breast, prostate and CRC survivors. The study will advance the literature regarding the benefits of mindfulness for cancer survivors by representing one of few large well controlled trials of a self-directed mindfulness-based program aimed at reducing FCR. Including a health economic evaluation of the program adds to the utility of the trial with the study providing information that budget holders and policy makers need when considering recommendations and support for supportive care programs. This trial will fill a gap in knowledge regarding the potential impact of mindfulness in supporting cancer survivors.[7] Extensive pilot work in identifying the type of program cancer survivors are interested in, involving consumers in designing the content and length of the program and providing reminders and practice tips increase the likelihood of participants engaging with the program and the intervention having a positive impact.

The study is being conducted in partnership with health services and cancer advocacy and community groups who have assisted in the design of the research trial and intervention. As partners in the study, they will ensure the intervention can be rolled out to cancer survivors if shown to be effective. In addition to consumer advocacy groups, the study is being conducted in partnership with government. As we expect the *MindOnLine* intervention to improve health outcomes, reduce the fear and distress in cancer survivorship and reduce health service and community costs our partnership with government will ensure that policy makers are informed of the study's findings particularly cost-effectiveness findings.

The study has a number of strengths and weaknesses. Development of the intervention through a review of the literature, input from consumers and findings from a pilot study and involvement of consumer advocacy groups and government are study strengths ensuring translation of the program into practice if shown to be effective. Involvement of the consumer advocacy groups also aid in recruitment. Incorporating an economic evaluation into the study design is a strength as it will complement clinical findings and support decision-making processes for potential implementation. However, several limitations also need to be acknowledged. Recruitment through social media platforms means we cannot accurately assess uptake of the intervention, as we will not be able to identify the number of eligible people exposed to our recruitment flyers. This may limit our ability to determine reach of the program. However, recording the time taken for recruitment and accessing google analytic data on internet traffic and page visits may provide some information in this area. Participants will need access to the internet to participate. While this may mean some people will be excluded from the study, we believe this will have minimal impact on the study. We envisage that the study will take approximately 4 years to complete. Advances in social platforms, technology and app-based programing can change substantially in a short period. While this may affect the actual online platform used for the program, we do not consider this will influence the program content or delivery mechanisms. As technology advances will likely increase interest in self-directed support programs for cancer survivors, it is essential that cancer survivors access programs with demonstrated effectiveness.

Trial Status

Protocol Version: Version 5, dated 18 December 2020

Recruitment commenced 12.10.2020, it is anticipated recruitment will be for a duration of 18 months finishing on 12.04.2022.

Abbreviations

AQoL-4D Assessment of Quality of Life – 4 Dimensions

BCNA Breast Cancer Network Australia

CAMSR Cognitive and Affective Mindfulness Scale-Revised

CI Confidence interval

CRC Colorectal Cancer

FCR Fear of cancer recurrence

FCRI Fear of Cancer Recurrence Inventory

GAD-7 General Anxiety Disorder scale

MBCT Mindfulness-based cognitive therapy

MCID Minimally clinically important difference

PCFA Prostate Cancer Foundation of Australia

PHQ-9 Patient Health Questionnaire

QALY Quality of Life Years

QoL Quality of Life

RA Research assistant

RCT Randomized controlled trial

SD standard deviation

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Declarations

Author's contributions

PML, LR, LO, NH, MJ, AU, RC, DWA, EO, VW, developed the program and study design with input from all authors; EO designed the web platform and analytics with input from LR, NH, RC, BS, PML. CM designed the economic component of the study. All authors provided substantial input into the development of the protocol. PML and NH drafted the manuscript with contributions from the co-authors. Each of the authors contributed to, read and approved, the final manuscript.

Each of the co-authors is on the steering committee, and will oversee implementation of the study and data collection.

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Competing interests

The authors declare they have no competing interests.

Figure Legend/Caption:

Figure 1. Study flowchart

FCRI (Fear of Cancer Recurrence Inventory); GAD-7 (General Anxiety and Distress scale; PHQ-9 (Patient Health Questionnaire); CAMS-R (Cognitive and Affective Mindfulness Scale – Revised); AQoL-4D (Assessment of Quality of Life – 4 Dimensions)

Figure 2. My Goal functionality in MindOnLine

718 Figure 3. My Journal guided self-reflection practise in MindOnLine.

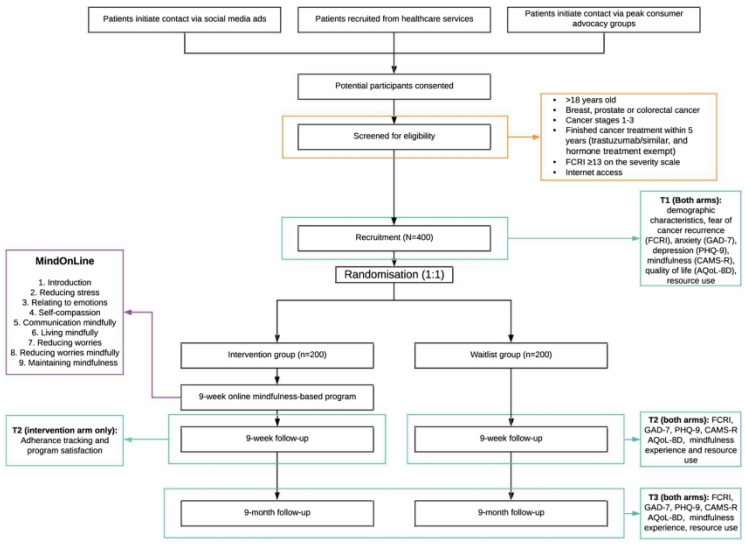

Figure 1. Study flowchart.

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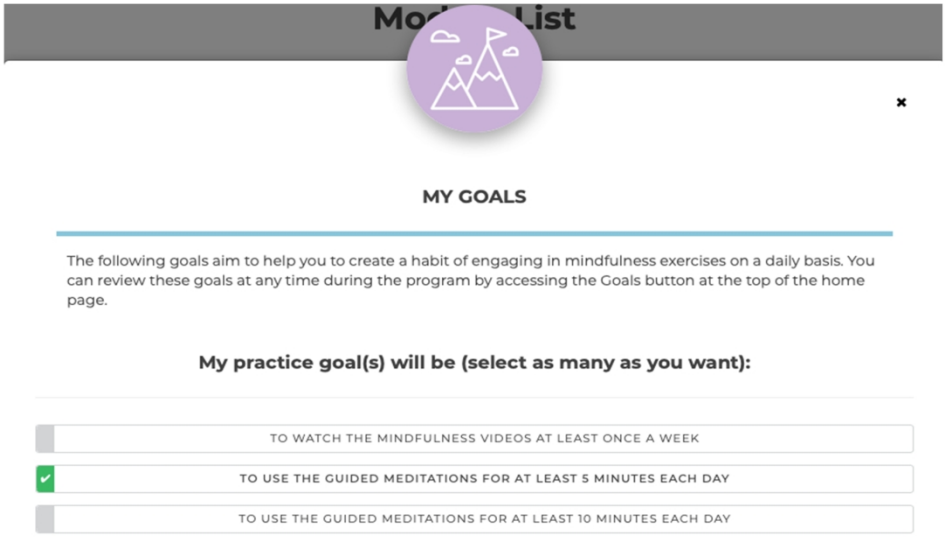

Figure 2. My goal functionality in MondOnLine.

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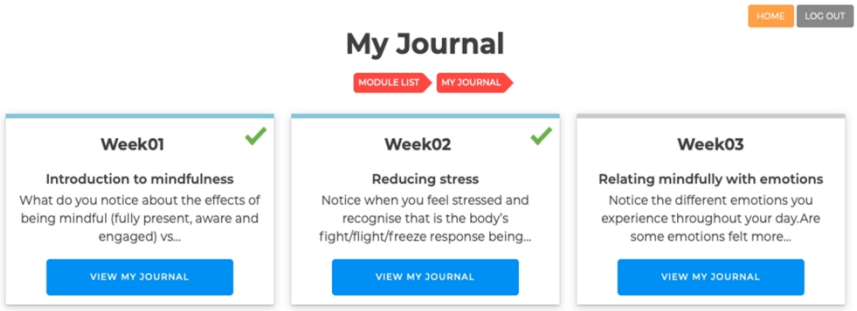

Figure 3. My journal guided self-reflection practice in MindOnLine.

308x99mm (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	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	23
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	1
	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	23
	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)	23

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	3-5
	6b	Explanation for choice of comparators	6
Objectives	7	Specific objectives or hypotheses	5-6
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)	6
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	6, 8
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)	8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11-14
	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)	n/a
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12-13, 16
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	16
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	15-17
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)	14

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	19
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
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	10
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	10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10
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	14
	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	14

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	21
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	19
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	19
	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)	19
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	21
	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	21
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	21
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	21
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	24
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)	21

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	n/a
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	21
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	24
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	21
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	21
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	21
	31b	Authorship eligibility guidelines and any intended use of professional writers	21
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	21
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	attached
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	n/a

*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

Efficacy and cost-effectiveness of an online mindfulness program (MindOnLine) to reduce fear of recurrence among people with cancer: study protocol for a randomized controlled trial

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Primary Subject Heading:	Oncology
Secondary Subject Heading:	Communication, Mental health, Public health
Keywords:	ONCOLOGY, Health economics < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, World Wide Web technology < BIOTECHNOLOGY & BIOINFORMATICS

Title

Efficacy and cost-effectiveness of an online mindfulness program (MindOnLine) to reduce fear of recurrence among people with cancer: study protocol for a randomized controlled trial

Authors

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Abstract

Introduction: Fear of cancer recurrence (FCR) is a common condition among cancer survivors that can lead to significant levels of distress, anxiety and depression. Online mindfulness programs may provide the mechanism to support cancer survivors manage FCR and distress, and improve people's wellbeing over the short, medium and long term. The primary aim of this study is to determine the potential efficacy of MindOnLine, a 9 session mindfulness-based program for survivors of breast, prostate and colorectal cancer. A formal economic program will also be conducted.

Methods and analysis: A single-blind randomized controlled trial to determine the efficacy and cost-efficacy of a MindOnLine program for cancer survivors. A total of 400 people living with cancer will be recruited via online advertisements on social media platforms, peak consumer advocacy groups, or through outpatient services at healthcare providers across Victoria Australia. People will be randomly allocated to either the MindOnLine program (n=200) or waitlist control (n=200). Participant assessments will occur at baseline, at 9 weeks and 9-month follow up. The primary outcome is change in Fear of Recurrence Index Score total score between baseline and 9 weeks; secondary outcomes are changes in depression and anxiety, quality of life and mindfulness. The economic analysis comprises a cost-consequences analysis where all outcomes will be compared to costs.

Ethics and dissemination: Ethics approval was obtained from the Peter MacCallum Cancer Centre (20-53) and Deakin University (2020-284). All participants will be required to provide written informed consent. Findings will be disseminated in peer reviewed journals and among key stakeholder organisations including hospitals, cancer and community organisations and Government. If successful the project will be rolled out nationally with a formal implementation plan.

Australian New Zealand Clinical Trials Registry: 12620000645954. Registered 06 June 2020, https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=379520&isReview=true

Keywords: mindfulness, cancer, fear of cancer recurrence, online; economics of cancer; supportive care; web-based platforms

Article Summary

Strengths and limitations of this study

Strengths

- This study will employ a single-blind randomized controlled trial to determine the efficacy and cost-efficacy of MindOnLine.
- Advances in social platforms, smartphone technology and web-based programming can change substantially in a short period and while this may affect the actual online platform used measures are in place to maintain the same intervention during the study period, so we do not consider this will influence the program content or delivery mechanisms.
- Involvement of consumer advocacy groups to support recruitment, interpretation of results, dissemination and translation
- Incorporating an economic evaluation into the study design will complement clinical findings and support decision-making processes for potential scaling

Limitations

- Recruitment primarily through social media platforms means we cannot accurately assess reach of the intervention, as we will not be able to identify the number of eligible people exposed to our advertisements
- Participants will need access to the internet which will result in some people unable to take part in the study.

Introduction

Over one million Australians are cancer survivors, and this population is expected to grow substantially due to an ageing population and improved community-based screening programs and treatments.[1] A cancer diagnosis can cause people to confront their own mortality, often for the first time,[2] so it may be unsurprising that three quarters of cancer survivors experience fear of cancer recurrence (FCR) and 49% report moderate to high levels of fear,[3] as well as high levels of clinical depression [3] and anxiety.[4]

FCR is a highly prevalent and persistent condition that can result in significant levels of anxiety and depression across the disease trajectory.[5] It is imperative to address this issue and our recent work into early psychosocial support indicates it may be possible to significantly reduce FCR through an online mindfulness program.[6] Mindfulness is a state of mind in which one pays attention to the present experience in a nonjudgmental, curious, and accepting way. Some studies have shown mindfulness is associated with improved mental health outcomes and management of the emotional consequences of cancer, [7, 8] while other have found no effect.[9]

Mindfulness-based interventions consist of regular informal and formal mindfulness meditation practices and are supported by educational principles that are person and relationship-centred.[10] Research into the use of mindfulness has mostly evaluated face-to-face programs which are time-intensive, of limited accessibility and costly.[11] Online mindfulness programs represent a potentially cost-effective mechanism to help people with physical health conditions.[12] For cancer survivors, there is evidence that online mindfulness programs may help manage FCR and distress, and improve mental wellbeing over the short, medium and long term.[2]

There is also some evidence that online mindfulness-based cognitive therapy (MBCT) can improve psychological outcomes. A recent study compared an online program to face-to-face MBCT which showed improved outcomes [13], however,the sample comprised of mainly breast cancer survivors and it is unclear whether the program would asist with other cancer types[13]. Although this intervention was found to be as effective as a face-to-face MBCT in reducing psychological distress and FCR in cancer patients, [13], there is a lack of robust evidence assessing the effectiveness of a general online mindfulness program for cancer survivors, limiting capacity for implementation and dissemination.[14, 15]

The aim of this study is to conduct a randomised controlled trial of *MindOnLine,* an online 9 session mindfulness-based intervention, for survivors of breast, prostate and colorectal cancer, the most common solid tumours among men and women in Australia, [1] to determine the effectiveness and cost-effectiveness of the program.

Preliminary work

To inform the development of *MindOnLine*, we undertook a systematic review of methodologies for internet based mindfulness interventions.[16] This review showed a dearth of studies with long-term follow up periods. Our team also conducted an exploratory study on the knowledge of, attitudes toward and behaviours regarding meditation among patients with melanoma.[17] Our study of 291 cancer survivors recruited at a single tertiary cancer hospital found that a key barrier to engaging with meditation was a lack of knowledge about its practice. Findings also indicated interest in an online meditation-based intervention once informed about possible benefits of meditation for people with cancer. Those interested in an online meditation-based program reported higher perceived stress, indicating a need for such a program.

MindOnline was initially developed as a 6-week online mindfulness-base intervention and follows the Framework for mindfulness-based program described by Crane and colleagues. [10] The program promoted awareness and acceptance of thoughts and emotions, and empowered participants to address their distressing thoughts and emotions in more adaptive ways. Through this action, participants learn to manage anxious and depressive moods. These moods are triggered by unhelpful and intrusive thoughts, which are strongly associated with moderate to high levels of fear of cancer recurrence. [18] A pilot study was conducted to assess the potential impact of a 6-week mindfulness program and explore whether the intervention impacted on FCR, worry, and perceived stress compared to usual care. Details of the pilot study are published elsewhere.[6]Briefly, 69 melanoma survivors agreed to participate, and 46 participants were randomised into the intervention group (2:1). Scores on all FCR Inventory (FCRI) subscales reduced in the intervention group, with the severity subscale decreasing significantly compared to the control group (-2.6, 95% CI=(-4.4, -0.7); p=0.008) after 6 weeks. The total FCRI score also showed a decrease albeit non-significant (−6.2, 95% CI=(−13.12, 0.68), p=0.07). Previous studies have indicated that a 4.1 point decrease on the severity scale is a clinically important change. [19]

Based on participant feedback from the pilot study [6] regarding the benefits of mindfulness practice and the suggestion of a maintenance period to enhance sustainability of the effects, *MindOnLine* was expanded to a 9-week program with the last 3 weeks revisiting concepts already explored in the program and supporting regular practice. The structure of MindOnLine reflects the Mindfulness Based Stress Reduction (MBSR) approach by incorporating characteristics typical of mindfulness-based programs, namely educational component, and formal and informal mindfulness practices. Keeping in line with Crane et al's., [10] Framework for adaptation of mindfulness-based programs, MindOnLine adapted the delivery of the program to an online version to facilitate access and convenience of use.

Methods and analysis

Aims and Hypotheses

The aims of this study are to determine the effect of *MindOnLine* on FCR, anxiety and depression in cancer survivors. The specific aims are:

Aim 1: To evaluate the impact of the *MindOnLine* intervention on the primary outcome (FCR), measured using the FCRI total score [20] at the end of the 9-week intervention period. *HYPOTHESIS 1:* Participants receiving the intervention will report lower average FCRI total scores at 9 weeks, compared to the waitlist group.

Aim 2: To evaluate the impact of *MindOnLine* on secondary outcomes at nine weeks: 1) Anxiety and Depression, using the Patient Health Questionnaire (PHQ-9)[21]and Generalised Anxiety Disorder (GAD-7) Scale;[22]2) Quality of Life (QoL) measured by AQOL-4D;[23]and 3) Mindfulness, using Cognitive and Affective Mindfulness Scale-Revised (CAMS-R).[24]*HYPOTHESIS 2*: Compared to the waitlist group, participants in the intervention group will report improvement in all of the secondary outcomes at nine weeks.

Aim 3: To assess To assess if the effect of the intervention on the primary and secondary outcomes, relative to usual care, are sustained at the nine-month follow-up. are sustained at the nine-month follow-up. *HYPOTHESIS 3*: Compared to the waitlist group, participants in the intervention group will report sustained improvement in primary and secondary outcomes at nine months.

Aim 4: To assess, from a health sector and broader societal perspective, the cost-effectiveness of *MindOnLine. HYPOTHESIS 4*: Compared to the waitlist group, *MindOnLine* will be cost-effective with an incremental cost-effectiveness ratio likely to fall below the commonly used threshold of $28,000 - $50,000/Quality of Life Year (QALY).

Study Design

This study is a randomised controlled trial, to test the effectiveness and cost-effectiveness of MindOnLine compared to usual care on FCR, anxiety, depression and QoL among people diagnosed with breast, prostate or colorectal cancer. Overall, 400 patients will be recruited with 200 patients randomly allocated to the intervention group and 200 to the waitlist group (usual care only). The intervention group will receive usual care and the online mindfulness program. Primary and secondary outcomes will be collected at baseline, nine weeks and nine months post randomisation. Nine months corresponds to approximately six months following the end of the intervention period. Following completion of the study (9 months), participants in the waitlist group will be offered the *MindOnLine* intervention (Figure 1).

Participants

People with a diagnosis of breast, prostate or colorectal cancer will be recruited via online advertisements on social media platforms, peak consumer advocacy groups for each cancer Breast Cancer Network Australia (BCNA), or Prostate Cancer Foundation Australia (PCFA), Bowel Cancer Australia social media platforms and colorectal cancer support groups, or through outpatient services at healthcare providers across Victoria, see Figure 1.

Figure 1. Study flowchart

(Insert Figue 1 here)

FCRI (Fear of Cancer Recurrence Inventory); GAD-7 (General Anxiety and Distress scale; PHQ-9 (Patient Health Questionnaire); CAMS-R (Cognitive and Affective Mindfulness Scale – Revised); AQoL-4D (Assessment of Quality of Life – 4 Dimensions)

Inclusion criteria

Adults, aged 18 year of older, living in Australia, who completed active treatment for Stage 1-3 breast, prostate or colorectal cancer (CRC), (trastuzumab/similar, and hormone treatment exempt) within the past 5 years and have no evidence of disease; have internet access and a FCRI severity score ≥13, indicating clinically significant FCR.[19] Our pilot study showed 74% of participants with melanoma were identified as having clinically significant FCR. [6]

Exclusion criteria

Insufficient English language skills to understand videos presented in English, complete surveys in English or living with advanced cancer (Stage IV disease with less than a 12 month prognosis of survival).

Recruitment procedures

Multiple methods will be applied to recruit people to the study:

1) online through *MindOnLine* social media pages including Facebook, Instagram, Twitter, Reddit and LinkedIn

2) sharing recruitment flyers through BCNA and PCFA social media platforms, and Australian based cancer groups

3) email invitations sent to BCNA and PCFA supporters (and colorectal cancer support groups) and cancer registries

4) paid Facebook and Instagram advertising

5) through outpatient clinics, chemotherapy and radiotherapy units and rooms of oncologists and surgeons at cancer treatment centres.

Online recruitment procedure

1) The *MindOnLine* social media pages will be shared among social networks and will allow people to post questions about the project. 2) A recruitment flyer will be distributed by BCNA,

PCFA, Bowel Cancer Australia and colorectal cancer Facebook support groups using their existing social media platforms. 3) Study invitations will be sent to supporters registered with BCNA and PCFA who have indicated an interest in learning about research projects. 4) Paid advertisements will run throughout the recruitment period on Facebook, Instagram and Twitter to distribute the project details to a wider audience. The use of paid advertisements in health research is becoming popular and a systematic review has shown this to be an effective recruitment strategy.[25]

In all online recruitment methods, people will have access to the recruitment flyer, which will provide a brief overview of the study, the link to the *MindOnLine* registration page and the contact number of the project manager.

Health service recruitment procedures

If recruitment across social media platforms, advertisements and peak consumer advocacy groups does not generate sufficient participation levels, participating health services oncologists or surgeons involved in the project, will support the recruitment process. The research assistant (RA) at each site will screen patients and confirm eligibility of patients with treating clinicians or with nurses working in the outpatient units. RAs will then contact patients by phone and interested patients will be emailed the study details with a link to the study webpage and registration page). If there is no response from patients, a message will be left on their phone. Two further attempts to reach patients will be made (a week apart), and after a third unsuccessful attempt no further contact will be made. If patients have not enrolled in the study within two weeks, one follow-up phone call will be made to answer any queries patients may have about the study and to assist with registration. We have used similar screening and recruitment approaches in previous studies and they were found to be acceptable and successful.[6]We anticipate a recruitment period of 18-months.

Consent and screening

Once directed to the *MindOnLine* registration page, participants will be presented with the plain language statement and then asked to provide consent (Supplementary file 1). Potential participants will be asked to provide basic demographic and disease information allowing screening to ensure they meet study eligibility criteria. Potential participants will also complete the severity subscale of the FCRI to allow those with scores ≥13 to be screening into the study. Those screened into the study will provide their email address and contact number, and directed to the baseline questionnaires. People who are not eligible will receive an online message thanking them for their interest in the study and referring them to local support services provided by leading cancer charities should they require support.

Randomisation

Eligible participants will be allocated to treatment groups using random sequences embedded in the online survey platform Qualtrics, ensuring allocation concealment. Randomisation (using stratified random permuted blocks) will be conducted in blocks of size 2, stratified by cancer type (breast, prostate, CRC) and age (<60; ≥60 years old). Participants will be unblinded to group assignment, while researchers and data analysts will be blinded to the group condition.

Waitlist Control group

Participants allocated to the waitlist group will receive usual care. Following randomisation, they will receive an email with a list of services they may contact for information and support. They will be informed that they will be granted access to *MindOnLine* intervention in 9-month's time, when intervention participants have completed the final survey.

Intervention group – MindOnLine program

Participants allocated to the intervention will be provided with the link to *MindOnLine,* which comprises three main components:

(1) an educational component to increase participants' knowledge about the science and practice of mindfulness and how it may benefit them in everyday life;

(2) a formal mindfulness meditation practice to improve awareness and emotion regulation; and

(3) an informal practice to teach participants how to bring mindfulness to daily activities.

A new theme is introduced each week, with a new meditation practice which participants will be encouraged to undertake every day *The MindOnLine* program is detailed in Table 1.

Table 1- Weekly content of the *MindOnLine* Program

Week	Theme	Meditation	Daily practice
1	Introduction to mindfulness	Breath	Being present with the experience
2	Reducing stress	Body Scan	Notice how the body responds to stress
3	Relating to emotions	Working mindfully with emotions	Noticing the cycle of emotions
4	Self-compassion	Self-compassion	Notice self-criticism
5	Communicating mindfully	Listening/ Sound meditations	Bringing attention back to the conversation
6	Living mindfully	Practising with gentleness and patience	Pause throughout the day
7	Reducing worries	Mindfully working with worries and fears	Notice when caught up overthinking

8	Reducing worries mindfully	Loving Kindness meditation	Notice acts of kindness
9	Maintaining mindfulness	Silence with bells	Notice when distracted from being present

Each module's theme will be explained through a short 5-10 minute video. At the end of each week, participants will receive an email with a link to the video introducing the theme for the upcoming week. The transcripts for the videos will be available for downloading and saving or printing in a pdf format so that participants can keep a copy for later reference. At the end of each module, participants will receive an automatically generated email reminding them to continue daily meditation practice (formal practice) and given specific everyday mindfulness exercises to apply during daily activities (informal practice).

To enhance adherence and retention to the 9-week program and deepen their mindfulness experience, participants will have access to additional program features. The features are guided by a framework proposed by Abraham and Michie [26] to facilitate behaviour change in interventions:

1) Twice daily reminders to complete mindfulness practice. Adapted from the pilot study, emails containing a link to a short, guided meditation audio file will be sent to participants twice daily. These emails will serve as reminders to meditate and will provide easy access to the meditation practice of the week.
2) Progress tracking. Participants will be able to monitor their own mindfulness practice each day by reviewing how many times they have used each section of the program, and the duration of use. Embedded usage data tracking systems records each login and provides real time representation of program use.

3) Goal setting. When enrolled in the program, participants will have the opportunity to set goals for their mindfulness practice (Figure 2). Goals are linked to usage data tracking to provide participants with feedback about whether they are reaching their goals. Goals may be practice orientated e.g. to practise mindfulness for five minutes each day, or may be specific to each person's situation e.g. I would like to manage my worries leading up to my oncologist appointment.

4) Reflective journaling. Participants will have the opportunity to journal their experiences during the mindfulness program by using the "My Journal" functionality (Figure 3). Each week's content will have a journal section, which will include prompts related to mindfulness program content, participants will be able to enter and save their responses within the program for future review. Prompts will be developed specifically for the study.

The mindfulness program can be accessed at any time via direct login to the website or via the hyperlink sent to participants in the daily e-mails.

Figure 2. My Goal functionality in MindOnLine

(Insert Figure 2 here)

Figure 3. My Journal guided self-reflection practise in MindOnLine

(Insert Figure 3 here)

Data collection

Table 2 illustrates the overall schedule for trial participants in both groups. All assessments will be performed online. The questionnaires at baseline, at nine weeks including the

satisfaction survey for those in the intervention group and at nine months, will be sent via Qualtrics through an automatically generated schedule. Participants who do not complete questionnaires will be followed up by telephone at each data collection point. At baseline, participants' demographic information (i.e., gender, age, marital status, current employment status, highest level of education, postcode, type of cancer, date of diagnosis, time since end of last treatment, type of treatment and previous meditation experience) will be collected.

Table 2. Schedule of enrolment, interventions, and assessments

	STUDY PERIOD										
	Enrolment	Allocation	Post-allocation								Post-Intervention
TIMEPOINT			*Week 1*	*Week 2*	*Week 3*	*Week 4*	*Week 5*	*Week 6*	*Week 7*	*Week 8*	*Week 9*	*9-months*
ENROLMENT:											
Eligibility screen	X										
Informed consent	X										
Allocation		X									
INTERVENTIONS:											
Immediate access to MindOnLine			←	—	—	—	—	—	—	—	→
Waitlist group											
ASSESSMENTS (Both groups):											
Demographic characteristics	X										
FCRI [18]	X									X	X
GAD-7 [20]	X									X	X
PHQ-9 [19]	X									X	X
CAMS-R [22]	X									X	X
AQoL-4D [21]	X									X	X
Mindfulness experience	X									X	X
Resource use	X									X	X

COVID-19 measures	X									X	X
ASSESSMENTS (Intervention group only):											
Adherence tracking and meditation log			X	X	X	X	X	X	X	X	X	X
Program satisfaction										X	X

Outcome measures

Primary outcome

Fear of Cancer Recurrence Inventory (FCRI)

The 42-item Fear of Cancer Recurrence Inventory (FCRI) is a multidimensional FCR scale intended for use with all cancer patients. Items were developed on the basis of a cognitive–behavioural formulation of FCR (range:0-168).[19] The FCRI consists of seven domains: triggers, severity, psychological distress, functional impairment, reassurance, insight and coping strategies (scoring range:0-36). It has shown high internal consistency, good construct and criterion validity in adults with different cancer types.[20]

Secondary outcomes:

Anxiety and Depression

The *Generalized Anxiety Disorder-7 scale (GAD-7*) [22]is a valid and efficient tool for assessing generalised anxiety symptoms and assessing severity in clinical practice and research. The seven items assess the frequency of core symptoms of generalised anxiety disorder within the past 2 weeks (scoring range:0-21).[22]

The *Patient Health Questionnaire-9 (PHQ-9)*[20] parallels the nine diagnostic symptom criteria that define DSM-IV major depressive disorder. At only 9 items (scoring range:0-27), the PHQ-9 is shorter than most depression tools. Unlike most other measures of depression, the PHQ-9 was developed, tested and refined for use with medical patients.[21]

The PHQ-9 and GAD-7 are recommended for use among cancer survivors in the American Society of Clinical Oncology Guidelines. [27]

Mindfulness

Trait mindfulness is measured using the Cognitive and Affective Mindfulness Scale-Revised (CAMS-R), [24] a 10-item self-report questionnaire. This scale uses everyday language appropriate for those with little meditation experience and is designed to capture mindfulness as a general daily experience. The questionnaire comprises four domains of mindfulness (attention, present-focus, awareness, and acceptance/non-judgment). Participants are asked to rate on a four-point Likert scale how much they relate to each statement (scoring range:4-40). Compared to other measures of mindfulness, the CAMS-R is unique in that it is related to psychological distress, [28] which is highly relevant to the current study population.[29]

Other outcome measures

Mindfulness experience

In order to control for access to external mindfulness-based programs particularly in the waitlist group, all participants will be asked whether they have enrolled in a mindfulness-based program in the period between surveys and/or used other supportive care services (e.g. peer support, psychologists, psychotherapy, counsellors, yoga and meditation).

Program satisfaction

Participants in the intervention group will be asked to provide feedback about the *MindOnLine* program. Quantitative and qualitative data using open ended questions will be collected in relation to satisfaction with program content, the helpfulness of the program, usability, and areas for improvement. The satisfaction questionnaire has been adapted from the satisfaction questionnaire used in the pilot study.[6]

Economic outcomes

Assessment of Quality of Life (*AQoL 4D*) [23]is a health-related quality of life utility measure. It is generally used in economic evaluations. The *Resource Use Questionnaire* covers general health care services usage (self-reported), use of other welfare services, and impacts on work force participation. The questionnaire has been successfully used in cancer psychosocial intervention studies. [30]

The surveys will take approximately 20 minutes to complete.

Adherence tracking and meditation log

The software package used to run *MindOnLine* was developed at Deakin University and has inbuilt functionality to collect and clean usage data. Google Analytics has been incorporated into the platform to allow for validation of findings. Both software will track participants' online activity, including login date/times, navigation patterns, page views and duration, and features used (video, audio, goals and reflective journaling).

Impact of COVID-19

To control for potential environmental impacts on mental wellbeing outcomes, participants will be asked whether COVID-19 has had an impact on their mental wellbeing in the two weeks prior to baseline, 9-weeks and 9-month assessments.

Sample size calculations

Power calculations are conservative, i.e. the detectable differences reported below are possibly larger than the true detectable differences, because they are based on two-group comparison of change while the main analysis (see Analysis Plan) will adjust for baseline values of the outcome and for factors used in the stratified randomisation.[31]The statistical software PASS version 14.0.9 (NCSS, LLC) was used for all calculations (α=0.05; two-sided tests).

Primary outcome

Change in FCRI total score between baseline and 9 weeks. The target sample size (200 participants per arm) achieves 94% (80%) power to detect a mean difference between arms of 10 points (8 points) change in FCRI score or 80% power to detect a difference of 8 points [standard deviation (SD): 23.5;[32])SD estimate obtained from Butow et al., [32]as their study included a heterogenous sample of cancer patients while our pilot study only included patients with melanoma Stage 2-3. The selected effect sizes correspond to Cohen's d of 0.43 (moderate/large) and 0.34 (small/moderate) respectively. Currently, there is no definition of a clinically significant improvement for FCRI score, however, the proposed effect size is comparable to that described in other studies.[32]

Secondary outcomes

The target sample size (200 participants per arm) achieves 80% power to detect an intervention effect of size 0.34 (Cohen's f, small/moderate) at 9 weeks for any of the outcomes. This effect size corresponds to mean differences between groups of: a) 1.5 point in PHQ-9 depression score (SD = 4.5, maximum SD reported in patients with breast, colorectal and prostate cancer;[33] PHQ-9 minimal clinically important difference (MCID) for cancer patients: 2.6 to 5);[34] b) 1.4 point in GAD-7 anxiety score (SD=4.1, maximum SD reported in patients with breast, colorectal and prostate cancer;[35] MCID=1.95);[33] and mean differences between group in change from baseline to 9 weeks of: c) 1.2 points in FCRI severity score (SD=3.6, pilot study effect: 2.6);[6] d) 1.1 points in CAMS-R score (SD=3.4); e) 2.5 points in Worry score [SD=7.3]; f) 3.0 points in PSS score [SD=8.9]; the last 3 reflecting moderate Cohen's *d* effect sizes (<0.35).

To meet the sample size needs of our desired statistical power, we will recruit 400 participants. In our pilot study, six participants (13%) withdrew in the intervention group and none in the control group. Assuming a conservative 30% attrition rate at nine months, we expect to have complete data for approximately 280 participants (140 per group).

Analysis plan

All statistical analysis will be conducted on an intention-to-treat basis whereby all randomised participants with at least one post-baseline measurement will be analysed by original treatment assignment regardless of adherence. Baseline characteristics will be described using summary measures selected based on variable distribution. The main analysis will adjust for baseline values of the outcome and for factors used in the stratified randomisation.[31]

Aims 1 and 2. The effect of the intervention on each of the outcomes, defined as change from baseline to nine weeks, will be assessed using linear models including group and the stratification factors. *Aim 3.* The effect of the intervention across the three measurement times will be estimated using linear mixed models, including study group, time (categorical: 9 weeks, 9 months) interaction group×time and the stratification factors as fixed effects and participant as a random effect. If there is a positive intervention effect on mental health outcomes, exploratory mediation analyses will be conducted to determine whether improvements are mediated by increases in mindfulness.[36] For outcomes where it is a plausible assumption that missing data are completely at random, we will use complete case analysis; if not plausible, we will use multiple imputation. *Subgroup analysis*: We will explore whether age or gender modify the effect of the intervention on FCR, depression and anxiety at 9 weeks.

Aim 4. This study will also comprise a cost-consequences analysis where incremental costs of the intervention will be compared with the full spectrum of outcomes included in the study. A series of cost-effectiveness ratios can be determined which have been shown to be useful for decision-makers. Inclusion of the AQoL 4D will also enable a cost-utility analysis to be undertaken, thereby allowing practical judgements to be made regarding value for money credentials of the intervention. Nevertheless, the economic analysis will be primarily from the perspective of the health care sector and a secondary analysis from the broader societal perspective will also be undertaken. A detailed costing of the intervention will be undertaken and the evaluation will first measure and value any change to the use of health care resources over the period of the study between the two arms of the trial and then compare any additional costs to the additional outcomes achieved. Standardised economic evaluation techniques will be used including incremental analysis of mean differences and bootstrapping to determine confidence intervals along with a net monetary analysis to determine the cost-effectiveness of the intervention for different value for money threshold criteria. The costs of routine roll-out will be estimated.

MindOnLine usage data by the intervention group will be reported using descriptive statistics. Linear mixed models, with random intercept and slope for each person, will be fitted to estimate time trends in usage.

Data management

Data will be exported from Qualtrics on a monthly basis and crossed checked during exportation to ensure accuracy in results. All identifying participant information will be removed from data sets. Documents containing sensitive information will be saved as password protected files and stored within the Deakin University One Drive.

Monitoring

Data

The adherence data will be monitored by the program developer. The program developer does not have any competing interests. Other project data will be monitored by the project steering committee with regular meetings and progress updates. No interim analysis will be performed during the trial.

Patient and Public Involvement

Representatives from three consumer organisations have been involved in the design and implementation of the project since its inception. Their contribution has included development of the intervention and its content, wording on recruitment material, and provided advice on recruitment strategies. Representatives from each consumer organisation has contributed to project steering meetings.

Ethics and Dissemination

Harms

All participants will be required to provide written informed consent. In the event that a participant reports distress to the project manager they will be advised to seek assistance from the regular medical professionals and provided with additional referrals to lifeline.org.au. Ethics approval was obtained from the Peter MacCallum Cancer Centre (20-53) and Deakin University (2020-284). Any adverse events will be reported to the ethics committees.

Auditing

The trial may be audited by the governing Human Research Ethics Committees.

Protocol amendments

Protocol amendments will be approved by the governing Human Research Ethics Committees. Any relevant changes will be submitted as a modification to the Australian and New Zealand Clinical Trial Registry.

Dissemination

The findings of this study will be written by study authors and published in peer reviewed journals project steering committee. All identifying participant information will be removed prior to publication.

Discussion

One of the most significant changes across society is the use of web-based technology. Online mindfulness-based interventions circumvent problems with traditional face-to-face delivery of the program, impacted by work commitments, caring responsibilities, geographic isolation and pandemics[37, 38].

This study will rigorously evaluate the efficacy of a self-directed online mindfulness program in reducing FCR in breast, prostate and CRC survivors. The study will advance the literature regarding the benefits of mindfulness for cancer survivors by representing one of few large well controlled trials of a self-directed mindfulness-based program, involving smartphone technology, aimed at reducing FCR. Including a health economic evaluation of the program adds to the utility of the trial with the study providing information that budget holders and policy makers need when considering recommendations and support for supportive care programs. This trial will fill a gap in knowledge regarding the potential impact of an online mindfulness program in supporting cancer survivors.[7] Extensive pilot work in identifying the type of program cancer survivors are interested in, involving consumers in designing the content and length of the program and providing reminders and practice tips increase the likelihood of participants engaging with the program and the intervention having a positive impact.

The study is being conducted in partnership with health services and cancer advocacy groups. As partners in the study, they will ensure the intervention can be rolled out to cancer survivors if shown to be effective. In addition to consumer advocacy groups, the study is being conducted in partnership with government. As we expect the *MindOnLine* intervention to improve health outcomes, reduce the fear and distress in cancer survivorship and reduce health service and community costs our partnership with government will ensure that policy makers are informed of the study's findings particularly cost-effectiveness findings.

The study has a number of strengths and weaknesses. Development of the intervention through a review of the literature, input from consumers and findings from a pilot study and involvement of consumer advocacy groups and government are study strengths ensuring translation of the program into practice if shown to be effective. For example, consumer advocacy groups have contributed to the design of the intervention program, recruitment of eligible patients, and will provide advice on the interpretation of results, dissemination and translation. Incorporating an economic evaluation into the study design is a strength as it will complement clinical findings and support decision-making processes for potential implementation.

However, several methodological limitations also need to be acknowledged. Recruitment through social media platforms means we cannot accurately assess uptake of the intervention, as we will not be able to identify the number of eligible people exposed to our advertisements. This may limit our ability to determine reach of the program. However, recording the time taken for recruitment and accessing google analytic data on internet traffic and page visits may provide some information in this area. Participants will need access to the internet to participate. While this may mean some people will be excluded from the study, we believe this

will have minimal impact on the study. We envisage that the study will take approximately 4 years to complete. Advances in social platforms, technology and app-based programming can change substantially in a short period. While this may affect the actual online platform used for the program, we do not consider this will influence the program content or delivery mechanisms. As technology advances will likely increase interest in self-directed support programs for cancer survivors, it is essential that cancer survivors access programs with demonstrated effectiveness.

Trial Registration ACTRN12620000645954

Protocol Version: Version 5, dated 18 December 2020

Recruitment commenced 12.10.2020, it is anticipated recruitment will be for a duration of 18 months finishing on 12.04.2022.

Abbreviations

AQoL-4D Assessment of Quality of Life – 4 Dimensions

BCNA Breast Cancer Network Australia

CAMSR Cognitive and Affective Mindfulness Scale-Revised

CI Confidence interval

CRC Colorectal Cancer

FCR Fear of cancer recurrence

FCRI Fear of Cancer Recurrence Inventory

GAD-7 General Anxiety Disorder scale

MBCT Mindfulness-based cognitive therapy

MCID Minimally clinically important difference

PCFA Prostate Cancer Foundation of Australia

PHQ-9 Patient Health Questionnaire

QALY Quality of Life Years

QoL Quality of Life

RA Research assistant

RCT Randomized controlled trial

SD standard deviation

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Declarations

Author's contributions

PML, LR, LO, NW, MJ, AG, DWA, EO, CM, AU, RC, J P-N, DH, MB, BR, KW, MF, ABS, KP, MS, DC and VW contributed to the conception of the program or design of the study. EO designed the web platform and analytics with input from LR, NW, RC, DWA, AW, PML. CM designed the economic component of the study. PML, LR, LO, NW, MJ, AG, DWA, EO, CM, AU, RC, J P-N, DH, MB, BR, KW, MF, ABS, KP, SS, AW, KG, MS, DC, BP and VW provided substantial input into the development of the protocol or revising it critically for important intellectual content. PML, LR, NW, LO and VW drafted the manuscript with contributions from MJ, AG, DWA, EO, CM, AU, RC, J P-N, DH, MB, BR, KW, MF, ABS, KP, SS, AW, KG, MS, DC, BP.

Each of the authors contributed to, read and approved the final manuscript.

Each of the co-authors, PML, LR, LO, NW, MJ, AG, DWA, EO, CM, AU, RC, J P-N, DH, MB, BR, KW, MF, ABS, KP, SS, AW, KG, MS, DC, BP and VW, are on the steering committee, will oversee implementation of the study and data collection and will contribute to the acquisition, analysis or interpretation of the data.

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Competing interests

The authors declare they have no competing interests.

Figure Legend/Caption:

Figure 1. Study flowchart

FCRI (Fear of Cancer Recurrence Inventory); GAD-7 (General Anxiety and Distress scale; PHQ-9 (Patient Health Questionnaire); CAMS-R (Cognitive and Affective Mindfulness Scale – Revised); AQoL-4D (Assessment of Quality of Life – 4 Dimensions)

Figure 2. My Goal functionality in MindOnLine

Figure 3. My Journal guided self-reflection practise in MindOnLine.

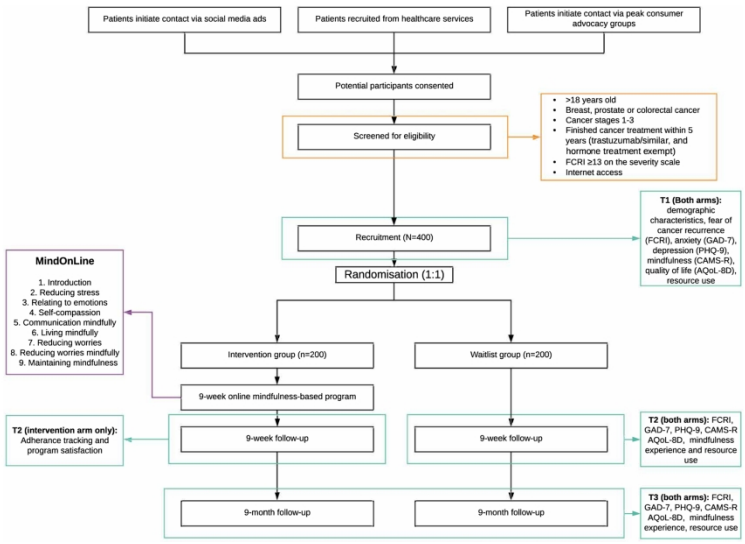

Figure 1. Study flowchart.

338x190mm (400 x 400 DPI)

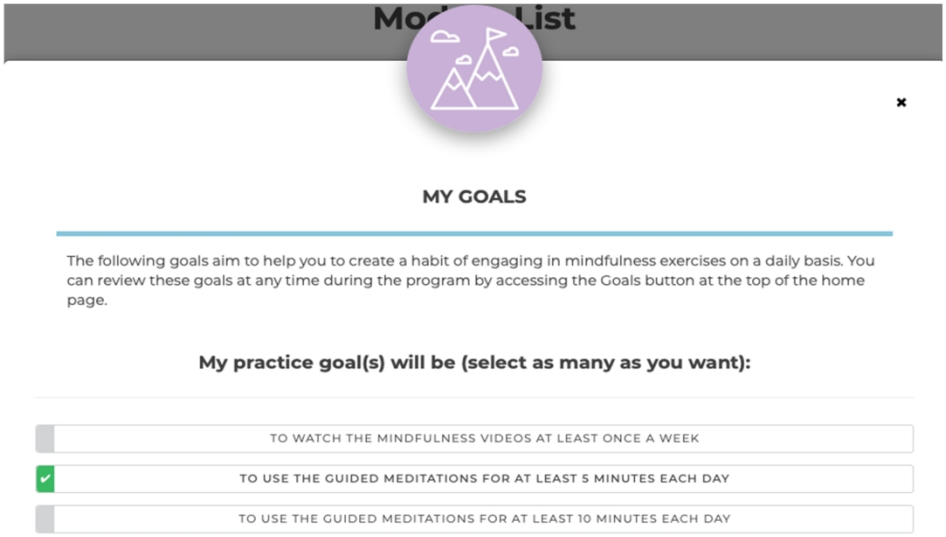

Figure 2. My goal functionality in MondOnLine.

218x120mm (400 x 400 DPI)

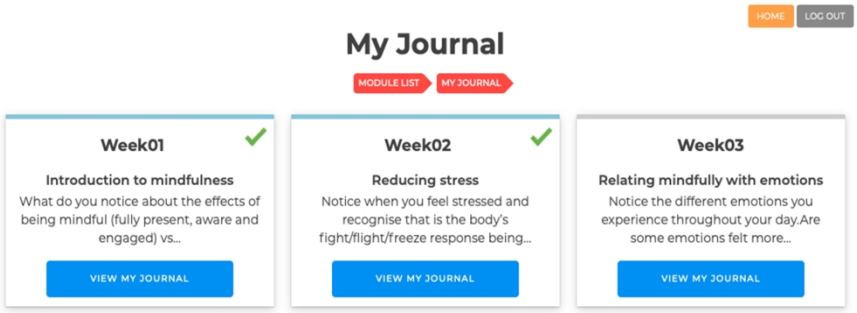

Figure 3. My journal guided self-reflection practice in MindOnLine.

308x100mm (400 x 400 DPI)

Participant Information Sheet/Consent Form

Title	MindOnLine: a mindfulness program for people with breast, bowel or prostate cancer.
Short Title	MindOnLine
Principal Investigator	Prof Trish Livingston
Location	Deakin University

Part 1 What does my participation involve?

1 Introduction

You are invited to take part in this research project, because you have received treatment for breast, prostate or bowel cancer. This research project is testing an online mindfulness-based program for people who have completed their treatment.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the procedures involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or healthcare worker.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether or not you take part.

If you decide you want to take part in the research project, you will be asked to provide consent online. By agreeing you are telling us that you:
- Understand what you have read
- Consent to take part in the research project
- Consent to have the tests and treatments that are described
- Consent to the use of your personal and health information as described.

2 What is the purpose of this research?

Following treatment for cancer, many people feel anxious and scared about the cancer coming back. This is one of the most common fears of cancer survivors, and it can affect people's ability to enjoy life

and plan for the future. In some people, this fear can decrease over time, but most people find that they worry at certain times. The mindfulness program aims to help cancer survivors to manage their fears and worries once treatment is completed.

Research has shown that mindfulness-based programs can help people cope with anxious thoughts about their cancer. The internet allows people to use the program from the comfort of their home, and at their most convenient times. We have tested an online mindfulness program for people who received treatment for melanoma, with promising results. This research is to find out whether mindfulness can help people with breast, prostate or bowel cancer.

This research is being conducted across healthcare services and cancer organisations and is led by researchers at the School of Nursing and Midwifery at Deakin University.

In this research project we will be testing a mindfulness program among people who meet the following criteria:

- People who are over 18 years of age
- People who speak English well enough to understand videos and surveys presented in English
- People who have access to a computer or device to receive the program
- People who received treatment for breast, bowel or prostate cancer
- People who finished chemotherapy, radiotherapy or surgery treatment within the last five years
- People who experience a high level of fear of cancer recurrence.

You will be asked some questions after providing consent to determine if you meet the eligibility criteria above. To measure your fear of cancer recurrence you will be asked 9 questions about how your thoughts and feelings towards cancer may impact on your everyday living.

3 What does participation involve?

To participate in this study, each participant will need to have access to a computer, a smartphone, or a similar tablet device, and internet. If you agree to take part in this project you will be allocated to either receive the mindfulness program (intervention group) or stay in your usual care (control group). We need to compare responses from people in these two groups to see if the mindfulness program provides any benefits to cancer survivors. In order to make sure the groups are the same, participants are put into one of the two groups by chance (random).

If you decide to take part in this study, you will need to provide your consent to participate by accessing the following website: https://mindonline.org.au Before providing your consent you will be asked a number of questions to make sure you are eligible for the study.

After consenting to take part in the study, you will be asked to complete a survey before being randomly allocated to the intervention or control group. The same survey will be completed again 9 weeks and 9 months later. The survey asks you questions about possible fears of the cancer coming back, how stressful and worrisome you perceive your life to be, and the type of thoughts you generally focus on. We will also collect your email address and contact number. Your email and contact number will be used to send you reminders and other information related to the study.

If you are randomised to the mindfulness program, you will receive an email informing you of your allocation group with instructions on how to access the website. Your participation will involve using the program for 9 weeks. The program is designed to help you understand and experience potential benefits of using mindfulness in your day to day life. You will be invited to:

- Watch short videos at the start of each week. The videos will introduce a new topic about mindfulness.
- Practice short meditations twice a day. We will help you create a meditation routine by emailing you a direct link to guided meditations at times you will have chosen.
- Apply mindfulness skills in your day-to-day life.

If you are assigned to the mindfulness program we will monitor how often the mindfulness program is used. This will be recorded by your study identification number, and no personal information such as your Internet Protocol (IP) address linked to your computer or device will be collected.

If you are randomised to the control group you will receive an email informing you of your allocation group and you will continue to receive your usual care from your healthcare providers. You will receive emails to ask you to complete the questionnaires at 9 weeks and 9 months. After the 9-month survey you will be able to use the mindfulness program.

We will compare the results between those in the mindfulness program and those who are not, to see if there are any differences in wellbeing between the two groups.

There are no additional costs associated with participating in this research project, nor will you be paid.

4 Other relevant information about the research project

This study will show if the mindfulness program is helpful for people with breast, prostate or colorectal cancer. If successful the program we be made open to the wider population.

For this study, approximately 400 people will be invited to participate from online and social media advertisements and from healthcare services.

5 Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part you don't have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your relationship with those treating you or involved in your follow-up care, or your relationship with Deakin University, Breast Cancer Network Australia, or Prostate Cancer Foundation of Australia.

6 What are the possible benefits of taking part?

We cannot guarantee or promise that you will receive any benefits from this research; however, possible benefits for the community may include additional support for people who have completed treatment for cancer.

7 What are the possible risks?

Some people may feel uncomfortable or upset when answering questions in this survey. If you do not wish to answer a question you may skip it and go to the next question, or you may stop immediately. In the event that you become upset or distressed as a result of your participation, the researcher can arrange for counselling or other appropriate support provided by staff who are not members of the research team. In addition, you may want to contact an external support service such as Lifeline services on 13 11 14, or www.mindhealthconnect.org.au or the Cancer Council 13 11 20 telephone service.
If you have any concerns or are unsure whether you should participate in this project, you may wish to speak to your healthcare professional about your feelings.

8 What if I withdraw from this research project?

If you decide to withdraw, please notify a member of the research team about this decision. This notice will ensure that we can remove you from our records and will mean you will not receive any notices about the project.

If you decide to withdraw from the project, we would like to keep the personal and health information about you that has been collected. This is to help us make sure that the results of the research can be measured properly. If you want to withdraw your data from the study as well, please let them know when you tell them about withdrawing from the study.

9 What happens when the research project ends?

If you wish to obtain a final copy of the research report describing the results of this study, please contact the project manager (Dr Natalie Heynsbergh on 03 9246 8225, or email n.heynsbergh@deakin.edu.au) and she will arrange for a copy to be sent to you after completion of the study in December 2022.

Part 2 How is the research project being conducted?

10 What will happen to information about me?

Any information obtained in connection with this research project that can identify you (e.g. email address) will remain confidential and will only be used for the purpose of this research project. It will only be disclosed with your permission, except as required by law.

All the information you provide will be coded so you cannot be identified by name, and only the research team will have access to the list that can link your name to your data. All identifying information will be stored in password-protected electronic files or in a locked filing cabinet in the office of the research staff, and will be disposed of as confidential waste after five years.

You will not be identified in any report or publication from this study. Information will be provided in such a way that you cannot be identified.

In accordance with relevant Australian and/or Victorian privacy and other relevant laws, you have the right to access the information collected and stored by the researchers about you. You also have the right to request that any information with which you disagree be corrected. Please contact one of the researchers named in the last section below if you would like to access your information.

11 Who is organising and funding the research?

This research project is being managed by Dr Natalie Heynsbergh at Deakin University, and is being funded by a National Health and Medical Research Council (NHMRC) grant.

12 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been

approved by the Peter MacCallum Human Research Ethics Committee (Reference number 20/53) and the Deakin University Human Research Ethics Committee.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

13 Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this project or if you have any problems which may be related to your involvement in the project, you can contact:

- The principal investigator: Prof Patricia Livingston on 03 9244 6609, or email trish.livingston@deakin.edu.au
- The project manager: Dr Natalie Heynsbergh on 03 92468225, or email: n.heynsbergh@deakin.edu.au

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Reviewing HREC name	Peter MacCallum Cancer Centre Ethics Committee
Project reference number	20/53
HREC Executive Officer	Ethics Coordinator
Telephone	03 8559 7540
Email	ethics@petermac.org

14 What do I do if I want to participate?

If you would like to participate in this study, please log on to https://mindonline.org.au, to answer the eligibility questions and provide your consent to participate.

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	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	23
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	1
	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	23
	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)	23

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	3-5
	6b	Explanation for choice of comparators	6
Objectives	7	Specific objectives or hypotheses	5-6
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)	6
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	6, 8
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)	8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11-14
	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)	n/a
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12-13, 16
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	16
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	15-17
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)	14

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	19
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
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	10
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	10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10
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	14
	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	14

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	21
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	19
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	19
	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)	19
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	21
	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	21
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	21
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	21
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	24
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)	21

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	n/a
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	21
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	24
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	21
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	21
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	21
	31b	Authorship eligibility guidelines and any intended use of professional writers	21
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	21
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	attached
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	n/a

*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.

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Efficacy and cost-effectiveness of an online mindfulness program (MindOnLine) to reduce fear of recurrence among people with cancer: study protocol for a randomized controlled trial

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Title

Efficacy and cost-effectiveness of an online mindfulness program (MindOnLine) to reduce fear of recurrence among people with cancer: study protocol for a randomized controlled trial

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Abstract

Introduction: Fear of cancer recurrence (FCR) is a common condition among cancer survivors that can lead to significant levels of distress, anxiety and depression. Online mindfulness programs may provide the mechanism to support cancer survivors manage FCR and distress, and improve people's wellbeing over the short, medium and long term. The primary aim of this study is to determine the potential efficacy of MindOnLine, a 9 session mindfulness-based program for survivors of breast, prostate and colorectal cancer. A formal economic program will also be conducted.

Methods and analysis: A single-blind randomized controlled trial to determine the efficacy and cost-efficacy of a MindOnLine program for cancer survivors. A total of 400 people living with cancer will be recruited via online advertisements on social media platforms, peak consumer advocacy groups, or through outpatient services at healthcare providers across Victoria Australia. People will be randomly allocated to either the MindOnLine program (n=200) or waitlist control (n=200). Participant assessments will occur at baseline, at 9 weeks and 9-month follow up. The primary outcome is change in Fear of Recurrence Index Score total score between baseline and 9 weeks; secondary outcomes are changes in depression and anxiety, quality of life and mindfulness. The economic analysis comprises a cost-consequences analysis where all outcomes will be compared to costs.

Ethics and dissemination: Ethics approval was obtained from the Peter MacCallum Cancer Centre (20-53) and Deakin University (2020-284). All participants will be required to provide written informed consent. Findings will be disseminated in peer reviewed journals and among key stakeholder organisations including hospitals, cancer and community organisations and Government. If successful the project will be rolled out nationally with a formal implementation plan.

Australian New Zealand Clinical Trials Registry: 12620000645954. Registered 06 June 2020, https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=379520&isReview=true

Keywords: mindfulness, cancer, fear of cancer recurrence, online; economics of cancer; supportive care; web-based platforms

Article Summary

Strengths and limitations of this study

- Strengths of our randomised controlled trial include the assessment of both the efficacy and cost-effectiveness of the MindOnLine program, and the involvement of consumer advocacy groups to support recruitment, interpretation of results, dissemination, and translation.
- Incorporating an economic evaluation into the study design will complement clinical findings and support decision-making processes for potential scaling.
- Advances in social platforms, smartphone technology and web-based programming can change substantially in a short period and, while this may affect the actual online platform used, measures are in place to maintain the same intervention during the study period, so we do not believe that this will influence the program content or delivery mechanisms.
- Recruitment primarily through social media platforms means we cannot accurately assess reach of the intervention, as we will not be able to identify the number of eligible people exposed to our advertisements.
- Participants will need access to the internet, which will result in some people unable to take part in the study.

Introduction

Over one million Australians are cancer survivors, and this population is expected to grow substantially due to an ageing population and improved community-based screening programs and treatments.[1] A cancer diagnosis can cause people to confront their own mortality, often for the first time,[2] so it may be unsurprising that three quarters of cancer survivors experience fear of cancer recurrence (FCR) and 49% report moderate to high levels of fear,[3] as well as high levels of clinical depression [3] and anxiety.[4]

FCR is a highly prevalent and persistent condition that can result in significant levels of anxiety and depression across the disease trajectory.[5] It is imperative to address this issue and our recent work into early psychosocial support indicates it may be possible to significantly reduce FCR through an online mindfulness program.[6] Mindfulness is a state of mind in which one pays attention to the present experience in a nonjudgmental, curious, and accepting way. Some studies have shown mindfulness is associated with improved mental health outcomes and management of the emotional consequences of cancer, [7, 8] while other have found no effect.[9]

Mindfulness-based interventions consist of regular informal and formal mindfulness meditation practices and are supported by educational principles that are person and relationship-centred.[10] Research into the use of mindfulness has mostly evaluated face-to-face programs which are time-intensive, of limited accessibility and costly.[11] Online mindfulness programs represent a potentially cost-effective mechanism to help people with physical health conditions.[12] For cancer survivors, there is evidence that online mindfulness programs may help manage FCR and distress, and improve mental wellbeing over the short, medium and long term.[2]

There is also some evidence that online mindfulness-based cognitive therapy (MBCT) can improve psychological outcomes. A recent study compared an online program to face-to-face MBCT which showed improved outcomes [13], however,the sample comprised of mainly breast cancer survivors and it is unclear whether the program would asist with other cancer types[13]. Although this intervention was found to be as effective as a face-to-face MBCT in reducing psychological distress and FCR in cancer patients, [13], there is a lack of robust evidence assessing the effectiveness of a general online mindfulness program for cancer survivors, limiting capacity for implementation and dissemination.[14, 15]

The aim of this study is to conduct a randomised controlled trial of *MindOnLine,* an online 9 session mindfulness-based intervention, for survivors of breast, prostate and colorectal cancer, the most common solid tumours among men and women in Australia, [1] to determine the effectiveness and cost-effectiveness of the program.

Preliminary work

To inform the development of *MindOnLine*, we undertook a systematic review of methodologies for internet based mindfulness interventions.[16] This review showed a dearth of studies with long-term follow up periods. Our team also conducted an exploratory study on the knowledge of, attitudes toward and behaviours regarding meditation among patients with melanoma.[17] Our study of 291 cancer survivors recruited at a single tertiary cancer hospital found that a key barrier to engaging with meditation was a lack of knowledge about its practice. Findings also indicated interest in an online meditation-based intervention once informed about possible benefits of meditation for people with cancer. Those interested in an online meditation-based program reported higher perceived stress, indicating a need for such a program.

MindOnline was initially developed as a 6-week online mindfulness-base intervention and follows the Framework for mindfulness-based program described by Crane and colleagues. [10] The program promoted awareness and acceptance of thoughts and emotions, and empowered participants to address their distressing thoughts and emotions in more adaptive ways. Through this action, participants learn to manage anxious and depressive moods. These moods are triggered by unhelpful and intrusive thoughts, which are strongly associated with moderate to high levels of fear of cancer recurrence. [18] A pilot study was conducted to assess the potential impact of a 6-week mindfulness program and explore whether the intervention impacted on FCR, worry, and perceived stress compared to usual care. Details of the pilot study are published elsewhere.[6]Briefly, 69 melanoma survivors agreed to participate, and 46 participants were randomised into the intervention group (2:1). Scores on all FCR Inventory (FCRI) subscales reduced in the intervention group, with the severity subscale decreasing significantly compared to the control group (-2.6, 95% CI=(-4.4, -0.7); p=0.008) after 6 weeks. The total FCRI score also showed a decrease albeit non-significant (−6.2, 95% CI=(−13.12, 0.68), p=0.07). Previous studies have indicated that a 4.1 point decrease on the severity scale is a clinically important change. [19]

Based on participant feedback from the pilot study [6] regarding the benefits of mindfulness practice and the suggestion of a maintenance period to enhance sustainability of the effects, *MindOnLine* was expanded to a 9-week program with the last 3 weeks revisiting concepts already explored in the program and supporting regular practice. The structure of MindOnLine reflects the Mindfulness Based Stress Reduction (MBSR) approach by incorporating characteristics typical of mindfulness-based programs, namely educational component, and formal and informal mindfulness practices. Keeping in line with Crane et al's., [10] Framework for adaptation of mindfulness-based programs, MindOnLine adapted the delivery of the program to an online version to facilitate access and convenience of use.

Methods and analysis

Aims and Hypotheses

The aims of this study are to determine the effect of *MindOnLine* on FCR, anxiety and depression in cancer survivors. The specific aims are:

Aim 1: To evaluate the impact of the *MindOnLine* intervention on the primary outcome (FCR), measured using the FCRI total score [20] at the end of the 9-week intervention period. *HYPOTHESIS 1:* Participants receiving the intervention will report lower average FCRI total scores at 9 weeks, compared to the waitlist group.

Aim 2: To evaluate the impact of *MindOnLine* on secondary outcomes at nine weeks: 1) Anxiety and Depression, using the Patient Health Questionnaire (PHQ-9)[21]and Generalised Anxiety Disorder (GAD-7) Scale;[22]2) Quality of Life (QoL) measured by AQOL-4D;[23]and 3) Mindfulness, using Cognitive and Affective Mindfulness Scale-Revised (CAMS-R).[24]*HYPOTHESIS 2*: Compared to the waitlist group, participants in the intervention group will report improvement in all of the secondary outcomes at nine weeks.

Aim 3: To assess To assess if the effect of the intervention on the primary and secondary outcomes, relative to usual care, are sustained at the nine-month follow-up. are sustained at the nine-month follow-up. *HYPOTHESIS 3*: Compared to the waitlist group, participants in the intervention group will report sustained improvement in primary and secondary outcomes at nine months.

Aim 4: To assess, from a health sector and broader societal perspective, the cost-effectiveness of *MindOnLine. HYPOTHESIS 4*: Compared to the waitlist group, *MindOnLine* will be cost-effective with an incremental cost-effectiveness ratio likely to fall below the commonly used threshold of $28,000 - $50,000/Quality of Life Year (QALY).

Study Design

This study is a randomised controlled trial, to test the effectiveness and cost-effectiveness of MindOnLine compared to usual care on FCR, anxiety, depression and QoL among people diagnosed with breast, prostate or colorectal cancer. Overall, 400 patients will be recruited with 200 patients randomly allocated to the intervention group and 200 to the waitlist group (usual care only). The intervention group will receive usual care and the online mindfulness program. Primary and secondary outcomes will be collected at baseline, nine weeks and nine months post randomisation. Nine months corresponds to approximately six months following the end of the intervention period. Following completion of the study (9 months), participants in the waitlist group will be offered the *MindOnLine* intervention (Figure 1).

Participants

People with a diagnosis of breast, prostate or colorectal cancer will be recruited via online advertisements on social media platforms, peak consumer advocacy groups for each cancer Breast Cancer Network Australia (BCNA), or Prostate Cancer Foundation Australia (PCFA), Bowel Cancer Australia social media platforms and colorectal cancer support groups, or through outpatient services at healthcare providers across Victoria, see Figure 1.

Figure 1. Study flowchart

(Insert Figue 1 here)

FCRI (Fear of Cancer Recurrence Inventory); GAD-7 (General Anxiety and Distress scale; PHQ-9 (Patient Health Questionnaire); CAMS-R (Cognitive and Affective Mindfulness Scale – Revised); AQoL-4D (Assessment of Quality of Life – 4 Dimensions)

Inclusion criteria

Adults, aged 18 year of older, living in Australia, who completed active treatment for Stage 1-3 breast, prostate or colorectal cancer (CRC), (trastuzumab/similar, and hormone treatment exempt) within the past 5 years and have no evidence of disease; have internet access and a FCRI severity score ≥13, indicating clinically significant FCR.[19] Our pilot study showed 74% of participants with melanoma were identified as having clinically significant FCR. [6]

Exclusion criteria

Insufficient English language skills to understand videos presented in English, complete surveys in English or living with advanced cancer (Stage IV disease with less than a 12 month prognosis of survival).

Recruitment procedures

Multiple methods will be applied to recruit people to the study:

1) online through *MindOnLine* social media pages including Facebook, Instagram, Twitter, Reddit and LinkedIn

2) sharing recruitment flyers through BCNA and PCFA social media platforms, and Australian based cancer groups

3) email invitations sent to BCNA and PCFA supporters (and colorectal cancer support groups) and cancer registries

4) paid Facebook and Instagram advertising

5) through outpatient clinics, chemotherapy and radiotherapy units and rooms of oncologists and surgeons at cancer treatment centres.

Online recruitment procedure

1) The *MindOnLine* social media pages will be shared among social networks and will allow people to post questions about the project. 2) A recruitment flyer will be distributed by BCNA,

PCFA, Bowel Cancer Australia and colorectal cancer Facebook support groups using their existing social media platforms. 3) Study invitations will be sent to supporters registered with BCNA and PCFA who have indicated an interest in learning about research projects. 4) Paid advertisements will run throughout the recruitment period on Facebook, Instagram and Twitter to distribute the project details to a wider audience. The use of paid advertisements in health research is becoming popular and a systematic review has shown this to be an effective recruitment strategy.[25]

In all online recruitment methods, people will have access to the recruitment flyer, which will provide a brief overview of the study, the link to the *MindOnLine* registration page and the contact number of the project manager.

Health service recruitment procedures

If recruitment across social media platforms, advertisements and peak consumer advocacy groups does not generate sufficient participation levels, participating health services oncologists or surgeons involved in the project, will support the recruitment process. The research assistant (RA) at each site will screen patients and confirm eligibility of patients with treating clinicians or with nurses working in the outpatient units. RAs will then contact patients by phone and interested patients will be emailed the study details with a link to the study webpage and registration page). If there is no response from patients, a message will be left on their phone. Two further attempts to reach patients will be made (a week apart), and after a third unsuccessful attempt no further contact will be made. If patients have not enrolled in the study within two weeks, one follow-up phone call will be made to answer any queries patients may have about the study and to assist with registration. We have used similar screening and recruitment approaches in previous studies and they were found to be acceptable and successful.[6]We anticipate a recruitment period of 18-months.

Consent and screening

Once directed to the *MindOnLine* registration page, participants will be presented with the plain language statement and then asked to provide consent (Supplementary file 1). Potential participants will be asked to provide basic demographic and disease information allowing screening to ensure they meet study eligibility criteria. Potential participants will also complete the severity subscale of the FCRI to allow those with scores ≥13 to be screening into the study. Those screened into the study will provide their email address and contact number, and directed to the baseline questionnaires. People who are not eligible will receive an online message thanking them for their interest in the study and referring them to local support services provided by leading cancer charities should they require support.

Randomisation

Eligible participants will be allocated to treatment groups using random sequences embedded in the online survey platform Qualtrics, ensuring allocation concealment. Randomisation (using stratified random permuted blocks) will be conducted in blocks of size 2, stratified by cancer type (breast, prostate, CRC) and age (<60; ≥60 years old). Participants will be unblinded to group assignment, while researchers and data analysts will be blinded to the group condition.

Waitlist Control group

Participants allocated to the waitlist group will receive usual care. Following randomisation, they will receive an email with a list of services they may contact for information and support. They will be informed that they will be granted access to *MindOnLine* intervention in 9-month's time, when intervention participants have completed the final survey.

Intervention group – MindOnLine program

Participants allocated to the intervention will be provided with the link to *MindOnLine,* which comprises three main components:

(1) an educational component to increase participants' knowledge about the science and practice of mindfulness and how it may benefit them in everyday life;

(2) a formal mindfulness meditation practice to improve awareness and emotion regulation; and

(3) an informal practice to teach participants how to bring mindfulness to daily activities.

A new theme is introduced each week, with a new meditation practice which participants will be encouraged to undertake every day *The MindOnLine* program is detailed in Table 1.

Table 1- Weekly content of the *MindOnLine* Program

Week	Theme	Meditation	Daily practice
1	Introduction to mindfulness	Breath	Being present with the experience
2	Reducing stress	Body Scan	Notice how the body responds to stress
3	Relating to emotions	Working mindfully with emotions	Noticing the cycle of emotions
4	Self-compassion	Self-compassion	Notice self-criticism
5	Communicating mindfully	Listening/ Sound meditations	Bringing attention back to the conversation
6	Living mindfully	Practising with gentleness and patience	Pause throughout the day
7	Reducing worries	Mindfully working with worries and fears	Notice when caught up overthinking

8	Reducing worries mindfully	Loving Kindness meditation	Notice acts of kindness
9	Maintaining mindfulness	Silence with bells	Notice when distracted from being present

Each module's theme will be explained through a short 5-10 minute video. At the end of each week, participants will receive an email with a link to the video introducing the theme for the upcoming week. The transcripts for the videos will be available for downloading and saving or printing in a pdf format so that participants can keep a copy for later reference. At the end of each module, participants will receive an automatically generated email reminding them to continue daily meditation practice (formal practice) and given specific everyday mindfulness exercises to apply during daily activities (informal practice).

To enhance adherence and retention to the 9-week program and deepen their mindfulness experience, participants will have access to additional program features. The features are guided by a framework proposed by Abraham and Michie [26] to facilitate behaviour change in interventions:

1) Twice daily reminders to complete mindfulness practice. Adapted from the pilot study, emails containing a link to a short, guided meditation audio file will be sent to participants twice daily. These emails will serve as reminders to meditate and will provide easy access to the meditation practice of the week.
2) Progress tracking. Participants will be able to monitor their own mindfulness practice each day by reviewing how many times they have used each section of the program, and the duration of use. Embedded usage data tracking systems records each login and provides real time representation of program use.

3) Goal setting. When enrolled in the program, participants will have the opportunity to set goals for their mindfulness practice (Figure 2). Goals are linked to usage data tracking to provide participants with feedback about whether they are reaching their goals. Goals may be practice orientated e.g. to practise mindfulness for five minutes each day, or may be specific to each person's situation e.g. I would like to manage my worries leading up to my oncologist appointment.

4) Reflective journaling. Participants will have the opportunity to journal their experiences during the mindfulness program by using the "My Journal" functionality (Figure 3). Each week's content will have a journal section, which will include prompts related to mindfulness program content, participants will be able to enter and save their responses within the program for future review. Prompts will be developed specifically for the study.

The mindfulness program can be accessed at any time via direct login to the website or via the hyperlink sent to participants in the daily e-mails.

Figure 2. My Goal functionality in MindOnLine

(Insert Figure 2 here)

Figure 3. My Journal guided self-reflection practise in MindOnLine

(Insert Figure 3 here)

Data collection

Table 2 illustrates the overall schedule for trial participants in both groups. All assessments will be performed online. The questionnaires at baseline, at nine weeks including the

satisfaction survey for those in the intervention group and at nine months, will be sent via Qualtrics through an automatically generated schedule. Participants who do not complete questionnaires will be followed up by telephone at each data collection point. At baseline, participants' demographic information (i.e., gender, age, marital status, current employment status, highest level of education, postcode, type of cancer, date of diagnosis, time since end of last treatment, type of treatment and previous meditation experience) will be collected.

Table 2. Schedule of enrolment, interventions, and assessments

	STUDY PERIOD										
	Enrolment	Allocation	Post-allocation								Post-Intervention
TIMEPOINT			*Week 1*	*Week 2*	*Week 3*	*Week 4*	*Week 5*	*Week 6*	*Week 7*	*Week 8*	*Week 9*	*9-months*
ENROLMENT:											
Eligibility screen	X										
Informed consent	X										
Allocation		X									
INTERVENTIONS:											
Immediate access to MindOnLine			←	—	—	—	—	—	—	—	→
Waitlist group											
ASSESSMENTS (Both groups):											
Demographic characteristics	X										
FCRI [18]	X									X	X
GAD-7 [20]	X									X	X
PHQ-9 [19]	X									X	X
CAMS-R [22]	X									X	X
AQoL-4D [21]	X									X	X
Mindfulness experience	X									X	X
Resource use	X									X	X

COVID-19 measures	X									X	X
ASSESSMENTS (Intervention group only):											
Adherence tracking and meditation log			X	X	X	X	X	X	X	X	X	X
Program satisfaction										X	X

Outcome measures

Primary outcome

Fear of Cancer Recurrence Inventory (FCRI)

The 42-item Fear of Cancer Recurrence Inventory (FCRI) is a multidimensional FCR scale intended for use with all cancer patients. Items were developed on the basis of a cognitive–behavioural formulation of FCR (range:0-168).[19] The FCRI consists of seven domains: triggers, severity, psychological distress, functional impairment, reassurance, insight and coping strategies (scoring range:0-36). It has shown high internal consistency, good construct and criterion validity in adults with different cancer types.[20]

Secondary outcomes:

Anxiety and Depression

The *Generalized Anxiety Disorder-7 scale (GAD-7*) [22]is a valid and efficient tool for assessing generalised anxiety symptoms and assessing severity in clinical practice and research. The seven items assess the frequency of core symptoms of generalised anxiety disorder within the past 2 weeks (scoring range:0-21).[22]

The *Patient Health Questionnaire-9 (PHQ-9)*[20] parallels the nine diagnostic symptom criteria that define DSM-IV major depressive disorder. At only 9 items (scoring range:0-27), the PHQ-9 is shorter than most depression tools. Unlike most other measures of depression, the PHQ-9 was developed, tested and refined for use with medical patients.[21]

The PHQ-9 and GAD-7 are recommended for use among cancer survivors in the American Society of Clinical Oncology Guidelines. [27]

Mindfulness

Trait mindfulness is measured using the Cognitive and Affective Mindfulness Scale-Revised (CAMS-R), [24] a 10-item self-report questionnaire. This scale uses everyday language appropriate for those with little meditation experience and is designed to capture mindfulness as a general daily experience. The questionnaire comprises four domains of mindfulness (attention, present-focus, awareness, and acceptance/non-judgment). Participants are asked to rate on a four-point Likert scale how much they relate to each statement (scoring range:4-40). Compared to other measures of mindfulness, the CAMS-R is unique in that it is related to psychological distress, [28] which is highly relevant to the current study population.[29]

Other outcome measures

Mindfulness experience

In order to control for access to external mindfulness-based programs particularly in the waitlist group, all participants will be asked whether they have enrolled in a mindfulness-based program in the period between surveys and/or used other supportive care services (e.g. peer support, psychologists, psychotherapy, counsellors, yoga and meditation).

Program satisfaction

Participants in the intervention group will be asked to provide feedback about the *MindOnLine* program. Quantitative and qualitative data using open ended questions will be collected in relation to satisfaction with program content, the helpfulness of the program, usability, and areas for improvement. The satisfaction questionnaire has been adapted from the satisfaction questionnaire used in the pilot study.[6]

Economic outcomes

Assessment of Quality of Life (*AQoL 4D*) [23]is a health-related quality of life utility measure. It is generally used in economic evaluations. The *Resource Use Questionnaire* covers general health care services usage (self-reported), use of other welfare services, and impacts on work force participation. The questionnaire has been successfully used in cancer psychosocial intervention studies. [30]

The surveys will take approximately 20 minutes to complete.

Adherence tracking and meditation log

The software package used to run *MindOnLine* was developed at Deakin University and has inbuilt functionality to collect and clean usage data. Google Analytics has been incorporated into the platform to allow for validation of findings. Both software will track participants' online activity, including login date/times, navigation patterns, page views and duration, and features used (video, audio, goals and reflective journaling).

Impact of COVID-19

To control for potential environmental impacts on mental wellbeing outcomes, participants will be asked whether COVID-19 has had an impact on their mental wellbeing in the two weeks prior to baseline, 9-weeks and 9-month assessments.

Sample size calculations

Power calculations are conservative, i.e. the detectable differences reported below are possibly larger than the true detectable differences, because they are based on two-group comparison of change while the main analysis (see Analysis Plan) will adjust for baseline values of the outcome and for factors used in the stratified randomisation.[31]The statistical software PASS version 14.0.9 (NCSS, LLC) was used for all calculations (α=0.05; two-sided tests).

Primary outcome

Change in FCRI total score between baseline and 9 weeks. The target sample size (200 participants per arm) achieves 94% (80%) power to detect a mean difference between arms of 10 points (8 points) change in FCRI score or 80% power to detect a difference of 8 points [standard deviation (SD): 23.5;[32])SD estimate obtained from Butow et al., [32]as their study included a heterogenous sample of cancer patients while our pilot study only included patients with melanoma Stage 2-3. The selected effect sizes correspond to Cohen's d of 0.43 (moderate/large) and 0.34 (small/moderate) respectively. Currently, there is no definition of a clinically significant improvement for FCRI score, however, the proposed effect size is comparable to that described in other studies.[32]

Secondary outcomes

The target sample size (200 participants per arm) achieves 80% power to detect an intervention effect of size 0.34 (Cohen's f, small/moderate) at 9 weeks for any of the outcomes. This effect size corresponds to mean differences between groups of: a) 1.5 point in PHQ-9 depression score (SD = 4.5, maximum SD reported in patients with breast, colorectal and prostate cancer;[33] PHQ-9 minimal clinically important difference (MCID) for cancer patients: 2.6 to 5);[34] b) 1.4 point in GAD-7 anxiety score (SD=4.1, maximum SD reported in patients with breast, colorectal and prostate cancer;[35] MCID=1.95);[33] and mean differences between group in change from baseline to 9 weeks of: c) 1.2 points in FCRI severity score (SD=3.6, pilot study effect: 2.6);[6] d) 1.1 points in CAMS-R score (SD=3.4); e) 2.5 points in Worry score [SD=7.3]; f) 3.0 points in PSS score [SD=8.9]; the last 3 reflecting moderate Cohen's *d* effect sizes (<0.35).

To meet the sample size needs of our desired statistical power, we will recruit 400 participants. In our pilot study, six participants (13%) withdrew in the intervention group and none in the control group. Assuming a conservative 30% attrition rate at nine months, we expect to have complete data for approximately 280 participants (140 per group).

Analysis plan

All statistical analysis will be conducted on an intention-to-treat basis whereby all randomised participants with at least one post-baseline measurement will be analysed by original treatment assignment regardless of adherence. Baseline characteristics will be described using summary measures selected based on variable distribution. The main analysis will adjust for baseline values of the outcome and for factors used in the stratified randomisation.[31]

Aims 1 and 2. The effect of the intervention on each of the outcomes, defined as change from baseline to nine weeks, will be assessed using linear models including group and the stratification factors. *Aim 3.* The effect of the intervention across the three measurement times will be estimated using linear mixed models, including study group, time (categorical: 9 weeks, 9 months) interaction group×time and the stratification factors as fixed effects and participant as a random effect. If there is a positive intervention effect on mental health outcomes, exploratory mediation analyses will be conducted to determine whether improvements are mediated by increases in mindfulness.[36] For outcomes where it is a plausible assumption that missing data are completely at random, we will use complete case analysis; if not plausible, we will use multiple imputation. *Subgroup analysis*: We will explore whether age or gender modify the effect of the intervention on FCR, depression and anxiety at 9 weeks.

Aim 4. This study will also comprise a cost-consequences analysis where incremental costs of the intervention will be compared with the full spectrum of outcomes included in the study. A series of cost-effectiveness ratios can be determined which have been shown to be useful for decision-makers. Inclusion of the AQoL 4D will also enable a cost-utility analysis to be undertaken, thereby allowing practical judgements to be made regarding value for money credentials of the intervention. Nevertheless, the economic analysis will be primarily from the perspective of the health care sector and a secondary analysis from the broader societal perspective will also be undertaken. A detailed costing of the intervention will be undertaken and the evaluation will first measure and value any change to the use of health care resources over the period of the study between the two arms of the trial and then compare any additional costs to the additional outcomes achieved. Standardised economic evaluation techniques will be used including incremental analysis of mean differences and bootstrapping to determine confidence intervals along with a net monetary analysis to determine the cost-effectiveness of the intervention for different value for money threshold criteria. The costs of routine roll-out will be estimated.

MindOnLine usage data by the intervention group will be reported using descriptive statistics. Linear mixed models, with random intercept and slope for each person, will be fitted to estimate time trends in usage.

Data management

Data will be exported from Qualtrics on a monthly basis and crossed checked during exportation to ensure accuracy in results. All identifying participant information will be removed from data sets. Documents containing sensitive information will be saved as password protected files and stored within the Deakin University One Drive.

Monitoring

Data

The adherence data will be monitored by the program developer. The program developer does not have any competing interests. Other project data will be monitored by the project steering committee with regular meetings and progress updates. No interim analysis will be performed during the trial.

Patient and Public Involvement

Representatives from three consumer organisations have been involved in the design and implementation of the project since its inception. Their contribution has included development of the intervention and its content, wording on recruitment material, and provided advice on recruitment strategies. Representatives from each consumer organisation has contributed to project steering meetings.

Ethics and Dissemination

Harms

All participants will be required to provide written informed consent. In the event that a participant reports distress to the project manager they will be advised to seek assistance from the regular medical professionals and provided with additional referrals to lifeline.org.au. Ethics approval was obtained from the Peter MacCallum Cancer Centre (20-53) and Deakin University (2020-284). Any adverse events will be reported to the ethics committees.

Auditing

The trial may be audited by the governing Human Research Ethics Committees.

Protocol amendments

Protocol amendments will be approved by the governing Human Research Ethics Committees. Any relevant changes will be submitted as a modification to the Australian and New Zealand Clinical Trial Registry.

Dissemination

The findings of this study will be written by study authors and published in peer reviewed journals project steering committee. All identifying participant information will be removed prior to publication.

Discussion

One of the most significant changes across society is the use of web-based technology. Online mindfulness-based interventions circumvent problems with traditional face-to-face delivery of the program, impacted by work commitments, caring responsibilities, geographic isolation and pandemics[37, 38].

This study will rigorously evaluate the efficacy of a self-directed online mindfulness program in reducing FCR in breast, prostate and CRC survivors. The study will advance the literature regarding the benefits of mindfulness for cancer survivors by representing one of few large well controlled trials of a self-directed mindfulness-based program, involving smartphone technology, aimed at reducing FCR. Including a health economic evaluation of the program adds to the utility of the trial with the study providing information that budget holders and policy makers need when considering recommendations and support for supportive care programs. This trial will fill a gap in knowledge regarding the potential impact of an online mindfulness program in supporting cancer survivors.[7] Extensive pilot work in identifying the type of program cancer survivors are interested in, involving consumers in designing the content and length of the program and providing reminders and practice tips increase the likelihood of participants engaging with the program and the intervention having a positive impact.

The study is being conducted in partnership with health services and cancer advocacy groups. As partners in the study, they will ensure the intervention can be rolled out to cancer survivors if shown to be effective. In addition to consumer advocacy groups, the study is being conducted in partnership with government. As we expect the *MindOnLine* intervention to improve health outcomes, reduce the fear and distress in cancer survivorship and reduce health service and community costs our partnership with government will ensure that policy makers are informed of the study's findings particularly cost-effectiveness findings.

The study has a number of strengths and weaknesses. Development of the intervention through a review of the literature, input from consumers and findings from a pilot study and involvement of consumer advocacy groups and government are study strengths ensuring translation of the program into practice if shown to be effective. For example, consumer advocacy groups have contributed to the design of the intervention program, recruitment of eligible patients, and will provide advice on the interpretation of results, dissemination and translation. Incorporating an economic evaluation into the study design is a strength as it will complement clinical findings and support decision-making processes for potential implementation.

However, several methodological limitations also need to be acknowledged. Recruitment through social media platforms means we cannot accurately assess uptake of the intervention, as we will not be able to identify the number of eligible people exposed to our advertisements. This may limit our ability to determine reach of the program. However, recording the time taken for recruitment and accessing google analytic data on internet traffic and page visits may provide some information in this area. Participants will need access to the internet to participate. While this may mean some people will be excluded from the study, we believe this

will have minimal impact on the study. We envisage that the study will take approximately 4 years to complete. Advances in social platforms, technology and app-based programming can change substantially in a short period. While this may affect the actual online platform used for the program, we do not consider this will influence the program content or delivery mechanisms. As technology advances will likely increase interest in self-directed support programs for cancer survivors, it is essential that cancer survivors access programs with demonstrated effectiveness.

Trial Registration ACTRN12620000645954

Protocol Version: Version 5, dated 18 December 2020

Recruitment commenced 12.10.2020, it is anticipated recruitment will be for a duration of 18 months finishing on 12.04.2022.

Abbreviations

AQoL-4D Assessment of Quality of Life – 4 Dimensions

BCNA Breast Cancer Network Australia

CAMSR Cognitive and Affective Mindfulness Scale-Revised

CI Confidence interval

CRC Colorectal Cancer

FCR Fear of cancer recurrence

FCRI Fear of Cancer Recurrence Inventory

GAD-7 General Anxiety Disorder scale

MBCT Mindfulness-based cognitive therapy

MCID Minimally clinically important difference

PCFA Prostate Cancer Foundation of Australia

PHQ-9 Patient Health Questionnaire

QALY Quality of Life Years

QoL Quality of Life

RA Research assistant

RCT Randomized controlled trial

SD standard deviation

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Declarations

Author's contributions

PML, LR, LO, NW, MJ, AG, DWA, EO, CM, AU, RC, J P-N, DH, MB, BR, KW, MF, ABS, KP, MS, DC and VW contributed to the conception of the program or design of the study. EO designed the web platform and analytics with input from LR, NW, RC, DWA, AW, PML. CM designed the economic component of the study. PML, LR, LO, NW, MJ, AG, DWA, EO, CM, AU, RC, J P-N, DH, MB, BR, KW, MF, ABS, KP, SS, AW, KG, MS, DC, BP and VW provided substantial input into the development of the protocol or revising it critically for important intellectual content. PML, LR, NW, LO and VW drafted the manuscript with contributions from MJ, AG, DWA, EO, CM, AU, RC, J P-N, DH, MB, BR, KW, MF, ABS, KP, SS, AW, KG, MS, DC, BP.

Each of the authors contributed to, read and approved the final manuscript.

Each of the co-authors, PML, LR, LO, NW, MJ, AG, DWA, EO, CM, AU, RC, J P-N, DH, MB, BR, KW, MF, ABS, KP, SS, AW, KG, MS, DC, BP and VW, are on the steering committee, will oversee implementation of the study and data collection and will contribute to the acquisition, analysis or interpretation of the data.

Funding

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Competing interests

The authors declare they have no competing interests.

Figure Legend/Caption:

Figure 1. Study flowchart

FCRI (Fear of Cancer Recurrence Inventory); GAD-7 (General Anxiety and Distress scale; PHQ-9 (Patient Health Questionnaire); CAMS-R (Cognitive and Affective Mindfulness Scale – Revised); AQoL-4D (Assessment of Quality of Life – 4 Dimensions)

Figure 2. My Goal functionality in MindOnLine

Figure 3. My Journal guided self-reflection practise in MindOnLine.

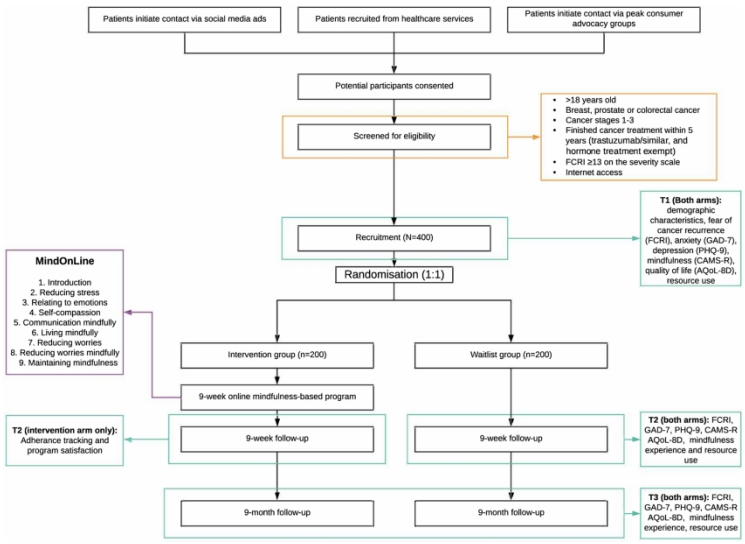

Figure 1. Study flowchart.

338x190mm (400 x 400 DPI)

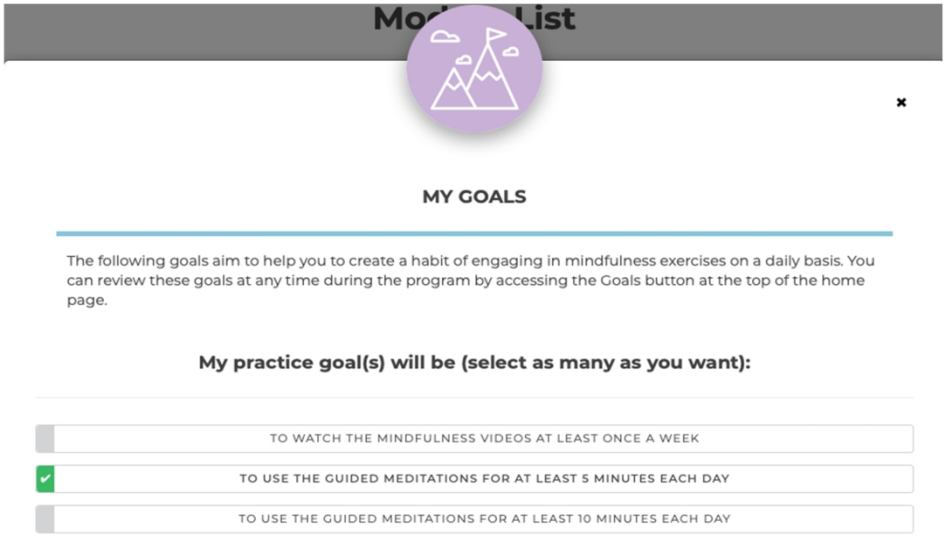

Figure 2. My goal functionality in MondOnLine.

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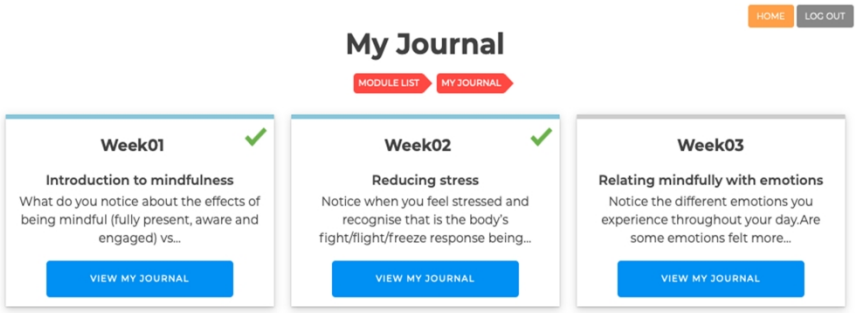

Figure 3. My journal guided self-reflection practice in MindOnLine.

308x100mm (400 x 400 DPI)

Participant Information Sheet/Consent Form

Title	MindOnLine: a mindfulness program for people with breast, bowel or prostate cancer.
Short Title	MindOnLine
Principal Investigator	Prof Trish Livingston
Location	Deakin University

Part 1 What does my participation involve?

1 Introduction

You are invited to take part in this research project, because you have received treatment for breast, prostate or bowel cancer. This research project is testing an online mindfulness-based program for people who have completed their treatment.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the procedures involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or healthcare worker.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether or not you take part.

If you decide you want to take part in the research project, you will be asked to provide consent online. By agreeing you are telling us that you:
- Understand what you have read
- Consent to take part in the research project
- Consent to have the tests and treatments that are described
- Consent to the use of your personal and health information as described.

2 What is the purpose of this research?

Following treatment for cancer, many people feel anxious and scared about the cancer coming back. This is one of the most common fears of cancer survivors, and it can affect people's ability to enjoy life

and plan for the future. In some people, this fear can decrease over time, but most people find that they worry at certain times. The mindfulness program aims to help cancer survivors to manage their fears and worries once treatment is completed.

Research has shown that mindfulness-based programs can help people cope with anxious thoughts about their cancer. The internet allows people to use the program from the comfort of their home, and at their most convenient times. We have tested an online mindfulness program for people who received treatment for melanoma, with promising results. This research is to find out whether mindfulness can help people with breast, prostate or bowel cancer.

This research is being conducted across healthcare services and cancer organisations and is led by researchers at the School of Nursing and Midwifery at Deakin University.

In this research project we will be testing a mindfulness program among people who meet the following criteria:

- People who are over 18 years of age
- People who speak English well enough to understand videos and surveys presented in English
- People who have access to a computer or device to receive the program
- People who received treatment for breast, bowel or prostate cancer
- People who finished chemotherapy, radiotherapy or surgery treatment within the last five years
- People who experience a high level of fear of cancer recurrence.

You will be asked some questions after providing consent to determine if you meet the eligibility criteria above. To measure your fear of cancer recurrence you will be asked 9 questions about how your thoughts and feelings towards cancer may impact on your everyday living.

3 What does participation involve?

To participate in this study, each participant will need to have access to a computer, a smartphone, or a similar tablet device, and internet. If you agree to take part in this project you will be allocated to either receive the mindfulness program (intervention group) or stay in your usual care (control group). We need to compare responses from people in these two groups to see if the mindfulness program provides any benefits to cancer survivors. In order to make sure the groups are the same, participants are put into one of the two groups by chance (random).

If you decide to take part in this study, you will need to provide your consent to participate by accessing the following website: https://mindonline.org.au Before providing your consent you will be asked a number of questions to make sure you are eligible for the study.

After consenting to take part in the study, you will be asked to complete a survey before being randomly allocated to the intervention or control group. The same survey will be completed again 9 weeks and 9 months later. The survey asks you questions about possible fears of the cancer coming back, how stressful and worrisome you perceive your life to be, and the type of thoughts you generally focus on. We will also collect your email address and contact number. Your email and contact number will be used to send you reminders and other information related to the study.

If you are randomised to the mindfulness program, you will receive an email informing you of your allocation group with instructions on how to access the website. Your participation will involve using the program for 9 weeks. The program is designed to help you understand and experience potential benefits of using mindfulness in your day to day life. You will be invited to:

- Watch short videos at the start of each week. The videos will introduce a new topic about mindfulness.
- Practice short meditations twice a day. We will help you create a meditation routine by emailing you a direct link to guided meditations at times you will have chosen.
- Apply mindfulness skills in your day-to-day life.

If you are assigned to the mindfulness program we will monitor how often the mindfulness program is used. This will be recorded by your study identification number, and no personal information such as your Internet Protocol (IP) address linked to your computer or device will be collected.

If you are randomised to the control group you will receive an email informing you of your allocation group and you will continue to receive your usual care from your healthcare providers. You will receive emails to ask you to complete the questionnaires at 9 weeks and 9 months. After the 9-month survey you will be able to use the mindfulness program.

We will compare the results between those in the mindfulness program and those who are not, to see if there are any differences in wellbeing between the two groups.

There are no additional costs associated with participating in this research project, nor will you be paid.

4 Other relevant information about the research project

This study will show if the mindfulness program is helpful for people with breast, prostate or colorectal cancer. If successful the program we be made open to the wider population.

For this study, approximately 400 people will be invited to participate from online and social media advertisements and from healthcare services.

5 Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part you don't have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your relationship with those treating you or involved in your follow-up care, or your relationship with Deakin University, Breast Cancer Network Australia, or Prostate Cancer Foundation of Australia.

6 What are the possible benefits of taking part?

We cannot guarantee or promise that you will receive any benefits from this research; however, possible benefits for the community may include additional support for people who have completed treatment for cancer.

7 What are the possible risks?

Some people may feel uncomfortable or upset when answering questions in this survey. If you do not wish to answer a question you may skip it and go to the next question, or you may stop immediately. In the event that you become upset or distressed as a result of your participation, the researcher can arrange for counselling or other appropriate support provided by staff who are not members of the research team. In addition, you may want to contact an external support service such as Lifeline services on 13 11 14, or www.mindhealthconnect.org.au or the Cancer Council 13 11 20 telephone service.
If you have any concerns or are unsure whether you should participate in this project, you may wish to speak to your healthcare professional about your feelings.

8 What if I withdraw from this research project?

If you decide to withdraw, please notify a member of the research team about this decision. This notice will ensure that we can remove you from our records and will mean you will not receive any notices about the project.

If you decide to withdraw from the project, we would like to keep the personal and health information about you that has been collected. This is to help us make sure that the results of the research can be measured properly. If you want to withdraw your data from the study as well, please let them know when you tell them about withdrawing from the study.

9 What happens when the research project ends?

If you wish to obtain a final copy of the research report describing the results of this study, please contact the project manager (Dr Natalie Heynsbergh on 03 9246 8225, or email n.heynsbergh@deakin.edu.au) and she will arrange for a copy to be sent to you after completion of the study in December 2022.

Part 2 How is the research project being conducted?

10 What will happen to information about me?

Any information obtained in connection with this research project that can identify you (e.g. email address) will remain confidential and will only be used for the purpose of this research project. It will only be disclosed with your permission, except as required by law.

All the information you provide will be coded so you cannot be identified by name, and only the research team will have access to the list that can link your name to your data. All identifying information will be stored in password-protected electronic files or in a locked filing cabinet in the office of the research staff, and will be disposed of as confidential waste after five years.

You will not be identified in any report or publication from this study. Information will be provided in such a way that you cannot be identified.

In accordance with relevant Australian and/or Victorian privacy and other relevant laws, you have the right to access the information collected and stored by the researchers about you. You also have the right to request that any information with which you disagree be corrected. Please contact one of the researchers named in the last section below if you would like to access your information.

11 Who is organising and funding the research?

This research project is being managed by Dr Natalie Heynsbergh at Deakin University, and is being funded by a National Health and Medical Research Council (NHMRC) grant.

12 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been

approved by the Peter MacCallum Human Research Ethics Committee (Reference number 20/53) and the Deakin University Human Research Ethics Committee.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

13 Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this project or if you have any problems which may be related to your involvement in the project, you can contact:

- The principal investigator: Prof Patricia Livingston on 03 9244 6609, or email trish.livingston@deakin.edu.au
- The project manager: Dr Natalie Heynsbergh on 03 92468225, or email: n.heynsbergh@deakin.edu.au

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Reviewing HREC name	Peter MacCallum Cancer Centre Ethics Committee
Project reference number	20/53
HREC Executive Officer	Ethics Coordinator
Telephone	03 8559 7540
Email	ethics@petermac.org

14 What do I do if I want to participate?

If you would like to participate in this study, please log on to https://mindonline.org.au, to answer the eligibility questions and provide your consent to participate.

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	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	23
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	1
	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	23
	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)	23

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	3-5
	6b	Explanation for choice of comparators	6
Objectives	7	Specific objectives or hypotheses	5-6
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)	6
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	6, 8
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)	8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11-14
	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)	n/a
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12-13, 16
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	16
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	15-17
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)	14

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	19
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
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	10
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	10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10
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	14
	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	14

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	21
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	19
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	19
	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)	19
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	21
	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	21
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	21
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	21
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	24
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)	21

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	n/a
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	21
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	24
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	21
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	21
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	21
	31b	Authorship eligibility guidelines and any intended use of professional writers	21
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	21
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	attached
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	n/a

*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.