BMJ Open

Smartphone problem-solving and behavioral activation therapy to reduce fear of recurrence among breast cancer patients (SMartphone Intervention to LEssen fear of cancer recurrence: SMILE project): protocol for a randomized control trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-024794
Article Type:	Protocol
Date Submitted by the Author:	24-Jun-2018
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Keywords:	neoplasma, fear of recurrence, cancer survivorship, psychosocial intervention, information and communication technology, quality of life

Study protocol

Title: Smartphone problem-solving and behavioral activation therapy to reduce fear of recurrence among breast cancer patients (**SM**artphone **I**ntervention to **LE**ssen fear of cancer recurrence: **SMILE** project): protocol for a randomized control trial

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Key words: neoplasma; fear of recurrence; cancer survivorship; psychosocial intervention; information and communication technology; quality of life

Protocol version 4.2 (June 12, 2018)

Word count: 4226

Abstract

Introduction: One of the most common distressing conditions experienced by breast cancer survivors is fear of cancer recurrence (FCR). There is, however, no standard intervention for ameliorating FCR. Our clinical experience and previous studies have suggested the potential benefits of problem-solving therapy (PST) and behavioral activation (BA). Given the huge number of cancer survivors and limited number of therapists to competently conduct PST and BA, we have developed PST and BA smartphone applications. This study aimed to evaluate the efficacy of the smartphone-based PST (Kaiketsu-App) and BA (Genki-App) apps in reducing FCR in breast cancer patients.

Methods and analysis: The SMartphone Intervention to LEssen fear of cancer recurrence (SMILE) project is an open-label, individually randomized, parallel-group trial. Allocation will be managed by a central server, using a computer-generated random allocation sequence provided by an independent data center. Participants will be randomized to smartphone-based intervention plus treatment as usual (TAU) or wait-list control with TAU alone. The primary end point of the study is the Japanese version of the Concerns About Recurrence Scale, which will be administered as an electronic patient-reported outcome on the patients' smartphone after 8 weeks.

Ethics and dissemination: The present study is subject to the ethical guidelines for clinical studies published by Japan's Ministry of Education, Science and Technology and Ministry of Health, Labour and Welfare and the modified Act on the Protection of Personal Information as well as the ethical principles established for research on humans stipulated in the Declaration of Helsinki and

further amendments thereto. The protocol was approved by the institutional review board of Nagoya City University on January 15, 2018 (ID: 60-00-1171).

Trial registration: UMIN-CTR: UMIN000031140

Article Summary

Strengths and limitations of this study

-This study is the first trial investigating the efficacy of smartphone-based psychological therapy for fear of cancer recurrence (FCR) among breast cancer survivors.

-Because many breast cancer survivors return to their households and work, easily accessible therapeutic interventions without hospital visits may offer benefits.

-This study focuses on younger breast cancer survivors who are iPhone users; this focus could reduce the external validity of the findings obtained.

-The use of the wait-list control conditions may overestimate the efficacy of the smartphone-based psychotherapy.

-We will apply two types of psychotherapy and both interventions consist of complex, multifactorial components; thus, we cannot be certain which intervention and components are most beneficial in managing FCR; however, we will adopt a mixed-method design to overcome those issues.

Introduction

Worldwide, breast cancer is one of the most common cancers among women. In Japan, it is also the most common cancer among women, and the incidence is increasing. At present, approximately 90,000 women in Japan are annually diagnosed with breast cancer. Advances in early detection and individualized medical treatment have improved the survival rate of breast cancer patients. The current 10-year survival rate for breast cancer patients is over 90%, which contributes to the increasing number of breast cancer survivors is increasing.[1]

Thus patients with breast cancer have on average a better prognosis than those with many other types of cancer; however, it has been suggested that many breast cancer survivors suffer from uncertainty anxiety and fear over recurrence. [2-4] Our previous study found that the most common unmet needs experienced by ambulatory breast cancer patients are psychological—especially fear of cancer recurrence (FCR); over half of patients complained of such needs.[5] Among breast cancer patients, FCR is, not only highly prevalent, bu also associated with poor quality of life.[2, 5-8]

Accordingly, there is an urgent need for an appropriate intervention for FCR. However, there is no standard intervention for ameliorating FCR.[8] Recent studies have demonstrated that the following can improve FCR among breast cancer survivors: mindfulness stress reduction (six weekly group sessions); cognitive behavioral therapy (CBT; five individual face-to-face sessions and three e-consultations over a period of 3 months); and the novel theoretically based intervention of ConquerFear, which includes attention training, metacognition, and acceptance and mindfulness (five individual face-to-face sessions over 10 weeks).[9-12] These interventions may be promising;

however, one problem with this kind of intervention is the low participation rate owing to time and distance issues (e.g., over 60% of potentially eligible subjects have been found to decline participation).[9, 11-14] In addition, the number of therapists who can provide such specialized care may be severely limited, which is a serious problem in many countries.

Our past experience and some studies indicate the effectiveness of CBT, including problem-solving therapy (PST) and behavioral activation (BA), for FCR among breast cancer survivors.[15-18] We have demonstrated that patients' problem-solving skills were significantly associated with FCR.[15] PST and BA are straightforward interventions that can be administered by less experienced therapists, including nurses.[19] However, patients willing to undergo PST or BA are rarely able to do so even in well-resourced countries because a typical course of PST or BA consists of eight to 12 face-to-face sessions lasting 1 or 1.5 hours led by an trained therapist.[20-22]

Though such programs seem promising, they appear to suffer similar limitations to those of the above-mentioned therapeutic interventions.[9-12] Given the growing number of women annually diagnosed with breast cancer and the high prevalence among them of unmet needs of FCR, a completely novel approach to therapy provision is required. Recent studies have demonstrated the effectiveness of computerized CBT. [23, 24] In light of recent developments in information and communication technology (ICT), CBT delivered via smartphones may be a better treatment option for FCR—in terms of accessibility and portability—than a computer-based one.[25] We have recently developed a smartphone CBT app, which teaches skills in BA and cognitive restructuring; we demonstrated its efficacy for antidepressant-resistant major depression in a randomized controlled

trial.[26] We have also developed PST programs as a smartphone app and demonstrated the acceptability and efficacy of the smartphone-based PST in a single-arm pilot study with breast cancer survivors.[27] The purpose of the present randomized study is to examine the efficacy of smartphone-based PST and BA interventions to reduce FCR in breast cancer patients in a randomized controlled trial.

Methods and analysis

This protocol has been written in accordance with the SPIRIT guideline.[28]

Trial design

The present study is an individually randomized, parallel-group trial (Figure 1). An independent data center will provide computer-generated random allocation sequences. The allocation sequences are maintained centrally, and the results of the assignment will be sent automatically to the study participants by e-mail. The participants are randomized to smartphone-based intervention plus treatment as usual (TAU) or wait-list control with TAU alone.

Interventions: Smartphone-based PST (Kaiketsu-App) and BA (Genki-App)

PST provides patients with a structured strategy for solving their problems. PST includes the following five steps[29]: (1) identification, definition, and breakdown of the problem; (2) establishing achievable goals; (3) generating solutions; (4) evaluating and choosing the solution; and (5)

implementing the chosen solution and evaluating the outcome after implementation.

The smartphone-based PST program, called Kaiketsu-App ("Kaiketsu" means "Solution" in Japanese), for iPhones and iPads (Apple Inc., Cupertino, CA, USA) was developed for this study (Figure 2). The development was based on our empirically supported PST manual.[18] Kaiketsu-App comprises nine sessions: three introductory session; four sessions about learning the PST in five steps; one session of actual training; and one concluding session. The shortest time necessary to complete Kaiketsu-App is 2 weeks. The main program consists of dialogues between characters, who explain the principles and skills of PST. After the first session, participants have to do homework. The time necessary to complete one session is approximately 30 minutes.

BA intervention was developed based on the hypothesis that anxiety can lead to less pleasurable behavior and more sedentary life, which then may lead to worsening anxiety.[29]

The smartphone-based BA program Genki-App ("Genki" means "Energy or Vitality" in Japanese), for iPhones and iPads (Figure 3) was developed as part of the smartphone-based CBT program which was developed for our previous study.[30] Genki-App consists of two sessions, and approximately 30 minutes is needed to complete each session.

Over the 8-week period of the programs, participants are encouraged to complete the sessions and homework through automated e-mail reminders once a week.

Participants

The inclusion criteria for participants are as follows: (1) diagnosis of breast cancer and awareness of

the cancer diagnosis; (2) age 20–49 years; (3) 1 year following breast surgery; (4) currently disease free; (5) ability to complete an electronic patient reported outcome (ePRO) using an iPhone or iPad; (6) being an iPhone or iPad user and having an apple ID to install applications using App Store. We limit the patients' age to 20–49 years because one study and our previous investigation demonstrated that individuals of that age are at high risk of FCR and that more than 50% of such people have smartphones.[8, 31, 32]

The exclusion criteria for participants are as follows: (1) having active, serious physical disease that affects household and light work and a current or past history of cancer other than breast cancer; (2) inability to understand Japanese; (3) currently undergoing follow-up and treatment in a psychiatry department or by other mental health professionals; (4) patients who have previously undergone structured PST, BA therapy, or CBT; (5) judged inappropriate for participation by the researchers.

Procedures

Newly developed research management system

To lessen patient inconvenience in visiting hospital for this study and oncologists' workload in enrolling study participants, we developed a research management system making full use of ICT technology (Figure 4). The study's Web site (https://smile-project.org/) provides information about this study. A poster briefly introducing the study and including a QR code for the Web site has been put up in several core cancer hospitals in Japan. The Web site explains the purpose of the study,

eligibility criteria, and methods used; it also features a video briefly introducing the study as well as providing full written information about it. Potential participants who are interested in the study can e-mail the study's central office, and clinical research coordinators (CRCs) at the central office ascertain their eligibility by telephone (Table 1).

Table 1 Schedule for outcome measurement

		Time points				
		0 week	2 weeks	4 wees	8 weeks	24 weeks
Assessment	Understanding of the e-Consent	●				
	Characteristic	●				
	CARS-J, HADS	●	●	●	●	●*
	FCRI, SCNS-SF34, PTGI-J	●			●	●*
	Satisfaction with interventions				●*	
	Qualitative assessment of apps				●*	

CARS-J: Japanese version of the Concerns About Recurrence Scale

HADS: Hospital Anxiety and Depression Scale

Fear of Cancer Recurrence Inventory short form (FCRI-SF)

SCNS-SF34: Short-form Supportive Care Needs Survey questionnaire

PTGI-J: Posttraumatic Growth Inventory-Japanese

*These would be evaluated only for intervention group

Electronic informed consent and randomization at week 0

After screening, the CRCs will seek to obtain the subjects' electronic informed consent (e-consent) via e-PRO system at week 0. Participants will be requested to upload a picture of identification materials (patients will be especially encouraged to attach a photo of the ID card of the hospital where they made regular follow-up visits for breast cancer). This e-consent procedure is in accordance with the guidance of the US Food and Drug Administration (FDA).[33]

After providing e-consent and completing the baseline investigation by e-PRO, the participants will be randomly allocated to either the smartphone-based PST and BA group or the wait-list control group in a 1:1 ratio using the electronic data-capturing Web program (EDC) at the data management center (Figure 1). The random allocation will therefore be concealed.

If a participant is allocated to the intervention group, they will receive a password unique to them for using Kaiketsu-App and Genki-App. Upon entering the password, participants will be able to proceed to the sections for Kaiketsu-App and Genki-App. If participants are allocated to the control group, they will be informed that use of Kaiketsu-App and Genki-App can be resumed if they wish after week 8.

Data management, central monitoring, and auditing

We will collect all data except qualitative interview data through e-PRO; we will obtain qualitative interview data by telephone (See below for details). If participants fail to provide their responses

regarding FCR, a CRC blinded to the assignment will telephone the subjects to elicit their answers. Data management and central monitoring will be performed using the EDC. The EDC consists of two different and independent parts, one including personal information and the other including trial-related data (e.g., assignment, outcomes, etc.) for security. Auditing is not planned for this study because the interventions are not invasive.

Dataset available

The de-identified anonymized dataset will be uploaded to UMIN-ICDR (http://www.umin.ac.jp/icdr/index-j.html) and researchers approved by the Steering Committee will be able to have access to the dataset.

Trial period: weeks 0–8

For participants allocated to the intervention group, an automated e-mail encouraging their adherence to Kaiketsu-App and Genki-App will be sent every week for 8 weeks. The research team can check the patient's progress (number of times and duration using each application) with Kaiketsu-App and Genki-App using Google Analytics. At weeks 2, 4, and 8, participants will receive an e-mail encouraging them to record their responses on e-PRO.

Follow-up period: weeks 8–24

Participants allocated to the control group can resume the Kaiketsu-App and Genki-App if they

wish. At week 24, participants allocated to the intervention group will receive an e-mail encouraging them to provide their responses on e-PRO.

Concomitant treatments

There is no restriction on concomitant treatments.

Stopping rules for participants

Discontinuation of protocol treatment

If a participant meets any of the following conditions, the research team can discontinue the Kaiketsu-App and Genki-App. However, the participant will not be considered to have dropped out of the trial at that stage and will receive the protocol assessments: (1) the participant wishes to stop the protocol treatment; (2) the research team judges that the risk of the protocol treatment is greater than the benefit for any reason; (3) the research team judges that it is inappropriate to continue the protocol treatment for any reason.

Stopping assessment

If a participant withdraws consent for assessment, she will not be followed up. Subjects will be excluded from the intention-to-treat (ITT) cohort of the trial only if their characteristics are found to meet any exclusion criteria at baseline (e.g., age over 50 years) after participation.

Assessment measures

Table 1 shows the schedule for outcome measurement.

Primary outcome measure

Fear of recurrence: CARS-J

Originally developed in the United States, CARS-J is a 26-item self-report scale to measure fear of recurrence of breast cancer.[34] The reliability and validity of CARS-J has been confirmed among Japanese breast cancer patients.[35] CARS-J assesses the overall fear of breast cancer recurrence and four domains of specific fear of recurrence. Overall fear comprises four items: questions on frequency; potential for upset; consistency; and intensity of fear. The overall fear score with CARS-J is our primary outcome. The range of possible scores for overall fear is 4–24; a higher score indicates greater fear of recurrence.

Secondary outcome measures

Fear of Cancer Recurrence Inventory–Short Form

The Fear of Cancer Recurrence Inventory–Short Form (FCRI-SF) is a nine-item self-report scale, originally developed in Canada.[36, 37] The FCRI evaluates the presence and severity of intrusive thoughts associated with FCR: scores range from 0 to 36; a higher score indicates severe FCR. Unlike with CARS-J, the FCRI-SF can measure fear of recurrence of any type of cancer. The Japanese version of the FCRI-SF was developed after obtaining permission from the original author and using a forward-backward translation process. In this study, the measure will be included as a

secondary outcome after its validity and reliability have been ascertained.

Psychological distress: Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS), a self-report questionnaire comprising 14 items, was developed for use with medically ill patients. The HADS consists of an anxiety and a depression subscale (0–21 points each). The total score ranges from 0 to 42; a higher score indicates more severe depression and anxiety.[38] The Japanese version of the HADS has been validated for cancer populations.[39]

Patients perceived needs: Short-form Supportive Care Needs Survey questionnaire

The Short-form Supportive Care Needs Survey questionnaire (SCNS-SF34) is a self-administered instrument for assessing the perceived needs of cancer patients.[40] The SCNS-SF34 comprises 34 items covering five domains of need: psychological; health system and information; physical and daily living; patient care and support; and sexuality. The total score is obtained by summing all the subscales (range, 34–170). A higher score indicates a higher perceived need. The validity and reliability of the Japanese version of SCNS-SF34 have been established.[41]

Posttraumatic Growth Inventory-Japanese version

The Posttraumatic Growth Inventory (PTGI) is a 21-item self-report scale, originally developed in the United States.[42] The PTGI includes items that measure positive psychological change

experienced as a result of struggle with major life crises or traumatic events. The PTGI-J consists of four subscales: relating to others; new possibilities; personal strength; and spiritual change and appreciation of life. The total score ranges from 0 to 90; a higher score indicates more positive changes.[43]

Satisfaction with intervention

To assess patients' perceived satisfaction with the intervention, we ask two additional items. The items are as follows. (1) "Please rate your satisfaction with the treatment in meeting your needs during the past 2 months by assigning it a score from 0 to 100; a score of 100 indicates complete satisfaction. A score of 60 is considered the passing level." (2) "Please rate your overall satisfaction with the treatment during the past 2 months by assigning it a score from 0 to 100; a score of 100 indicates complete satisfaction. A score of 60 is considered the passing level." A lower score indicates lower satisfaction. We used this method in our previous study.[44]

Understanding e-consent

We will ask ten questions will be asked at week 0 related to the participants' understanding of e-consent: purpose of the study; randomization; voluntarily participation; duration of study; risks and benefits of study participation; free withdrawal anytime from the study; contact method for questions and more detailed information about the study; method of participant identification (uploading a photo of the hospital registration card); which of the video or written documentation in

the Web site was the more helpful in understanding the study contents ; and free opinions regarding e-consent.

Qualitative evaluation of intervention

The intervention will consist of multiple complex components; accordingly, simple structured telephone interviews will be conducted at 8 weeks for approximately 30 subjects willing to participate in this additional survey to evaluate the effective parts of the complex intervention. The interview items will be as follows. (1) “Please talk freely about the usefulness of the smartphone PST and smartphone behavioral intervention.” (2) “Please talk freely about the usefulness of each of the five steps of the smartphone PST and give your reasons for your opinions.” (3) “Please talk freely about the usefulness of the two parts of the smartphone behavioral intervention and give your reasons for your opinions.” (4) “Please talk freely about the effectiveness of the intervention, for example, the regular encouraging e-mail, and if any other components contributed to improving your fear of recurrence.” If the participants permit, the answers will be recorded using a voice recorder.

Sociodemographic and biomedical factors

e-PRO will also be used to obtain information about the patients’ sociodemographic and biomedical status (marital status, level of education, and employment status) and biomedical information (physical function, time since diagnosis, clinical stage, and anti-cancer treatment).

Data analysis

Primary analyses

To examine the treatment effect parameters of all randomly assigned subjects in the primary analysis set according to the ITT principle, we will analyze the primary outcome (CARS-J score at weeks 2, 4, and 8) using a generalized linear model with unstructured covariance and robust standard errors. The fixed effects are CARS-J score at baseline, treatment allocation (intervention versus control), time (2, 4, and 8 weeks as categorical variable), and treatment-by-time interaction; the random effects are subjects (as intercepts). The primary outcome of interest is the difference in CARS-J scores between the two groups at week 8. A two-sided P value of less than 0.05 will be used to indicate statistical significance.

Secondary analyses

We will perform secondary analyses to supplement our primary analysis and to obtain a clearer understanding of our clinical questions. The secondary analyses will use models similar to that of the primary analysis and will also examine data for the secondary outcome measures. The secondary analyses will include an assessment of the validity and reliability of FCR-J. These analyses will be conducted for exploratory purposes.

Interim analyses

We do not plan any interim analysis.

Sample size estimation

Our previous phase II study revealed that the mean CARS-J scores were 12.8 at pre-intervention (baseline), 12.4 at 4 weeks, and 11.2 at 8 weeks.[27] We assumed the following: the mean CARS-J score at 2 weeks would be 12.6; the overall CARS-J scores in the control arms would not change (12.8 at 0, 2, 4, and 8 weeks); the variance of the score would be 30 at all times; and the intra-class correlation would be 0.82 (i.e., we assumed a compound symmetry working covariance structure). Thus, for a sample size based on 0.8 power to detect a significant difference at $P = .05$ (two-sided), 211 participants would be required for each arm. Assuming that 5% of the initial entries would drop out, we would need to recruit 444 participants into the trial.

Publication policy

The protocol paper and study results will be submitted to peer-reviewed journals. The first author of the main paper will be a member of the steering committee (authors of the protocol paper). Another person could be the first author if approved by the steering committee. The list of co-authors will be determined before submitting each paper.

Study period

The study period of this trial will be from April 2017 to March 2020; the participant entry period

will be April 2018 to September 2019.

Patient and public involvement statement

The study protocol was designed with a patient (breast cancer survivor) and she participated in this study as a researcher. She appropriately discussed with other patients when a patient's preferences and/or opinions should be considered. She will play a same role on implementing the study. Thus patients were and will be always involved in the study. Results of the study will be shown in the study home page.

Ethics and dissemination

The present study is subject to ethical guidelines for clinical studies published by Japan's Ministry of Education, Science and Technology and Ministry of Health, Labour and Welfare and the modified Act on the Protection of Personal Information as well as the ethical principles established for research on humans stipulated in the Declaration of Helsinki and further amendments thereto.

The protocol was approved by the institutional review board of Nagoya City University on January 15, 2018 (ID: 60-00-1171). If important protocol modifications are needed, the investigators will discuss them and report to the review board for approval.

With regard to dissemination, the results obtained will be submitted for publication in peer-reviewed journals. The main and relevant findings will be presented at conferences.

Discussion

To our knowledge, the present study is the first trial investigating the efficacy of smartphone-based psychological therapy for fear of recurrence among breast cancer survivors. Considering the huge number of breast cancer survivors and low participant rate with other types of therapeutic interventions, smartphone-based psychological therapy may offer a more accessible option. As many cancer survivors return to their households and to work, easily accessible therapeutic interventions may offer additional benefits in managing fear of recurrence. The present study focuses on younger breast cancer patients who are iPhone users. However, many other patients suffering from fear of recurrence use other types of smartphones (e.g., Android); in addition, including patients aged 50 years and above would constitute a broader targeted population. If the efficacy of the smartphone-based intervention program among our participants is confirmed, the program will have promising applicability in real clinical settings.

The present study has some methodological limitations. First, not all patients who are interested in and willing to use Kaiketsu-App and Genki-App possess a smartphone. This may weaken the applicability of the results from this trial to all breast cancer patients with fear of recurrence. Especially, the results may not be applicable to patients in developing countries and to those with poor ICT literacy.

Second, we will use a wait-list control as the comparator owing to feasibility and ethical considerations. The odds of response was found to be statistically significantly greater for no treatment than the wait list.[45] The wait list may therefore lead to some overestimation of the

efficacy of smartphone-based psychotherapy.

Third, we will apply two types of psychotherapy—BA and PST—as interventions. Both psychotherapeutic interventions consist of complex, multifactorial components. Thus, if the interventions prove superior to the wait-list controls, we cannot determine which intervention and components are most efficacious or beneficial in managing fear of recurrence. However, to overcome this limitation, we will adopt a mixed-method design and can check adherence with each intervention (detailed in "Methods and analysis") so that we can identify the most useful components of the interventions.

Fourth, we will request that participants upload images for identification (they will be especially encouraged to attach a photo of the hospital registration card) to avoid individuals masquerading as breast cancer patients. However, possible deception cannot be completely prevented in our recruitment system.

Author contributions

TA, TAF, and MH developed the smartphone applications and MU and FI also contributed to modification of these applications. TA, TY, MK, FK, NS, TM, TAF, HI, and YU participated in the design of the study. TY played a chief role of the statistical parts. TA drafted the manuscript. All authors participated in, read and approved final manuscript.

Funding

This study is supported by a Grant-in-Aid for Japan Agency for Medical Research and Development (Number JP17ck0106324h). This study is also partly supported in part by a Grant-in-Aid for Scientific Research (Number 25285194) and Young scientists (Number 17k13942) from the Japanese Ministry of Education, Culture, Science, and Technology, grant from Nagoya City University, Foundation for Promotion of Cancer Research in Japan and The National Cancer Center Research and Development Fund (Number 27-A-3 & 30-A-11).

Competing interests

The authors have no conflicts of interests to declare that may be affected by the publication of the manuscript. TA has received lectures fees from AstraZeneca, Daiichi-Sankyo, Dainippon-Sumitomo, Eizai, Hisamitsu, Lilly, MSD, Meiji-seika Pharma, Mochida, Pfizer, Novartis, Otsuka, Shionogi, Takeda, Tanabe-Mitsubishi, Terumo, and Yoshitomi. TA has received research funds from Daiichi-Sankyo, Eizai, MSD, Pfizer, Novartis, and Tanabe-Mitsubishi. TY received research funds from AC MEDICAL INC., A2 Healthcare Corporation, CAC Croit Corporation, FMD K&L Japan K.K., Japan Tobacco Inc., Japan Media Corporation, Luminary Medical K.K., Medidata Solutions, Inc., ONO PHARMACEUTICAL CO., LTD., Kyowa Hakko Kirin Co., Ltd., DAIICHI SANKYO COMPANY, LIMITED. Also TY received consulting fee from ONO PHARMACEUTICAL CO., LTD., Kowa Company, Ltd., Japan Tobacco Inc., CHUGAI PHARMACEUTICAL CO.,LTD.,

TSUMURA & CO., CAC Croit Corporation, TSUMURA & CO., ASAHI INTECC CO., LTD., Asahi Kasei Pharma Corporation, Clinical Trial Co.,Ltd. FK has received lecture fees from MSD. TAF has received lecture fees from Janssen, Meiji, Mitsubishi-Tanabe, MSD and Pfizer. He has received research support from Mitsubishi-Tanabe. HI has received lecture fees from Daiichi Sankyo, Chugai, AstraZeneca, Pfizer, and Eisai. He has received research support from Daiichi Sankyo, Chugai, AstraZeneca, Pfizer, MSD, Kyowahakou Kirin, GSK, Lilly, Novartis, and a Bayer. YU has received lectures fees from Asteras, Daiichi-Sankyo, Dainippon-Sumitomo, Eizai, Jannsen, Kyowahakko-Kirin, Ono, Meiji-seika Pharma, Mochida, Pfizer, Novartis, Otsuka, Sawai, Shionogi, Taiho, Tanabe-Mitsubishi, Tsumura Pharma.

Trial status

The randomized trial, which commenced on 2th, April, 2018, currently enrolls participants. The estimated end date for this study is in March 2020.

Acknowledgments

We thank to Ms. T Mashiko for her data management support. We also thank to Ms. Y Yanase, Ms. A Nomura , Ms. K Tojima, Ms. I. Sakakima, and Ms. K Kobori for their support for the study. We thank Edanz Group (www.edanzediting.com) for editing a draft of this manuscript.

Figure legend

Fig. 1 Participant flow diagram

Fig. 2 Kaiketsu App

Application for smartphone based problem-solving treatment

Fig. 3Genki App

Application for smartphone based behavioral activation

Fig. 4 Study management system

e-Consent: electric informed consent; e-PRO: electric patient reported outcome

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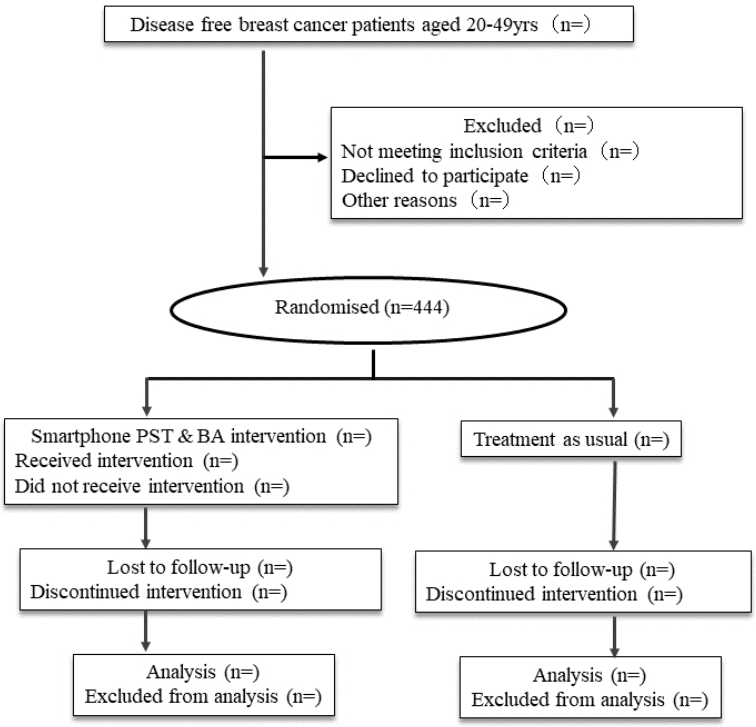

Fig. 1 Participant flow diagram

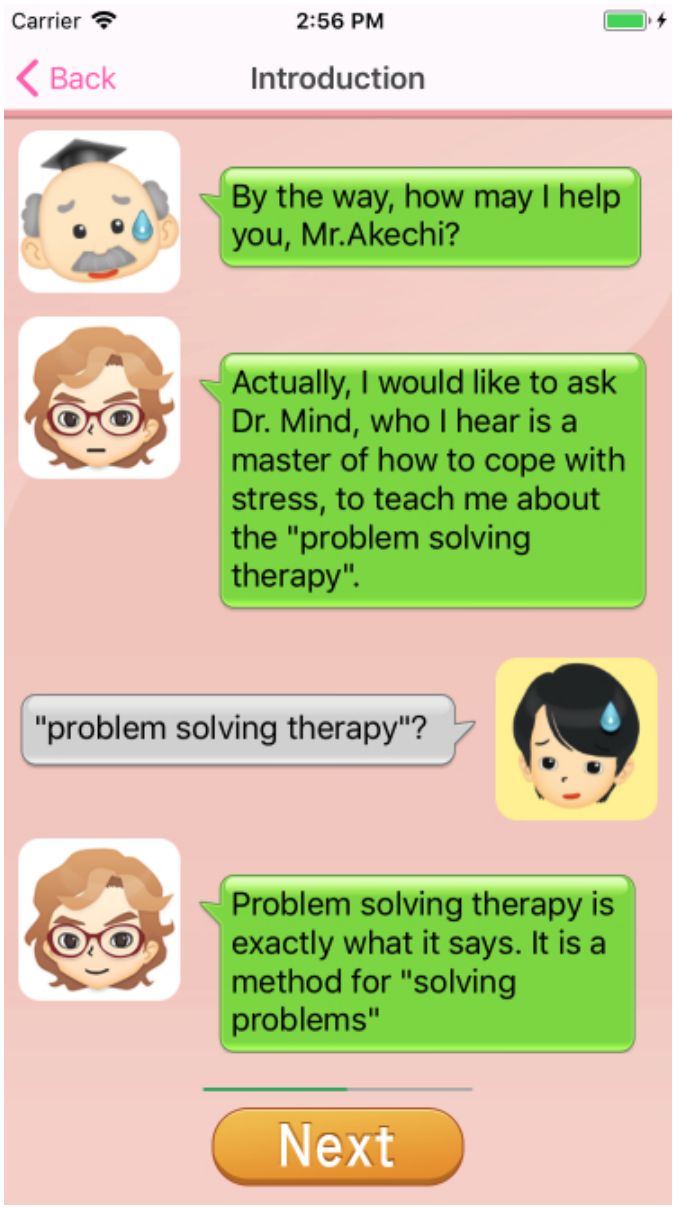

Fig. 2 Kaiketsu App
Application for smartphone based problem-solving treatment

130x234mm (72 x 72 DPI)

Fig. 3 Genki App
Application for smartphone based behavioral activation

131x234mm (72 x 72 DPI)

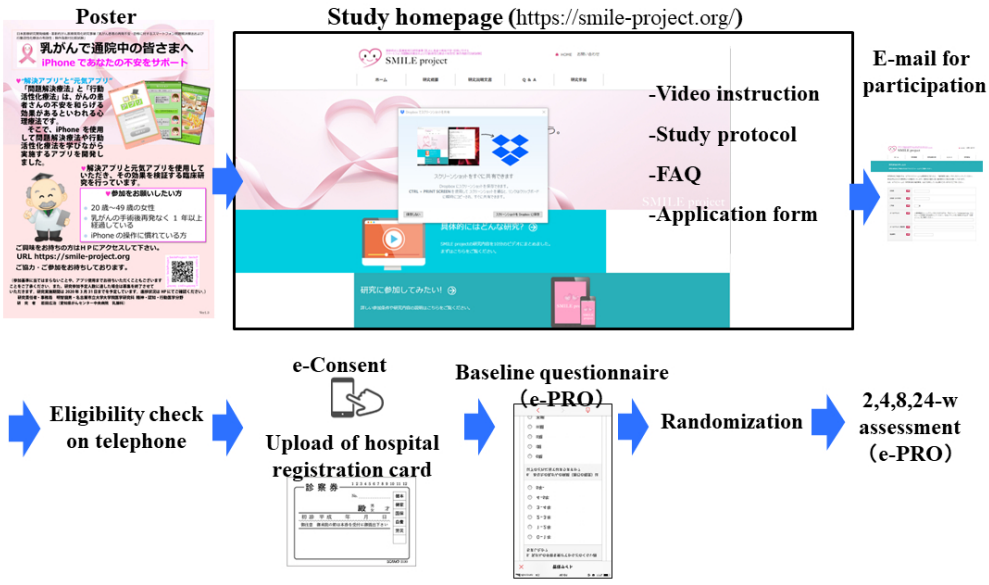

Fig. 4 Study management system
e-Consent: electric informed consent; e-PRO: electric patient reported outcome

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

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Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
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	5
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	5
Protocol version	#3	Date and version identifier	3
Funding	#4	Sources and types of financial, material, and other support	22-23
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	22
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	22

sponsor contact information			
Roles and responsibilities: sponsor and funder	#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
Roles and responsibilities: committees	#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)	12
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	6-8
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	8
Objectives	#7	Specific objectives or hypotheses	8
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, non-inferiority, exploratory)	8
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	10-11
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)	9-10
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-9

Interventions: modifications	#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)	13
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	12-13
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	13
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	14-17
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)	Fig 1
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	10-11
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	11
Allocation concealment	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed	11

mechanism		envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	8, 12
Data collection plan	#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	Table 1 14-18
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Table 1 12
Statistics: outcomes	#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	18
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	18
Statistics: analysis population and missing data	#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)	13-14 18

Data monitoring: formal committee	#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	12
Data monitoring: interim analysis	#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	19
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	12 17
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	20
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)	20
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	20
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	12
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	23-24
Data access	#29	Statement of who will have access to the final trial dataset,	12

		and disclosure of contractual agreements that limit such access for investigators	
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	NA
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	19 24
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	12
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	11
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

BMJ Open

Smartphone problem-solving and behavioral activation therapy to reduce fear of recurrence among breast cancer patients (SMartphone Intervention to LEssen fear of cancer recurrence: SMILE project): protocol for a randomized controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-024794.R1
Article Type:	Protocol
Date Submitted by the Author:	29-Aug-2018
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Primary Subject Heading:	Mental health
Secondary Subject Heading:	Mental health
Keywords:	neoplasma, fear of recurrence, cancer survivorship, psychosocial intervention, information and communication technology, quality of life

Study protocol

Title: Smartphone problem-solving and behavioral activation therapy to reduce fear of recurrence among breast cancer patients (**SM**artphone **I**ntervention to **LE**ssen fear of cancer recurrence: **SMILE** project): protocol for a randomized **controlled** trial

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Key words: neoplasma; fear of recurrence; cancer survivorship; psychosocial intervention; information and communication technology; quality of life

Protocol version 4.3 (August 24, 2018)

Word count: 4577

Abstract

Introduction: One of the most common distressing conditions experienced by breast cancer survivors is fear of cancer recurrence (FCR). There is, however, no standard intervention for ameliorating FCR. Our clinical experience and previous studies have suggested the potential benefits of problem-solving therapy (PST) and behavioral activation (BA). Given the huge number of cancer survivors and limited number of therapists to competently conduct PST and BA, we have developed PST and BA smartphone applications. This study aimed to evaluate the efficacy of the smartphone-based PST (Kaiketsu-App) and BA (Genki-App) apps in reducing FCR in breast cancer patients.

Methods and analysis: The SMartphone Intervention to LEssen fear of cancer recurrence (SMILE) project is an open-label, individually randomized, parallel-group trial. Allocation will be managed by a central server, using a computer-generated random allocation sequence provided by an independent data center. Participants will be randomized to smartphone-based intervention plus treatment as usual (TAU) or wait-list control with TAU alone. The primary end point of the study is the Japanese version of the Concerns About Recurrence Scale, which will be administered as an electronic patient-reported outcome on the patients' smartphone after 8 weeks.

Ethics and dissemination: The present study is subject to the ethical guidelines for clinical studies published by Japan's Ministry of Education, Science and Technology and Ministry of Health, Labour and Welfare and the modified Act on the Protection of Personal Information as well as the ethical principles established for research on humans stipulated in the Declaration of Helsinki and

further amendments thereto. The protocol was approved by the institutional review board of Nagoya City University on January 15, 2018 (ID: 60-00-1171).

Trial registration: UMIN-CTR: UMIN000031140

Article Summary

Strengths and limitations of this study

-This study is the first trial investigating the efficacy of smartphone-based psychological therapy for fear of cancer recurrence (FCR) among breast cancer survivors.

-Because many breast cancer survivors return to their households and work, easily accessible therapeutic interventions without hospital visits may offer benefits.

-This study focuses on younger breast cancer survivors who are iPhone users; this focus could reduce the external validity of the findings obtained.

-The use of the wait-list control conditions may overestimate the efficacy of the smartphone-based psychotherapy.

-We will apply two types of psychotherapy and both interventions consist of complex, multifactorial components; thus, we cannot be certain which intervention and components are most beneficial in managing FCR; however, we will adopt a mixed-method design to overcome those issues.

Introduction

Worldwide, breast cancer is one of the most common cancers among women. In Japan, it is also the most common cancer among women, and the incidence is increasing. At present, approximately 90,000 women in Japan are annually diagnosed with breast cancer. Advances in early detection and individualized medical treatment have improved the survival rate of breast cancer patients. The current 10-year survival rate for breast cancer patients is over 90%, which contributes to the increasing number of breast cancer survivors.[1]

Thus patients with breast cancer have on average a better prognosis than those with many other types of cancer; however, it has been suggested that many breast cancer survivors suffer from uncertainty anxiety and fear over recurrence. [2-4] Our previous study found that the most common unmet needs experienced by ambulatory breast cancer patients are psychological—especially fear of cancer recurrence (FCR); over half of patients complained of such needs.[5] Among breast cancer patients, FCR is, not only highly prevalent, bu also associated with poor quality of life.[2, 5-8]

Accordingly, there is an urgent need for an appropriate intervention for FCR. However, there is no standard intervention for ameliorating FCR.[8] Recent studies have demonstrated that the following can improve FCR among breast cancer survivors: mindfulness stress reduction (six weekly group sessions); cognitive behavioral therapy (CBT; five individual face-to-face sessions and three e-consultations over a period of 3 months); and the novel theoretically based intervention of ConquerFear, which includes attention training, metacognition, and acceptance and mindfulness (five individual face-to-face sessions over 10 weeks).[9-12] These interventions may be promising;

however, one problem with this kind of intervention is the low participation rate owing to time and distance issues (e.g., over 60% of potentially eligible subjects have been found to decline participation).[9, 11-14] In addition, the number of therapists who can provide such specialized care may be severely limited, which is a serious problem in many countries.

Our past experience and some studies indicate the effectiveness of CBT, including problem-solving therapy (PST) and behavioral activation (BA), for FCR among breast cancer survivors.[15-18] We have demonstrated that patients' problem-solving skills were significantly associated with FCR.[15] **Our hypotheses of their underlying mechanisms are that PST contributes to patients' better coping with situations commonly triggering FOR (e.g., pain, exposure to news about cancer, regular visit to cancer hospital, etc.) and other stressful situations that increase FOR and that BA also improves FOR through distraction and through increased sense of mastery and pleasure.** PST and BA are straightforward interventions that can be administered by less experienced therapists, including nurses.[19] However, patients willing to undergo PST or BA are rarely able to do so even in well-resourced countries because a typical course of PST or BA consists of eight to 12 face-to-face sessions lasting 1 or 1.5 hours led by an trained therapist.[20-22]

Though such programs seem promising, they appear to suffer similar limitations to those of the above-mentioned therapeutic interventions.[9-12] Given the growing number of women annually diagnosed with breast cancer and the high prevalence among them of unmet needs of FCR, a completely novel approach to therapy provision is required. Recent studies have demonstrated the effectiveness of computerized CBT. [23, 24] In light of recent developments in information and

communication technology (ICT), CBT delivered via smartphones may be a better treatment option for FCR—in terms of accessibility and portability—than a computer-based one.[25] We have recently developed a smartphone CBT app, which teaches skills in BA and cognitive restructuring; we demonstrated its efficacy for antidepressant-resistant major depression in a randomized controlled trial.[26] We have also developed PST programs as a smartphone app and demonstrated the acceptability and efficacy of the smartphone-based PST in a single-arm pilot study with breast cancer survivors.[27] The purpose of the present randomized study is to examine the efficacy of smartphone-based PST and BA interventions to reduce FCR in breast cancer patients in a randomized controlled trial. **Since there is no specific standard intervention for ameliorating FCR as mentioned above and our research team's discussion suggests that setting wait-list control will be more feasible than no intervention, wait-list control is used as a comparator.**

Methods and analysis

This protocol has been written in accordance with the SPIRIT guideline.[28]

Trial design

The present study is an individually randomized, parallel-group trial (Figure 1). An independent data center will provide computer-generated random allocation sequences. The allocation sequences are maintained centrally, and the results of the assignment will be sent automatically to the study participants by e-mail. The participants are randomized to smartphone-based intervention plus

treatment as usual (TAU) or wait-list control with TAU alone. **TAU means general treatment and/or care commonly provided by each patient's hospital (e.g., nurse's support etc.).**

Interventions: Smartphone-based PST (Kaiketsu-App) and BA (Genki-App)

PST provides patients with a structured strategy for solving their problems. PST includes the following five steps[29]: (1) identification, definition, and breakdown of the problem; (2) establishing achievable goals; (3) generating solutions; (4) evaluating and choosing the solution; and (5) implementing the chosen solution and evaluating the outcome after implementation.

The smartphone-based PST program, called Kaiketsu-App ("Kaiketsu" means "Solution" in Japanese), for iPhones and iPads (Apple Inc., Cupertino, CA, USA) was developed for this study (Figure 2). The development was based on our empirically supported PST manual.[18] Kaiketsu-App comprises nine sessions **(An appendix table)**: three introductory session; four sessions about learning the PST in five steps; one session of actual training; and one concluding session. The shortest time necessary to complete Kaiketsu-App is 2 weeks. The main program consists of dialogues between characters, who explain the principles and skills of PST. After the first session, participants have to do homework. The time necessary to complete one session is approximately 30 minutes.

An appendix table

Details of sessions in smartphone problem-solving and behavioral activation therapies

Smartphone app	Details of each session
Problem-solving therapy (9 sessions)	1. Outline of problem-solving therapy 2. Introduction of 5 step of problem-solving 3. Example of problem-solving 4. First step (identification, definition, and breakdown of the problem) 5. Second step (establishing achievable goals) 6. Third step (generating solutions) 7. Fourth (evaluating and choosing the solution) and fifth step (implementing the chosen solution and evaluating the outcome after implementation) 8. Actual training 9. Concluding session
Behavioral activation therapy (2 sessions)	1. Outline and introduction of behavioral activation therapy including two types of activation (e.g., do pleasurable activity again and challenge new activity) and their actual training 2. Review of the session, learning knack of behavioral activation and concluding session

BA intervention was developed based on the hypothesis that anxiety can lead to less pleasurable behavior and more sedentary life, which then may lead to worsening anxiety.[29]

The smartphone-based BA program Genki-App ("Genki" means "Energy or Vitality" in Japanese), for iPhones and iPads (Figure 3) was developed as part of the smartphone-based CBT program which was developed for our previous study.[30] Genki-App consists of two sessions **(An appendix table)**, and approximately 30 minutes is needed to complete each session: **one is outline and introduction of behavioral activation therapy including two types of activation (e.g., do pleasurable activity again and challenge new activity) and their actual training; the other is review of the session, learning knack of behavioral activation and concluding session. The shortest time necessary to complete Genki-App is also 2 weeks. The Genki-App program also mainly consists of dialogues between characters and homework.**

Over the 8-week period of the programs, participants are encouraged to complete the sessions and homework through automated e-mail reminders once a week. **Although we cannot know the contents of homework for privacy security, treatment adherence (e.g., times and length of using each App) can be checked by Google analytics.**

Participants

The inclusion criteria for participants are as follows: (1) diagnosis of breast cancer and awareness of the cancer diagnosis; (2) age 20–49 years; (3) 1 year following breast surgery; (4) currently disease free; (5) ability to complete an electronic patient reported outcome (ePRO) using an iPhone or iPad; (6) being an iPhone or iPad user and having an apple ID to install applications using App Store. We limit the patients' age to 20–49 years because one study and our previous investigation demonstrated that individuals of that age are at high risk of FCR and that more than 50% of such people have smartphones.[8, 31, 32]

The exclusion criteria for participants are as follows: (1) having active, serious physical disease that affects household and light work and a current or past history of cancer other than breast cancer; (2) inability to understand Japanese; (3) currently undergoing follow-up and treatment in a psychiatry department or by other mental health professionals; (4) patients who have previously undergone structured PST, BA therapy, or CBT; (5) judged inappropriate for participation by the researchers **(e.g., identity theft, duplicate entry, etc.)**.

Procedures

Newly developed research management system

To lessen patient inconvenience in visiting hospital for this study and oncologists' workload in enrolling study participants, we developed a research management system making full use of ICT technology (Figure 4). The study's Web site (https://smile-project.org/) provides information about this study. **A poster briefly introducing the study and including a QR code for the Web site has been put up in 10 core cancer hospitals in Japan and study information will be disseminated repeatedly by using several social networking systems (e.g., facebook, patient's mailing list etc.).** The Web site explains the purpose of the study, eligibility criteria, and methods used; it also features a video briefly introducing the study as well as providing full written information about it. Potential participants who are interested in the study can e-mail the study's central office, and clinical research coordinators (CRCs) at the central office ascertain their eligibility by telephone (Table 1).

Table 1 Schedule for outcome measurement

		Time points				
		0 week	2 weeks	4 wees	8 weeks	24 weeks
Assessment	Understanding of the e-Consent	●				
	Characteristic	●				
	CARS-J, HADS	●	●	●	●	●*
	FCRI, SCNS-SF34, PTGI-J	●			●	●*
	Satisfaction with interventions				●*	
	Qualitative assessment of apps				●*	

CARS-J: Japanese version of the Concerns About Recurrence Scale

HADS: Hospital Anxiety and Depression Scale

Fear of Cancer Recurrence Inventory short form (FCRI-SF)

SCNS-SF34: Short-form Supportive Care Needs Survey questionnaire

PTGI-J: Posttraumatic Growth Inventory-Japanese

*These would be evaluated only for intervention group

Electronic informed consent and randomization at week 0

After screening, the CRCs will seek to obtain the subjects' electronic informed consent (e-consent) via e-PRO system at week 0. Participants will be requested to upload a picture of identification materials (patients will be especially encouraged to attach a photo of the ID card of the hospital where they made regular follow-up visits for breast cancer). This e-consent procedure is in accordance with the guidance of the US Food and Drug Administration (FDA).[33] **Informed consent material-original is shown in an appendix.**

After providing e-consent and completing the baseline investigation by e-PRO, the participants will be randomly allocated to either the smartphone-based PST and BA group or the wait-list control group in a 1:1 ratio using the electronic data-capturing Web program (EDC) at the data management center (Figure 1). The random allocation will therefore be concealed.

If a participant is allocated to the intervention group, they will receive a password unique to them for using Kaiketsu-App and Genki-App. Upon entering the password, participants will be able to proceed to the sections for Kaiketsu-App and Genki-App. If participants are allocated to the control group, they will be informed that use of Kaiketsu-App and Genki-App can be resumed if they wish after week 8.

Data management, central monitoring, **data monitoring**, and auditing

We will collect all data except qualitative interview data through e-PRO; we will obtain qualitative

interview data by telephone (See below for details). If participants fail to provide their responses regarding FCR, a CRC blinded to the assignment will telephone the subjects to elicit their answers. Data management and central monitoring will be performed using the EDC. The EDC consists of two different and independent parts, one including personal information and the other including trial-related data (e.g., assignment, outcomes, etc.) for security. **Since the psychological intervention provided by apps will not be invasive and also not produce serious harms, data monitoring committee will not be organized. Similarly auditing is not also planned for this study.**

Dataset available

The de-identified anonymized dataset will be uploaded to UMIN-ICDR (http://www.umin.ac.jp/icdr/index-j.html) and researchers approved by the Steering Committee will be able to have access to the dataset.

Trial period: weeks 0–8

For participants allocated to the intervention group, an automated e-mail encouraging their adherence to Kaiketsu-App and Genki-App will be sent every week for 8 weeks. The research team can check the patient's progress (number of times and duration using each application) with Kaiketsu-App and Genki-App using Google Analytics. At weeks 2, 4, and 8, participants will receive an e-mail encouraging them to record their responses on e-PRO.

Follow-up period: weeks 8–24

Participants allocated to the control group can resume the Kaiketsu-App and Genki-App if they wish. At week 24, participants allocated to the intervention group will receive an e-mail encouraging them to provide their responses on e-PRO.

Concomitant treatments

There is no restriction on concomitant treatments.

Stopping rules for participants

Discontinuation of protocol treatment

If a participant meets any of the following conditions, the research team can discontinue the Kaiketsu-App and Genki-App. However, the participant will not be considered to have dropped out of the trial at that stage and will receive the protocol assessments: (1) the participant wishes to stop the protocol treatment; (2) the research team judges that the risk of the protocol treatment is greater than the benefit for any reason; **(3) the research team judges that it is difficult to continue the protocol treatment because of clinical deterioration**; (4) the research team judges that it is inappropriate to continue the protocol treatment for any reason **(e.g., when identity theft, duplicate entry, etc. is detected)**.

Stopping assessment

If a participant withdraws consent for assessment, she will not be followed up. Subjects will be excluded from the intention-to-treat (ITT) cohort of the trial only if their characteristics are found to meet any exclusion criteria at baseline (e.g., age over 50 years) after participation.

Assessment measures

Table 1 shows the schedule for outcome measurement.

Primary outcome measure

Fear of recurrence: CARS-J

Originally developed in the United States, CARS-J is a 26-item self-report scale to measure fear of recurrence of breast cancer.[34] The reliability and validity of CARS-J has been confirmed among Japanese breast cancer patients.[35] CARS-J assesses the overall fear of breast cancer recurrence and four domains of specific fear of recurrence. Overall fear comprises four items: questions on frequency; potential for upset; consistency; and intensity of fear. The overall fear score with CARS-J is our primary outcome. The range of possible scores for overall fear is 4–24; a higher score indicates greater fear of recurrence.

Secondary outcome measures

Fear of Cancer Recurrence Inventory–Short Form

The Fear of Cancer Recurrence Inventory–Short Form (FCRI-SF) is a nine-item self-report scale,

originally developed in Canada.[36, 37] The FCRI evaluates the presence and severity of intrusive thoughts associated with FCR: scores range from 0 to 36; a higher score indicates severe FCR. Unlike with CARS-J, the FCRI-SF can measure fear of recurrence of any type of cancer. The Japanese version of the FCRI-SF was developed after obtaining permission from the original author and using a forward-backward translation process. In this study, the measure will be included as a secondary outcome after its validity and reliability have been ascertained.

Psychological distress: Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS), a self-report questionnaire comprising 14 items, was developed for use with medically ill patients. The HADS consists of an anxiety and a depression subscale (0–21 points each). The total score ranges from 0 to 42; a higher score indicates more severe depression and anxiety.[38] The Japanese version of the HADS has been validated for cancer populations.[39]

Patients perceived needs: Short-form Supportive Care Needs Survey questionnaire

The Short-form Supportive Care Needs Survey questionnaire (SCNS-SF34) is a self-administered instrument for assessing the perceived needs of cancer patients.[40] The SCNS-SF34 comprises 34 items covering five domains of need: psychological; health system and information; physical and daily living; patient care and support; and sexuality. The total score is obtained by summing all the subscales (range, 34–170). A higher score indicates a higher perceived need. The

validity and reliability of the Japanese version of SCNS-SF34 have been established.[41]

Posttraumatic Growth Inventory-Japanese version

The Posttraumatic Growth Inventory (PTGI) is a 21-item self-report scale, originally developed in the United States.[42] The PTGI includes items that measure positive psychological change experienced as a result of struggle with major life crises or traumatic events. The PTGI-J consists of four subscales: relating to others; new possibilities; personal strength; and spiritual change and appreciation of life. The total score ranges from 0 to 90; a higher score indicates more positive changes.[43]

Satisfaction with intervention

To assess patients' perceived satisfaction with the intervention, we ask two additional items. The items are as follows. (1) "Please rate your satisfaction with the treatment in meeting your needs during the past 2 months by assigning it a score from 0 to 100; a score of 100 indicates complete satisfaction. A score of 60 is considered the passing level." (2) "Please rate your overall satisfaction with the treatment during the past 2 months by assigning it a score from 0 to 100; a score of 100 indicates complete satisfaction. A score of 60 is considered the passing level." A lower score indicates lower satisfaction. We used this method in our previous study.[44]

Understanding e-consent

We will ask ten questions will be asked at week 0 related to the participants' understanding of e-consent: purpose of the study; randomization; voluntarily participation; duration of study; risks and benefits of study participation; free withdrawal anytime from the study; contact method for questions and more detailed information about the study; method of participant identification (uploading a photo of the hospital registration card); which of the video or written documentation in the Web site was the more helpful in understanding the study contents ; and free opinions regarding e-consent.

Qualitative evaluation of intervention

The intervention will consist of multiple complex components; accordingly, simple structured telephone interviews will be conducted at 8 weeks for approximately 30 subjects willing to participate in this additional survey to evaluate the **perceived usability and/or merit** of the complex intervention. The interview items will be as follows. (1) "Please talk freely about the usefulness of the smartphone PST and smartphone behavioral intervention." (2) "Please talk freely about the usefulness of each of the five steps of the smartphone PST and give your reasons for your opinions." (3) "Please talk freely about the usefulness of the two parts of the smartphone behavioral intervention and give your reasons for your opinions." (4) "Please talk freely about the effectiveness and **harms** of the intervention, for example, the regular encouraging e-mail, and if any other components contributed to improving **or deteriorating** your fear of recurrence." If the participants permit, the answers will be recorded using a voice recorder.

Sociodemographic and biomedical factors

e-PRO will also be used to obtain information about the patients' sociodemographic and biomedical status (marital status, level of education, and employment status) and biomedical information (physical function, time since diagnosis, clinical stage, and anti-cancer treatment).

Harms

No specific and serious adverse events are presumed in participants who use the Kaiketsu and Genki-Apps. However, using these apps might lead to psychological distress in some participants depending on their psychological state. We will evaluate these potential adverse events by qualitative evaluation of intervention as mentioned before.

Compensation

Our previous and preliminary trials suggest that few harms occur in this trial. However, if any health hazards occur, these will be covered by the National Health Insurance.

Data analysis

Primary analyses

To examine the treatment effect parameters of all randomly assigned subjects in the primary analysis set according to the ITT principle, we will analyze the primary outcome (CARS-J score at

weeks 2, 4, and 8) using a generalized linear model with unstructured covariance and robust standard errors. The fixed effects are CARS-J score at baseline, treatment allocation (intervention versus control), time (2, 4, and 8 weeks as categorical variable), and treatment-by-time interaction; the random effects are subjects (as intercepts). The primary outcome of interest is the difference in CARS-J scores between the two groups at week 8. A two-sided P value of less than 0.05 will be used to indicate statistical significance.

Secondary analyses

We will perform secondary analyses to supplement our primary analysis and to obtain a clearer understanding of our clinical questions. The secondary analyses will use models similar to that of the primary analysis and will also examine data for the secondary outcome measures. The secondary analyses will include an assessment of the validity and reliability of FCR-J. These analyses will be conducted for exploratory purposes.

Interim analyses

We do not plan any interim analysis.

Sample size estimation

Our previous phase II study revealed that the mean CARS-J scores were 12.8 at pre-intervention (baseline), 12.4 at 4 weeks, and 11.2 at 8 weeks.[27] We assumed the following: the mean CARS-J

score at 2 weeks would be 12.6; the overall CARS-J scores in the control arms would not change (12.8 at 0, 2, 4, and 8 weeks); the variance of the score would be 30 at all times; and the intra-class correlation would be 0.82 (i.e., we assumed a compound symmetry working covariance structure). Thus, for a sample size based on 0.8 power to detect a significant difference at $P = .05$ (two-sided), 211 participants would be required for each arm. Assuming that 5% of the initial entries would drop out, we would need to recruit 444 participants into the trial.

Publication policy

The protocol paper and study results will be submitted to peer-reviewed journals. The first author of the main paper will be a member of the steering committee (authors of the protocol paper). Another person could be the first author if approved by the steering committee. The list of co-authors will be determined before submitting each paper.

Study period

The study period of this trial will be from April 2017 to March 2020; the participant entry period will be April 2018 to September 2019.

Patient and public involvement statement

The study protocol was designed with a patient (breast cancer survivor) and she participated in this study as a researcher. She appropriately discussed with other patients when a patient's preferences

and/or opinions should be considered. She will play a same role on implementing the study. Thus patients were and will be always involved in the study. Results of the study will be shown in the study home page.

Ethics and dissemination

The present study is subject to ethical guidelines for clinical studies published by Japan's Ministry of Education, Science and Technology and Ministry of Health, Labour and Welfare and the modified Act on the Protection of Personal Information as well as the ethical principles established for research on humans stipulated in the Declaration of Helsinki and further amendments thereto.

The protocol was approved by the institutional review board of Nagoya City University on January 15, 2018 (ID: 60-00-1171). If important protocol modifications are needed, the investigators will discuss them and report to the review board for approval.

With regard to dissemination, the results obtained will be submitted for publication in peer-reviewed journals. The main and relevant findings will be presented at conferences.

Discussion

To our knowledge, the present study is the first trial investigating the efficacy of smartphone-based psychological therapy for fear of recurrence among breast cancer survivors. Considering the huge number of breast cancer survivors and low participant rate with other types of therapeutic interventions, smartphone-based psychological therapy may offer a more accessible

option. As many cancer survivors return to their households and to work, easily accessible therapeutic interventions may offer additional benefits in managing fear of recurrence. The present study focuses on younger breast cancer patients who are iPhone users. However, many other patients suffering from fear of recurrence use other types of smartphones (e.g., Android); in addition, including patients aged 50 years and above would constitute a broader targeted population. If the efficacy of the smartphone-based intervention program among our participants is confirmed, the program will have promising applicability in real clinical settings.

The present study has some methodological limitations. First, not all patients who are interested in and willing to use Kaiketsu-App and Genki-App possess a smartphone. This may weaken the applicability of the results from this trial to all breast cancer patients with fear of recurrence. Especially, the results may not be applicable to patients in developing countries and to those with poor ICT literacy.

Second, we will use a wait-list control as the comparator owing to feasibility and ethical considerations. The odds of response was found to be statistically significantly greater for no treatment than the wait list.[45] The wait list may therefore lead to some overestimation of the efficacy of smartphone-based psychotherapy.

Third, we will apply two types of psychotherapy—BA and PST—as interventions. Both psychotherapeutic interventions consist of complex, multifactorial components. Thus, if the interventions prove superior to the wait-list controls, we cannot determine which intervention and components are most efficacious or beneficial in managing fear of recurrence. However, to

overcome this limitation, we will adopt a mixed-method design and can check adherence with each intervention (detailed in "Methods and analysis") so that we can identify the most useful components of the interventions.

Fourth, we will request that participants upload images for identification (they will be especially encouraged to attach a photo of the hospital registration card) to avoid individuals masquerading as breast cancer patients. However, possible deception cannot be completely prevented in our recruitment system.

Author contributions

TA, TAF, and MH developed the smartphone applications and MU and FI also contributed to modification of these applications. TA, TY, MK, FK, NS, TM, TAF, HI, and YU participated in the design of the study. TY played a chief role of the statistical parts. TA drafted the manuscript. All authors participated in, read and approved final manuscript.

Funding

This study is supported by a Grant-in-Aid for Japan Agency for Medical Research and Development (Number JP17ck0106324h). This study is also partly supported in part by a Grant-in-Aid for Scientific Research (Number 25285194) and Young scientists (Number 17k13942) from the Japanese Ministry of Education, Culture, Science, and Technology, grant from Nagoya City

University, Foundation for Promotion of Cancer Research in Japan and The National Cancer Center Research and Development Fund (Number 27-A-3 & 30-A-11).

Competing interests

The authors have no conflicts of interests to declare that may be affected by the publication of the manuscript. TA has received lectures fees from AstraZeneca, Daiichi-Sankyo, Dainippon-Sumitomo, Eizai, Hisamitsu, Lilly, MSD, Meiji-seika Pharma, Mochida, Pfizer, Novartis, Otsuka, Shionogi, Takeda, Tanabe-Mitsubishi, Terumo, and Yoshitomi. TA has received research funds from Daiichi-Sankyo, Eizai, MSD, Pfizer, Novartis, and Tanabe-Mitsubishi. TY received research funds from AC MEDICAL INC., A2 Healthcare Corporation, CAC Croit Corporation, FMD K&L Japan K.K., Japan Tobacco Inc., Japan Media Corporation, Luminary Medical K.K., Medidata Solutions, Inc., ONO PHARMACEUTICAL CO., LTD., Kyowa Hakko Kirin Co., Ltd., DAIICHI SANKYO COMPANY, LIMITED. Also TY received consulting fee from ONO PHARMACEUTICAL CO., LTD., Kowa Company, Ltd., Japan Tobacco Inc., CHUGAI PHARMACEUTICAL CO.,LTD., TSUMURA & CO., CAC Croit Corporation, TSUMURA & CO., ASAHI INTECC CO., LTD., Asahi Kasei Pharma Corporation, Clinical Trial Co.,Ltd. FK has received lecture fees from MSD. TAF has received lecture fees from Janssen, Meiji, Mitsubishi-Tanabe, MSD and Pfizer. He has received research support from Mitsubishi-Tanabe. HI has received lecture fees from Daiichi Sankyo, Chugai, AstraZeneca, Pfizer, and Eisai. He has received research support from Daiichi

Sankyo, Chugai, AstraZeneca, Pfizer, MSD, Kyowahakou Kirin, GSK, Lilly, Novartis, and a Bayer. YU has received lectures fees from Asteras, Daiichi-Sankyo, Dainippon-Sumitomo, Eizai, Jannsen, Kyowahakko-Kirin, Ono, Meiji-seika Pharma, Mochida, Pfizer, Novartis, Otsuka, Sawai, Shionogi, Taiho, Tanabe-Mitsubishi, Tsumura Pharma.

Trial status

The randomized trial, which commenced on 2th, April, 2018, currently enrolls participants. The estimated end date for this study is in March 2020.

Acknowledgments

We thank to Ms. T Mashiko for her data management support. We also thank to Ms. Y Yanase, Ms. A Nomura , Ms. K Tojima, Ms. I. Sakakima, and Ms. K Kobori for their support for the study. We thank Edanz Group (www.edanzediting.com) for editing a draft of this manuscript.

Figure legend

Fig. 1 Participant flow diagram

Fig. 2 Kaiketsu App

Application for smartphone based problem-solving treatment

Fig. 3 Genki App

Application for smartphone based behavioral activation

Fig. 4 Study management system

e-Consent: electric informed consent; e-PRO: electric patient reported outcome

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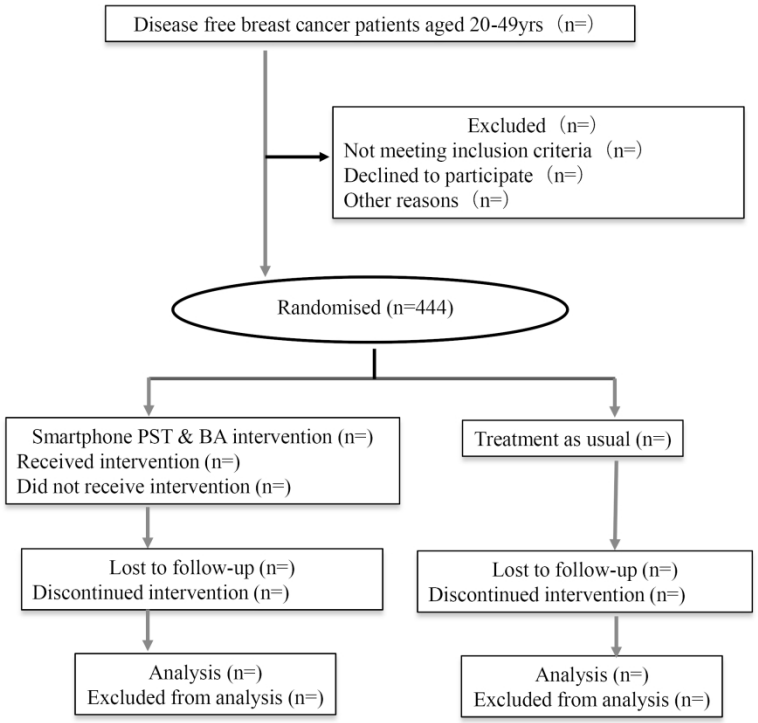


Fig. 1 Participant flow diagram

190x285mm (300 x 300 DPI)

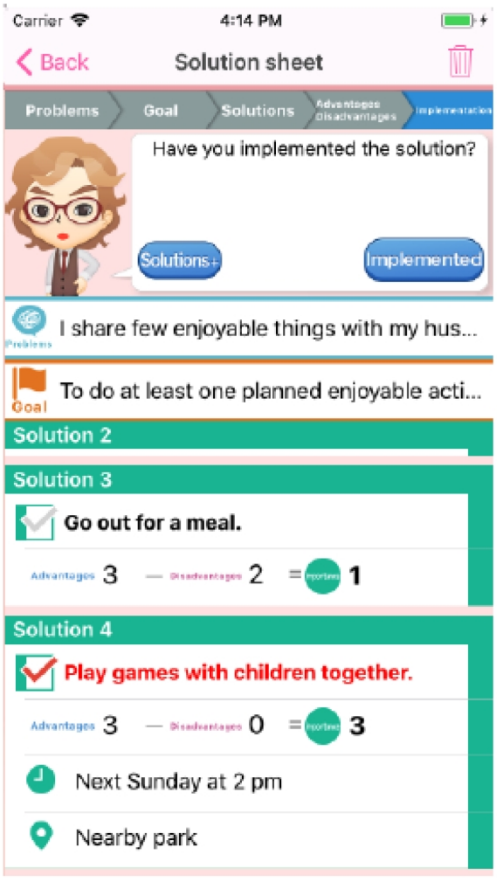


Fig. 2 Kaiketsu App
Application for smartphone based problem-solving treatment

190x285mm (300 x 300 DPI)

Fig. 3 Genki App
Application for smartphone based behavioral activation

190x285mm (300 x 300 DPI)

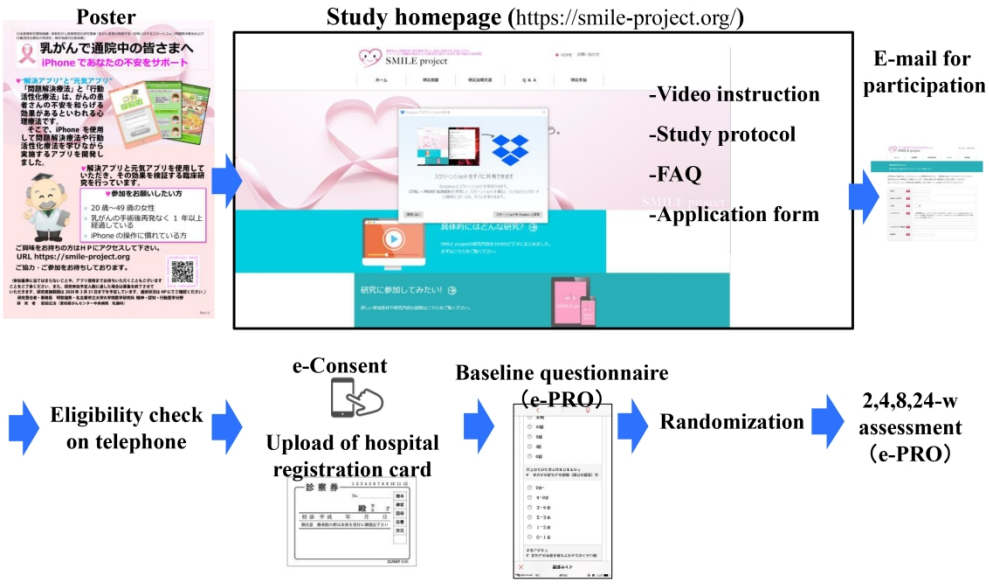


Fig. 4 Study management system
e-Consent: electric informed consent; e-PRO: electric patient reported outcome

285x190mm (300 x 300 DPI)

An appendix table

Details of sessions in smartphone problem-solving and behavioral activation therapies

Smartphone app	Details of each session
Problem-solving therapy (9 sessions)	1. Outline of problem-solving therapy 2. Introduction of 5 step of problem-solving 3. Example of problem-solving 4. First step (identification, definition, and breakdown of the problem) 5. Second step (establishing achievable goals) 6. Third step (generating solutions) 7. Fourth (evaluating and choosing the solution) and fifth step (implementing the chosen solution and evaluating the outcome after implementation) 8. Actual training 9. Concluding session
Behavioral activation therapy (2 sessions)	1. Outline and introduction of behavioral activation therapy including two types of activation (e.g., do pleasurable activity again and challenge new activity) and their actual training 2. Review of the session, learning knack of behavioral activation and concluding session

SMILE project

乳がん患者の再発不安・恐怖に対するスマートフォン問題解決療法および行動活性化療法の有効性のための無作為割付比較試験

メニュー

- ホーム
- 研究説明ビデオ
- 研究概要
- 研究説明文書
- Q & A
- 研究参加

ホーム

はじめに

このホームページは Smile project 研究の内容を説明しています。研究に参加を希望される方は、研究説明ビデオ、研究概要、研究説明文書をご覧ください。

研究説明文書

この試験は、公立大学法人　名古屋市立大学大学院　医学研究科長および名古屋市立大学病院長が設置する医学系研究倫理審査委員会（所在地：名古屋市瑞穂区瑞穂町字川澄１）において医学、歯学、薬学その他の医療又は臨床試験に関する専門家や専門以外の方々により倫理性や科学性が十分であるかどうかの審査を受け、実施することが承認されています。またこの委員会では、この試験が適正に実施されているか継続して審査を行います。なお、本委員会にかかわる規程等は、以下、ホームページよりご確認いただくことができます。

名古屋市立大学病院　臨床研究開発支援センター　ホームページ　“患者の皆様へ”　http://ncu-cr.jp/patient

１説明書の趣旨

【研究参加をお願いする理由】

皆様におかれましては、療養しながら様々な負担を抱えた日々を送っていらっしゃることと推察いたします。私たちのグループは、がんの患者さんによりよいケアを提供するための研究に取り組んでおります。がんの手術後再発なく過ごされていらっしゃる皆様において、再発に対して不安に思われていることを深く理解しております。現在、私たちの研究グループは、スマー

トフォンを用いて日常生活の困り事を解決し、活動の幅を広げることで、再発の不安をどれくらい和らげることができるのかを知るための研究を行っています。この支援方法は有用である可能性がありますが、まだ科学的に証明されていません。

以下に研究の内容について説明してありますので、よくお読みになった上で、ご協力いただける場合には、ウェブで同意をお願いいたします。操作が難しい場合、こちらから文書をダウンロードしていただき、書面として同意書にご署名をお願いいたします。

【研究目的】

多くのがんの患者さんが、治療後の再発の不安を抱えていらっしゃることが明らかになっています。がんの患者さんの不安や恐怖に対し、日常生活の困り事を解決していくこと（これを「問題解決療法」といいます）、楽しくやりがいのある活動を生活に取り入れること（これを「行動活性化療法」といいます）を通して気持ちを和らげることが有効であると言われています。また、近年、スマートフォンが普及し、生活のうえで身近なものになってきていることを踏まえ、私たちのグループはスマートフォンを用いた問題解決療法、行動活性化療法を開発いたしました。この研究は、スマートフォンを

用いてこれら支援を行うことによって、どの程度、精神的な苦痛を和らげることができるかを調べます。

【研究への協力について】

1）研究方法について

このスマートフォンを用いたアプリによる治療が、皆様にとって本当に有用であるかどうかを明らかにするために、コンピューターを使ってランダムに五分五分の確率で、２つのグループに分けて研究を行います。この研究を無作為割り付け対照試験といいます。この方法では患者さんの希望でもなく、医師が選択するのでもなく、誰の意志も入れずに決めることができます。この方法は世界中の臨床試験や医学研究で使われており、治療法に対する医師の先入観が入らずに、より客観的に治療法の効果を確かめることが出来ます。

今回、研究への参加に同意をいただけましたら、皆様は a）「すぐにスマホアプリを開始するグループ」または b）「２ヶ月（8 週間）後からスマホアプリ開始するグループ」のどちらかに割り付けられます。b）「２ヶ月後からスマホアプリ開始するグループ」に割り当てられた場合は、研究開始後 2 カ月（8 週間）たって皆様のご希望があれば、アプリを使用し参加して頂くことができます。

2）皆様に具体的にお願いしたいこと

①アンケート調査

研究に参加していただく皆様に対して、普段の治療やスマートフォンを用いた問題解決療法、行動活性化療法が行われる前後の状態を把握するために、アンケート調査を行います。これによって不安などの気持ちの状態、皆様が必要とする援助（これをニードといいます）、生活の質（クォリティー・オブ・ライフ）などを把握します。

a）「すぐにスマホアプリを開始するグループ」に割り付けられた方は、調査を 5 回実施させて頂く予定で、時期は研究に参加されてから同意時（第 0 週）、第 2 週、第 4 週、第 8 週、第 24 週になります。

b）「２ヶ月（8 週間）後からスマホアプリ開始するグループ」に割り付けられた方は、調査を 4 回実施させて頂く予定で、時期は研究に参加されてから同意時（第 0 週）、第 2 週、第 4 週、第 8 週になります。

この時期になりましたら、iPhone のウェブ上でアンケートにお答えください。（アンケートの入力が完了していない場合、研究事務局からメールやお電話をさせていただく予定ですのでご了承ください）。

また、a）「すぐにスマホアプリを開始するグループ」に割り付けられた方の中でご協力がいただける方に、8 週後の時点で、アプリの有用性をどれぐ

らい感じたか、またどのような点がよかったかなど、電話で聞き取りをさせていただく予定です。

②スマートフォンを用いた問題解決療法、行動活性化療法への参加

1 回目、同意時（第 0 週）のアンケート記入後、a）「すぐにスマホアプリを開始するグループ」に割り付けられた方は、スマートフォンを用いた問題解決療法、行動活性化療法をすぐに実施していただきます。スマートフォンを用いた問題解決療法、行動活性化療法は「解決アプリ」「元気アプリ」を使い、ご自分で進めていただきます（アプリは週におおよそ各 30 分程度かかります。アプリはたくさん実施していただいたほうがより効果的ですので、みなさんの自習を励ますために、事務局からメールを第 8 週までは毎週お送りいたします。）。b）「２ヶ月（8 週間）後からスマホアプリ開始するグループ」に割り付けられた方は、ご希望に応じて、２ヶ月（8 週間）後からアプリを使っていただきます。

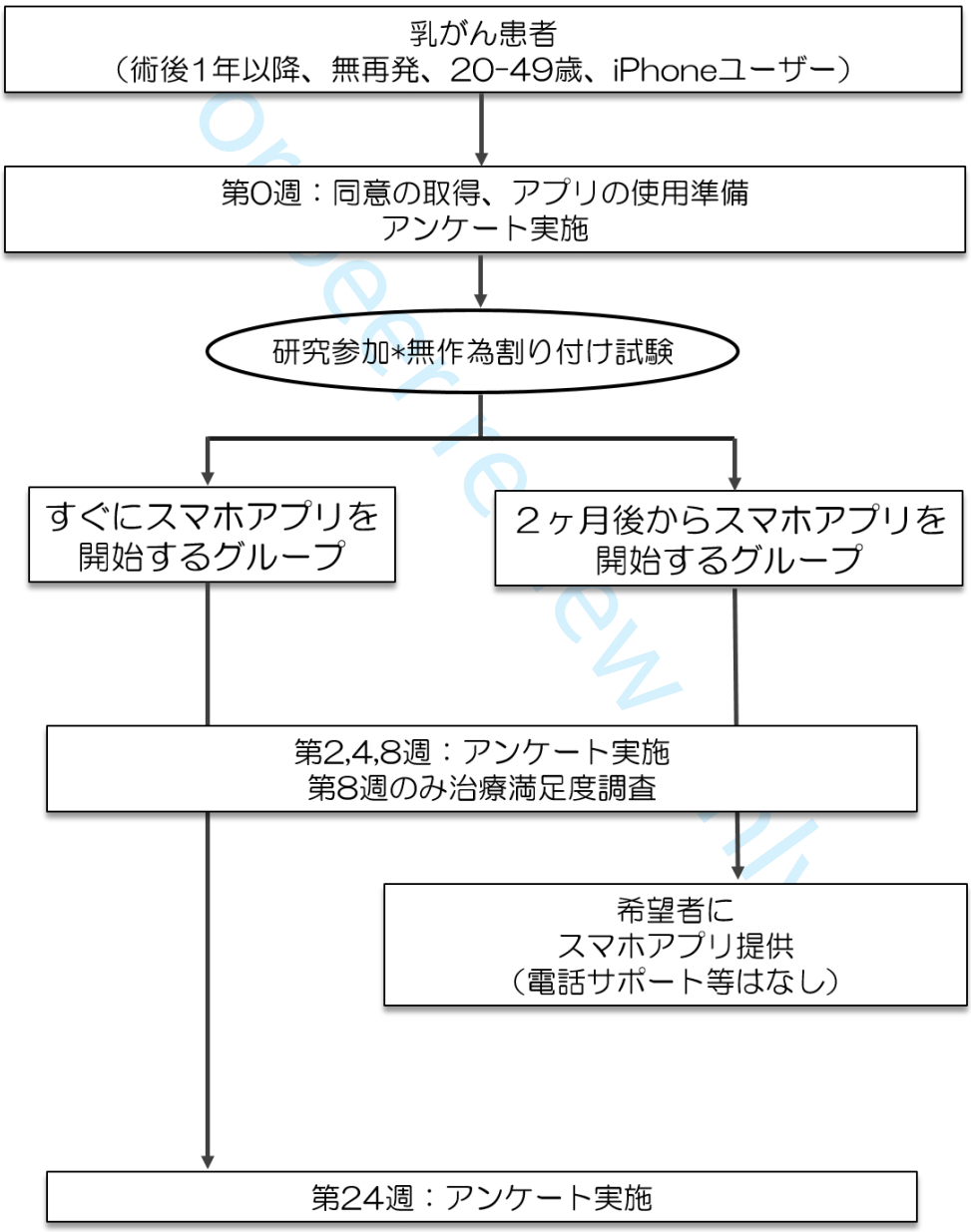
③アプリ内容についての調査

【a）「すぐにスマホアプリを開始するグループ」に割り付けられた方のみ】

研究が終了した時点（第 8 週）で、協力して頂ける方に、アプリを使ってみてよかった点や問題解決療法、行動活性化療法で役に立った部分とその理

由について調査をさせて頂きます。調査は電話で行わせて頂きます（10 分程度を予定しております）。

【研究の流れと研究参加基準】



以下のすべてに当てはまる方は、研究に参加いただけます。

1）同意するときに 20 歳以上 49 歳以下の女性

2）乳がん患者

3）再発や転移がない

4）同意するときに手術から 1 年以上経過していること

5）アンケートに記入・協力できる

6）iPhone または iPad を使用していること（iPad についてはネット環境下での使用をお願いできる方）

また、以下の条件に 1 つでもあてはまる方は、この研究に参加いただけません。

1）重い身体疾患（症状のために家事や軽作業ができない）や乳がん以外のがんをもっている、または、かかったことがある（完治を含む）

2）日本語の読み書きが難しい

3）現在、心療内科、精神科に受診している

4）問題解決療法、行動活性化療法、認知行動療法を経験したことがある

5）研究者が研究への参加を不適当であると判断させていただいた場合

	項目	第 0 週	第 2 週	第 4 週	第 8 週	第 24 週
研究者	説明と同意	○				
データセンター	割り付け	○				
参加者	アンケート	○	○	○	○	○(＊)
	治療満足度				○(＊)	
	アプリの内容調査				○(＊)(**)	

(＊)すぐにスマホアプリを開始するグループのみ

(**) 対象はご協力いただける一部の方のみ

【研究参加は自由意思に任されること】

本研究へのご協力は皆様個人の自由意思によるものです。いったん同意された後でも、理由を明確にすることなくいつでも同意を撤回することができます。不参加や途中撤回の場合でも、何ら不利益は生じません。

2 研究に参加した場合に予想される利益および不利益

本研究では、再発の不安や恐怖に対してスマートフォンを用いた問題解決療法、行動活性化療法を行います。研究に参加して頂くことによって、精神的な負担が軽減し、生活の質が改善する可能性があります。

また、本研究は、アンケートへの記入、メール、スマートフォンのアプリ操作が主で、皆様の身体に与える悪影響はございません。しかしながら、内面的なことに触れることで皆様に不快感を与えることがあるかもしれません。一方、これまでの私どもの同様の研究の経験からは、不利益はほとんどないと考えております。

3 健康被害等への補償

本研究は、ほぼ危険性は伴わないため、研究を行うことによる健康被害に対して補償や賠償保険などは準備しておりません。もし、身体状態や精神状態が悪化した場合には、お手数ですがかかりつけの医療機関でご相談いただければ幸いです。

4 研究の資金源等

本研究は以下の研究費の支援のもと行われています。

- 日本医療研究開発機構研究費「乳がん患者の再発不安・恐怖に対するスマートフォン行動活性化および問題解決療法の有効性-無作為割付比較試験（主任研究者　明智龍男）」
- 名古屋市立大学特別研究奨励費「乳がんサバイバーの再発不安・恐怖に対する Information and communication technology (ICT) を応用した問題解決療法の有用性に関する予備的検討（研究代表者　明智龍男）」
- 文部科学省科学研究費補助金基盤研究 B 「致死的疾患の再発・転移の不安、恐怖の評価法の確立および新規心理学的介入方法の開発（主任研究者　明智龍男）」
- 国立がん研究センター研究開発費「支持療法の開発および検証のための基盤整備（主任研究者　内富庸介）」
- 文部科学省科学研究費補助金若手研究 B 「がん罹患に伴う心理的成長を促すスマートフォンによる問題解決療法の開発と効果検証（主任研究者　今井文信）」

5　個人情報の保護

研究において得られたプライバシーに関する情報は厳重に守られます。皆様の名前などの個人を識別する情報は、この研究の結果の報告や発表に使用されることはございません。

6　研究計画等の開示

皆様が希望すれば、他の参加者の個人情報や本研究の独創性の確保に支障がない範囲内で、研究計画および研究の方法に関する資料を閲覧することができます。閲覧希望の場合は事務局までお問合せください。

7　研究結果及び記録の公表

個人情報が分からないようにした上で、本研究の結果を統計学的に分析し、結果及び臨床試験を通じて得られた皆様に係わる記録が、医学および看護学の発展のため学会や学術雑誌等で公表される予定であることをご了承下さい。なお、アプリによる治療経過における治療内容、アンケートの結果などすべてが分析の対象となります。研究の進み具合やその成果については、ご希望がありましたら説明いたします。

8　研究から生ずる知的所有権について

本研究によって特許が生じた場合は、名古屋市立大学に帰属するものといたします。

9　研究期間中のデータ等について

この研究で得られたアンケート（データ）の結果は、主にスマートフォンを用いた問題解決療法、行動活性化療法の介入前後の状態を比較するために

用います。これらデータ（要配慮個人情報）は、別に作成した対応表で名前や年齢などの個人情報と照合できるような形にいたします。なお前述の対応表は、名古屋市立大学大学院医学研究科精神・認知・行動医学分野内の金庫にて厳重に保管いたします。

10　研究終了後のデータ等について

この研究で得られたデータは、原則として研究終了後 5 年で、名古屋市立大学病院の機密書類として廃棄します。

将来、本データを別の医学・看護学の研究に用いる場合には、改めてその研究について倫理審査委員会に申請し、承認を得た上で実施いたします。

11　費用負担について

スマホアプリはすべて無料でご利用いただけます。ただし、ご利用の携帯電話会社にはアプリの使用時やデータの送受信にかかる通信料はお支払いいただく必要があります。アプリを使って頂くためにパケット定額サービスの加入をお勧めします。また、本研究へのご参加に関して、些少ながら謝礼（アマゾンギフト券を予定）をお送りさせていただきます。

研究組織

研究責任者

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研究分担者

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桜井　なおみ　キャンサー・ソリューションズ株式会社　代表取締役社長

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益子　友恵　　国立がん研究センター社会と健康研究センター健康支援研究部

研究参加

本研究への参加を希望される方は、必要事項をご記入いただき、参加に関する条件に該当しているかを確認の上「参加する」ボタンを 1 回押してください。

氏名	姓　　名
ふりがな	姓　　名
年齢	※20-49 歳がプルダウン等で選択できるようにしてはどうか
携帯番号	
メールアドレス 携帯電話のメールアドレスを入力される方は、予めドメイン「mail.sports-web.jp（仮）」からのメールを受信できる設定にしてください。 Gmail アドレスをご使用の方は必ず「迷惑メール」をご確認ください。	
メールアドレス （確認用）	
乳がん治療のため通院されている病院名	

- ☐ ホームページ上の研究説明ビデオおよび研究概要を確認した
- ☐ 申込時の年齢が 20 歳以上から 49 歳以下である
- ☐ 乳がんと診断されており、現在までに再発・転移はない
- ☐ 乳がんの手術後 1 年以上経過している
- ☐ iPhone または iPad を日常的に使用している

研究に参加する

（研究参加ボタンを押した後）

研究に申込みいただき、ありがとうございました。

参加受付のメールが登録いただいたメールアドレスに届きますので、ご確認をお願いいたします。後日、事務局から問い合わせの電話をさせていただきます。

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Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
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Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	5
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Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	25

sponsor contact information			
Roles and responsibilities: sponsor and funder	#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	25
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Data monitoring: formal committee	#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	13-14
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BMJ Open

Smartphone problem-solving and behavioral activation therapy to reduce fear of recurrence among breast cancer patients (SMartphone Intervention to LEssen fear of cancer recurrence: SMILE project): protocol for a randomized controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-024794.R2
Article Type:	Protocol
Date Submitted by the Author:	27-Sep-2018
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Primary Subject Heading:	Mental health
Secondary Subject Heading:	Mental health
Keywords:	neoplasma, fear of recurrence, cancer survivorship, psychosocial intervention, information and communication technology, quality of life

Study protocol

Title: Smartphone problem-solving and behavioral activation therapy to reduce fear of recurrence among breast cancer patients (**SM**artphone **I**ntervention to **LE**ssen fear of cancer recurrence: **SMILE** project): protocol for a randomized controlled trial

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Protocol version 4.3 (Augst 24, 2018)

Word count: 4577

Abstract

Introduction: One of the most common distressing conditions experienced by breast cancer survivors is fear of cancer recurrence (FCR). There is, however, no standard intervention for ameliorating FCR. Our clinical experience and previous studies have suggested the potential benefits of problem-solving therapy (PST) and behavioral activation (BA). Given the huge number of cancer survivors and limited number of therapists to competently conduct PST and BA, we have developed PST and BA smartphone applications. This study aimed to evaluate the efficacy of the smartphone-based PST (Kaiketsu-App) and BA (Genki-App) apps in reducing FCR in breast cancer patients.

Methods and analysis: The SMartphone Intervention to LEssen fear of cancer recurrence (SMILE) project is an open-label, individually randomized, parallel-group trial. Allocation will be managed by a central server, using a computer-generated random allocation sequence provided by an independent data center. Participants will be randomized to smartphone-based intervention plus treatment as usual (TAU) or wait-list control with TAU alone. The primary end point of the study is the Japanese version of the Concerns About Recurrence Scale, which will be administered as an electronic patient-reported outcome on the patients' smartphone after 8 weeks.

Ethics and dissemination: The present study is subject to the ethical guidelines for clinical studies published by Japan's Ministry of Education, Science and Technology and Ministry of Health, Labour and Welfare and the modified Act on the Protection of Personal Information as well as the ethical principles established for research on humans stipulated in the Declaration of Helsinki and

further amendments thereto. The protocol was approved by the institutional review board of Nagoya City University on January 15, 2018 (ID: 60-00-1171).

Trial registration: UMIN-CTR: UMIN000031140

Article Summary

Strengths and limitations of this study

-This study is the first trial investigating the efficacy of smartphone-based psychological therapy for fear of cancer recurrence (FCR) among breast cancer survivors.

-Because many breast cancer survivors return to their households and work, easily accessible therapeutic interventions without hospital visits may offer benefits.

-This study focuses on younger breast cancer survivors who are iPhone users; this focus could reduce the external validity of the findings obtained.

-The use of the wait-list control conditions may overestimate the efficacy of the smartphone-based psychotherapy.

-We will apply two types of psychotherapy and both interventions consist of complex, multifactorial components; thus, we cannot be certain which intervention and components are most beneficial in managing FCR; however, we will adopt a mixed-method design to overcome those issues.

Introduction

Worldwide, breast cancer is one of the most common cancers among women. In Japan, it is also the most common cancer among women, and the incidence is increasing. At present, approximately 90,000 women in Japan are annually diagnosed with breast cancer. Advances in early detection and individualized medical treatment have improved the survival rate of breast cancer patients. The current 10-year survival rate for breast cancer patients is over 90%, which contributes to the increasing number of breast cancer survivors is increasing.[1]

Thus patients with breast cancer have on average a better prognosis than those with many other types of cancer; however, it has been suggested that many breast cancer survivors suffer from uncertainty anxiety and fear over recurrence. [2-4] Our previous study found that the most common unmet needs experienced by ambulatory breast cancer patients are psychological—especially fear of cancer recurrence (FCR); over half of patients complained of such needs.[5] Among breast cancer patients, FCR is, not only highly prevalent, bu also associated with poor quality of life.[2, 5-8]

Accordingly, there is an urgent need for an appropriate intervention for FCR. However, there is no standard intervention for ameliorating FCR.[8] Recent studies have demonstrated that the following can improve FCR among breast cancer survivors: mindfulness stress reduction (six weekly group sessions); cognitive behavioral therapy (CBT; five individual face-to-face sessions and three e-consultations over a period of 3 months); and the novel theoretically based intervention of ConquerFear, which includes attention training, metacognition, and acceptance and mindfulness (five individual face-to-face sessions over 10 weeks).[9-12] These interventions may be promising;

however, one problem with this kind of intervention is the low participation rate owing to time and distance issues (e.g., over 60% of potentially eligible subjects have been found to decline participation).[9, 11-14] In addition, the number of therapists who can provide such specialized care may be severely limited, which is a serious problem in many countries.

Our past experience and some studies indicate the effectiveness of CBT, including problem-solving therapy (PST) and behavioral activation (BA), for FCR among breast cancer survivors.[15-18] We have demonstrated that patients' problem-solving skills were significantly associated with FCR.[15] Our hypotheses of their underlying mechanisms are that PST contributes to patients' better coping with situations commonly triggering FOR (e.g., pain, exposure to news about cancer, regular visit to cancer hospital, etc.) and other stressful situations that increase FOR and that BA also improves FOR through distraction and through increased sense of mastery and pleasure. PST and BA are straightforward interventions that can be administered by less experienced therapists, including nurses.[19] However, patients willing to undergo PST or BA are rarely able to do so even in well-resourced countries because a typical course of PST or BA consists of eight to 12 face-to-face sessions lasting 1 or 1.5 hours led by a trained therapist.[20-22]

Though such programs seem promising, they appear to suffer similar limitations to those of the above-mentioned therapeutic interventions.[9-12] Given the growing number of women annually diagnosed with breast cancer and the high prevalence among them of unmet needs of FCR, a completely novel approach to therapy provision is required. Recent studies have demonstrated the effectiveness of computerized CBT. [23, 24] In light of recent developments in information and

communication technology (ICT), CBT delivered via smartphones may be a better treatment option for FCR—in terms of accessibility and portability—than a computer-based one.[25] We have recently developed a smartphone CBT app, which teaches skills in BA and cognitive restructuring; we demonstrated its efficacy for antidepressant-resistant major depression in a randomized controlled trial.[26] We have also developed PST programs as a smartphone app and demonstrated the acceptability and efficacy of the smartphone-based PST in a single-arm pilot study with breast cancer survivors.[27] The purpose of the present randomized study is to examine the efficacy of smartphone-based PST and BA interventions to reduce FCR in breast cancer patients in a randomized controlled trial. Since there is no specific standard intervention for ameliorating FCR as mentioned above and our research team's discussion suggests that setting wait-list control will be more feasible than no intervention, wait-list control is used as a comparator.

Methods and analysis

This protocol has been written in accordance with the SPIRIT guideline.[28]

Trial design

The present study is an individually randomized, parallel-group trial (Figure 1). An independent data center will provide computer-generated random allocation sequences. The allocation sequences are maintained centrally, and the results of the assignment will be sent automatically to the study participants by e-mail. The participants are randomized to smartphone-based intervention plus

treatment as usual (TAU) or wait-list control with TAU alone. TAU means general treatment and/or care commonly provided by each patient's hospital (e.g., nurse's support etc.).

Interventions: Smartphone-based PST (Kaiketsu-App) and BA (Genki-App)

PST provides patients with a structured strategy for solving their problems. PST includes the following five steps[29]: (1) identification, definition, and breakdown of the problem; (2) establishing achievable goals; (3) generating solutions; (4) evaluating and choosing the solution; and (5) implementing the chosen solution and evaluating the outcome after implementation.

The smartphone-based PST program, called Kaiketsu-App ("Kaiketsu" means "Solution" in Japanese), for iPhones and iPads (Apple Inc., Cupertino, CA, USA) was developed for this study (Figure 2). The development was based on our empirically supported PST manual.[18] Kaiketsu-App comprises nine sessions **(An appendix table)**: three introductory session; four sessions about learning the PST in five steps; one session of actual training; and one concluding session. The shortest time necessary to complete Kaiketsu-App is 2 weeks. The main program consists of dialogues between characters, who explain the principles and skills of PST. After the first session, participants have to do homework. The time necessary to complete one session is approximately 30 minutes.

BA intervention was developed based on the hypothesis that anxiety can lead to less pleasurable behavior and more sedentary life, which then may lead to worsening anxiety.[29]

The smartphone-based BA program Genki-App ("Genki" means "Energy or Vitality" in Japanese), for iPhones and iPads (Figure 3) was developed as part of the smartphone-based CBT

program which was developed for our previous study.[30] Genki-App consists of two sessions **(**An appendix table), and approximately 30 minutes is needed to complete each session: one is outline and introduction of behavioral activation therapy including two types of activation (e.g., do pleasurable activity again and challenge new activity) and their actual training (**Genki-App includes a self-learning sheet for planning and doing pleasurable and new activity, and for evaluating achievement after conducting its activity.**); the other is review of the session, learning knack of behavioral activation **(Start an activity to be able to conduct by yourself; divide big aim into some smaller ones; plan a schedule to conduct an activity; image a situation when you can do it well)** and concluding session. The shortest time necessary to complete Genki-App is also 2 weeks. The Genki-App program also mainly consists of dialogues between characters and homework.

Over the 8-week period of the programs, participants are encouraged to complete the sessions and homework through automated e-mail reminders once a week. Although we cannot know the contents of homework for privacy security, treatment adherence (e.g., times and length of using each App) can be checked by Google analytics.

Participants

The inclusion criteria for participants are as follows: (1) diagnosis of breast cancer and awareness of the cancer diagnosis; (2) age 20–49 years; (3) 1 year following breast surgery; (4) currently disease free; (5) ability to complete an electronic patient reported outcome (ePRO) using an iPhone or iPad;

(6) being an iPhone or iPad user and having an apple ID to install applications using App Store. We limit the patients' age to 20–49 years because one study and our previous investigation demonstrated that individuals of that age are at high risk of FCR and that more than 50% of such people have smartphones.[8, 31, 32]

The exclusion criteria for participants are as follows: (1) having active, serious physical disease that affects household and light work and a current or past history of cancer other than breast cancer; (2) inability to understand Japanese; (3) currently undergoing follow-up and treatment in a psychiatry department or by other mental health professionals; (4) patients who have previously undergone structured PST, BA therapy, or CBT; (5) judged inappropriate for participation by the researchers (e.g., identity theft, duplicate entry, etc.).

Procedures

Newly developed research management system

To lessen patient inconvenience in visiting hospital for this study and oncologists' workload in enrolling study participants, we developed a research management system making full use of ICT technology (Figure 4). The study's Web site (https://smile-project.org/) provides information about this study. A poster briefly introducing the study and including a QR code for the Web site has been put up in 10 core cancer hospitals in Japan and study information will be disseminated repeatedly by using several social networking systems (e.g., facebook, patient's mailing list etc.). The Web site explains the purpose of the study, eligibility criteria, and methods used; it also features a video

briefly introducing the study as well as providing full written information about it. Potential participants who are interested in the study can e-mail the study's central office, and clinical research coordinators (CRCs) at the central office ascertain their eligibility by telephone (Table 1).

Table 1 Schedule for outcome measurement

		Time points				
		0 week	2 weeks	4 wees	8 weeks	24 weeks
Assessment	Understanding of the e-Consent	●				
	Characteristic	●				
	CARS-J, HADS	●	●	●	●	●*
	FCRI, SCNS-SF34, PTGI-J	●			●	●*
	Satisfaction with interventions				●*	
	Qualitative assessment of apps				●*	

CARS-J: Japanese version of the Concerns About Recurrence Scale

HADS: Hospital Anxiety and Depression Scale

Fear of Cancer Recurrence Inventory short form (FCRI-SF)

SCNS-SF34: Short-form Supportive Care Needs Survey questionnaire

PTGI-J: Posttraumatic Growth Inventory-Japanese

*These would be evaluated only for intervention group

Electronic informed consent and randomization at week 0

After screening, the CRCs will seek to obtain the subjects' electronic informed consent (e-consent) via e-PRO system at week 0. Participants will be requested to upload a picture of identification materials (patients will be especially encouraged to attach a photo of the ID card of the hospital where they made regular follow-up visits for breast cancer). This e-consent procedure is in accordance with the guidance of the US Food and Drug Administration (FDA).[33] Informed consent material-original is shown in an appendix.

After providing e-consent and completing the baseline investigation by e-PRO, the participants will be randomly allocated to either the smartphone-based PST and BA group or the wait-list control group in a 1:1 ratio using the electronic data-capturing Web program (EDC) at the data management center (Figure 1). The random allocation will therefore be concealed.

If a participant is allocated to the intervention group, they will receive a password unique to them for using Kaiketsu-App and Genki-App. Upon entering the password, participants will be able to proceed to the sections for Kaiketsu-App and Genki-App. If participants are allocated to the control group, they will be informed that use of Kaiketsu-App and Genki-App can be resumed if they wish after week 8.

Data management, central monitoring, data monitoring, and auditing

We will collect all data except qualitative interview data through e-PRO; we will obtain qualitative

interview data by telephone (See below for details). If participants fail to provide their responses regarding FCR, a CRC blinded to the assignment will telephone the subjects to elicit their answers. Data management and central monitoring will be performed using the EDC. The EDC consists of two different and independent parts, one including personal information and the other including trial-related data (e.g., assignment, outcomes, etc.) for security. Since the psychological intervention provided by apps will not be invasive and also not produce serious harms, data monitoring committee will not be organized. Similarly auditing is not also planned for this study.

Dataset available

The de-identified anonymized dataset will be uploaded to UMIN-ICDR (http://www.umin.ac.jp/icdr/index-j.html) and researchers approved by the Steering Committee will be able to have access to the dataset.

Trial period: weeks 0–8

For participants allocated to the intervention group, an automated e-mail encouraging their adherence to Kaiketsu-App and Genki-App will be sent every week for 8 weeks. The research team can check the patient's progress (number of times and duration using each application) with Kaiketsu-App and Genki-App using Google Analytics. At weeks 2, 4, and 8, participants will receive an e-mail encouraging them to record their responses on e-PRO.

Follow-up period: weeks 8–24

Participants allocated to the control group can resume the Kaiketsu-App and Genki-App if they wish. At week 24, participants allocated to the intervention group will receive an e-mail encouraging them to provide their responses on e-PRO.

Concomitant treatments

There is no restriction on concomitant treatments.

Stopping rules for participants

Discontinuation of protocol treatment

If a participant meets any of the following conditions, the research team can discontinue the Kaiketsu-App and Genki-App. However, the participant will not be considered to have dropped out of the trial at that stage and will receive the protocol assessments: (1) the participant wishes to stop the protocol treatment; (2) the research team judges that the risk of the protocol treatment is greater than the benefit for any reason; (3) the research team judges that it is difficult to continue the protocol treatment because of clinical deterioration; (4) the research team judges that it is inappropriate to continue the protocol treatment for any reason (e.g., when identity theft, duplicate entry, etc. is detected).

Stopping assessment

If a participant withdraws consent for assessment, she will not be followed up. Subjects will be excluded from the intention-to-treat (ITT) cohort of the trial only if their characteristics are found to meet any exclusion criteria at baseline (e.g., age over 50 years) after participation.

Assessment measures

Table 1 shows the schedule for outcome measurement.

Primary outcome measure

Fear of recurrence: CARS-J

Originally developed in the United States, CARS-J is a 26-item self-report scale to measure fear of recurrence of breast cancer.[34] The reliability and validity of CARS-J has been confirmed among Japanese breast cancer patients.[35] CARS-J assesses the overall fear of breast cancer recurrence and four domains of specific fear of recurrence. Overall fear comprises four items: questions on frequency; potential for upset; consistency; and intensity of fear. The overall fear score with CARS-J is our primary outcome. The range of possible scores for overall fear is 4–24; a higher score indicates greater fear of recurrence.

Secondary outcome measures

Fear of Cancer Recurrence Inventory–Short Form

The Fear of Cancer Recurrence Inventory–Short Form (FCRI-SF) is a nine-item self-report scale, originally developed in Canada.[36, 37] The FCRI evaluates the presence and severity of intrusive

thoughts associated with FCR: scores range from 0 to 36; a higher score indicates severe FCR. Unlike with CARS-J, the FCRI-SF can measure fear of recurrence of any type of cancer. The Japanese version of the FCRI-SF was developed after obtaining permission from the original author and using a forward-backward translation process. In this study, the measure will be included as a secondary outcome after its validity and reliability have been ascertained.

Psychological distress: Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS), a self-report questionnaire comprising 14 items, was developed for use with medically ill patients. The HADS consists of an anxiety and a depression subscale (0–21 points each). The total score ranges from 0 to 42; a higher score indicates more severe depression and anxiety.[38] The Japanese version of the HADS has been validated for cancer populations.[39]

Patients perceived needs: Short-form Supportive Care Needs Survey questionnaire

The Short-form Supportive Care Needs Survey questionnaire (SCNS-SF34) is a self-administered instrument for assessing the perceived needs of cancer patients.[40] The SCNS-SF34 comprises 34 items covering five domains of need: psychological; health system and information; physical and daily living; patient care and support; and sexuality. The total score is obtained by summing all the subscales (range, 34–170). A higher score indicates a higher perceived need. The validity and reliability of the Japanese version of SCNS-SF34 have been established.[41]

Posttraumatic Growth Inventory-Japanese version

The Posttraumatic Growth Inventory (PTGI) is a 21-item self-report scale, originally developed in the United States.[42] The PTGI includes items that measure positive psychological change experienced as a result of struggle with major life crises or traumatic events. The PTGI-J consists of four subscales: relating to others; new possibilities; personal strength; and spiritual change and appreciation of life. The total score ranges from 0 to 90; a higher score indicates more positive changes.[43]

Satisfaction with intervention

To assess patients' perceived satisfaction with the intervention, we ask two additional items. The items are as follows. (1) "Please rate your satisfaction with the treatment in meeting your needs during the past 2 months by assigning it a score from 0 to 100; a score of 100 indicates complete satisfaction. A score of 60 is considered the passing level." (2) "Please rate your overall satisfaction with the treatment during the past 2 months by assigning it a score from 0 to 100; a score of 100 indicates complete satisfaction. A score of 60 is considered the passing level." A lower score indicates lower satisfaction. We used this method in our previous study.[44]

Understanding e-consent

We will ask ten questions will be asked at week 0 related to the participants' understanding of e-

consent: purpose of the study; randomization; voluntarily participation; duration of study; risks and benefits of study participation; free withdrawal anytime from the study; contact method for questions and more detailed information about the study; method of participant identification (uploading a photo of the hospital registration card); which of the video or written documentation in the Web site was the more helpful in understanding the study contents ; and free opinions regarding e-consent.

Qualitative evaluation of intervention

The intervention will consist of multiple complex components; accordingly, simple structured telephone interviews will be conducted at 8 weeks for approximately 30 subjects willing to participate in this additional survey to evaluate the perceived usability and/or merit of the complex intervention. The interview items will be as follows. (1) “Please talk freely about the usefulness of the smartphone PST and smartphone behavioral intervention.” (2) “Please talk freely about the usefulness of each of the five steps of the smartphone PST and give your reasons for your opinions.” (3) “Please talk freely about the usefulness of the two parts of the smartphone behavioral intervention and give your reasons for your opinions.” (4) “Please talk freely about the effectiveness and harms of the intervention, for example, the regular encouraging e-mail, and if any other components contributed to improving or deteriorating your fear of recurrence.” If the participants permit, the answers will be recorded using a voice recorder.

Sociodemographic and biomedical factors

e-PRO will also be used to obtain information about the patients' sociodemographic and biomedical status (marital status, level of education, and employment status) and biomedical information (physical function, time since diagnosis, clinical stage, and anti-cancer treatment).

Harms

No specific and serious adverse events are presumed in participants who use the Kaiketsu and Genki-Apps. However, using these apps might lead to psychological distress in some participants depending on their psychological state. We will evaluate these potential adverse events by qualitative evaluation of intervention as mentioned before.

Compensation

Our previous and preliminary trials suggest that few harms occur in this trial. However, if any health hazards occur, these will be covered by the National Health Insurance.

Data analysis

Primary analyses

To examine the treatment effect parameters of all randomly assigned subjects in the primary analysis set according to the ITT principle, we will analyze the primary outcome (CARS-J score at weeks 2, 4, and 8) using a generalized linear model with unstructured covariance and robust

standard errors. The fixed effects are CARS-J score at baseline, treatment allocation (intervention versus control), time (2, 4, and 8 weeks as categorical variable), and treatment-by-time interaction; the random effects are subjects (as intercepts). The primary outcome of interest is the difference in CARS-J scores between the two groups at week 8. A two-sided P value of less than 0.05 will be used to indicate statistical significance.

Secondary analyses

We will perform secondary analyses to supplement our primary analysis and to obtain a clearer understanding of our clinical questions. The secondary analyses will use models similar to that of the primary analysis and will also examine data for the secondary outcome measures. The secondary analyses will include an assessment of the validity and reliability of FCR-J. These analyses will be conducted for exploratory purposes.

Interim analyses

We do not plan any interim analysis.

Sample size estimation

Our previous phase II study revealed that the mean CARS-J scores were 12.8 at pre-intervention (baseline), 12.4 at 4 weeks, and 11.2 at 8 weeks.[27] We assumed the following: the mean CARS-J score at 2 weeks would be 12.6; the overall CARS-J scores in the control arms would not change

(12.8 at 0, 2, 4, and 8 weeks); the variance of the score would be 30 at all times; and the intra-class correlation would be 0.82 (i.e., we assumed a compound symmetry working covariance structure). Thus, for a sample size based on 0.8 power to detect a significant difference at $P = .05$ (two-sided), 211 participants would be required for each arm. Assuming that 5% of the initial entries would drop out, we would need to recruit 444 participants into the trial.

Publication policy

The protocol paper and study results will be submitted to peer-reviewed journals. The first author of the main paper will be a member of the steering committee (authors of the protocol paper). Another person could be the first author if approved by the steering committee. The list of co-authors will be determined before submitting each paper.

Study period

The study period of this trial will be from April 2017 to March 2020; the participant entry period will be April 2018 to September 2019.

Patient and public involvement statement

The study protocol was designed with a patient (breast cancer survivor) and she participated in this study as a researcher. She appropriately discussed with other patients when a patient's preferences and/or opinions should be considered. She will play a same role on implementing the study. Thus

patients were and will be always involved in the study. Results of the study will be shown in the study home page.

Ethics and dissemination

The present study is subject to ethical guidelines for clinical studies published by Japan's Ministry of Education, Science and Technology and Ministry of Health, Labour and Welfare and the modified Act on the Protection of Personal Information as well as the ethical principles established for research on humans stipulated in the Declaration of Helsinki and further amendments thereto.

The protocol was approved by the institutional review board of Nagoya City University on January 15, 2018 (ID: 60-00-1171). If important protocol modifications are needed, the investigators will discuss them and report to the review board for approval.

With regard to dissemination, the results obtained will be submitted for publication in peer-reviewed journals. The main and relevant findings will be presented at conferences.

Discussion

To our knowledge, the present study is the first trial investigating the efficacy of smartphone-based psychological therapy for fear of recurrence among breast cancer survivors. Considering the huge number of breast cancer survivors and low participant rate with other types of therapeutic interventions, smartphone-based psychological therapy may offer a more accessible option. As many cancer survivors return to their households and to work, easily accessible

therapeutic interventions may offer additional benefits in managing fear of recurrence. The present study focuses on younger breast cancer patients who are iPhone users. However, many other patients suffering from fear of recurrence use other types of smartphones (e.g., Android); in addition, including patients aged 50 years and above would constitute a broader targeted population. If the efficacy of the smartphone-based intervention program among our participants is confirmed, the program will have promising applicability in real clinical settings.

The present study has some methodological limitations. First, not all patients who are interested in and willing to use Kaiketsu-App and Genki-App possess a smartphone. This may weaken the applicability of the results from this trial to all breast cancer patients with fear of recurrence. Especially, the results may not be applicable to patients in developing countries and to those with poor ICT literacy.

Second, we will use a wait-list control as the comparator owing to feasibility and ethical considerations. The odds of response was found to be statistically significantly greater for no treatment than the wait list.[45] The wait list may therefore lead to some overestimation of the efficacy of smartphone-based psychotherapy.

Third, we will apply two types of psychotherapy—BA and PST—as interventions. Both psychotherapeutic interventions consist of complex, multifactorial components. Thus, if the interventions prove superior to the wait-list controls, we cannot determine which intervention and components are most efficacious or beneficial in managing fear of recurrence. However, to overcome this limitation, we will adopt a mixed-method design and can check adherence with each

intervention (detailed in "Methods and analysis") so that we can identify the most useful components of the interventions.

Fourth, we will request that participants upload images for identification (they will be especially encouraged to attach a photo of the hospital registration card) to avoid individuals masquerading as breast cancer patients. However, possible deception cannot be completely prevented in our recruitment system.

Finally, lack of the third group, which is the in-person PST and BA treatment arm, would lessen the impact of this study. If we set the in-person PST and BA treatment arm to compare effect sizes in this group to the other two groups, we would be able to dissect the specific mechanisms of change.

Author contributions

TA, TAF, and MH developed the smartphone applications and MU and FI also contributed to modification of these applications. TA, TY, MK, FK, NS, TM, TAF, HI, and YU participated in the design of the study. TY played a chief role of the statistical parts. TA drafted the manuscript. All authors participated in, read and approved final manuscript.

Funding

This study is supported by a Grant-in-Aid for Japan Agency for Medical Research and Development (Number JP17ck0106324h). This study is also partly supported in part by a Grant-in-Aid for

Scientific Research (Number 25285194) and Young scientists (Number 17k13942) from the Japanese Ministry of Education, Culture, Science, and Technology, grant from Nagoya City University, Foundation for Promotion of Cancer Research in Japan and The National Cancer Center Research and Development Fund (Number 27-A-3 & 30-A-11).

Competing interests

The authors have no conflicts of interests to declare that may be affected by the publication of the manuscript. TA has received lectures fees from AstraZeneca, Daiichi-Sankyo, Dainippon-Sumitomo, Eizai, Hisamitsu, Lilly, MSD, Meiji-seika Pharma, Mochida, Pfizer, Novartis, Otsuka, Shionogi, Takeda, Tanabe-Mitsubishi, Terumo, and Yoshitomi. TA has received research funds from Daiichi-Sankyo, Eizai, MSD, Pfizer, Novartis, and Tanabe-Mitsubishi. TY received research funds from AC MEDICAL INC., A2 Healthcare Corporation, CAC Croit Corporation, FMD K&L Japan K.K., Japan Tobacco Inc., Japan Media Corporation, Luminary Medical K.K., Medidata Solutions, Inc., ONO PHARMACEUTICAL CO., LTD., Kyowa Hakko Kirin Co., Ltd., DAIICHI SANKYO COMPANY, LIMITED. Also TY received consulting fee from ONO PHARMACEUTICAL CO., LTD., Kowa Company, Ltd., Japan Tobacco Inc., CHUGAI PHARMACEUTICAL CO.,LTD., TSUMURA & CO., CAC Croit Corporation, TSUMURA & CO., ASAHI INTECC CO., LTD., Asahi Kasei Pharma Corporation, Clinical Trial Co.,Ltd. FK has received lecture fees from MSD. TAF has received lecture fees from Janssen, Meiji, Mitsubishi-Tanabe, MSD and Pfizer. He has

received research support from Mitsubishi-Tanabe. HI has received lecture fees from Daiichi Sankyo, Chugai, AstraZeneca, Pfizer, and Eisai. He has received research support from Daiichi Sankyo, Chugai, AstraZeneca, Pfizer, MSD, Kyowahakou Kirin, GSK, Lilly, Novartis, and a Bayer. YU has received lectures fees from Asteras, Daiichi-Sankyo, Dainippon-Sumitomo, Eizai, Jannsen, Kyowahakko-Kirin, Ono, Meiji-seika Pharma, Mochida, Pfizer, Novartis, Otsuka, Sawai, Shionogi, Taiho, Tanabe-Mitsubishi, Tsumura Pharma.

Trial status

The randomized trial, which commenced on 2th, April, 2018, currently enrolls participants. The estimated end date for this study is in March 2020.

Acknowledgments

We thank to Ms. T Mashiko for her data management support. We also thank to Ms. Y Yanase, Ms. A Nomura , Ms. K Tojima, Ms. I. Sakakima, and Ms. K Kobori for their support for the study. We thank Edanz Group (www.edanzediting.com) for editing a draft of this manuscript.

Figure legend

Fig. 1 Participant flow diagram

Fig. 2 Kaiketsu App

Application for smartphone based problem-solving treatment

Fig. 3 Genki App

Application for smartphone based behavioral activation

Fig. 4 Study management system

e-Consent: electric informed consent; e-PRO: electric patient reported outcome

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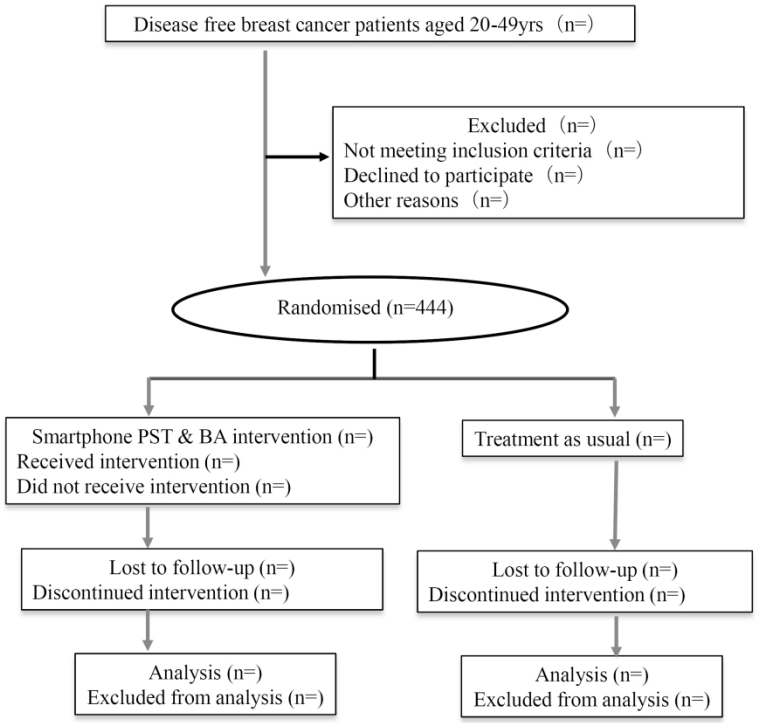


Fig. 1 Participant flow diagram

190x285mm (300 x 300 DPI)

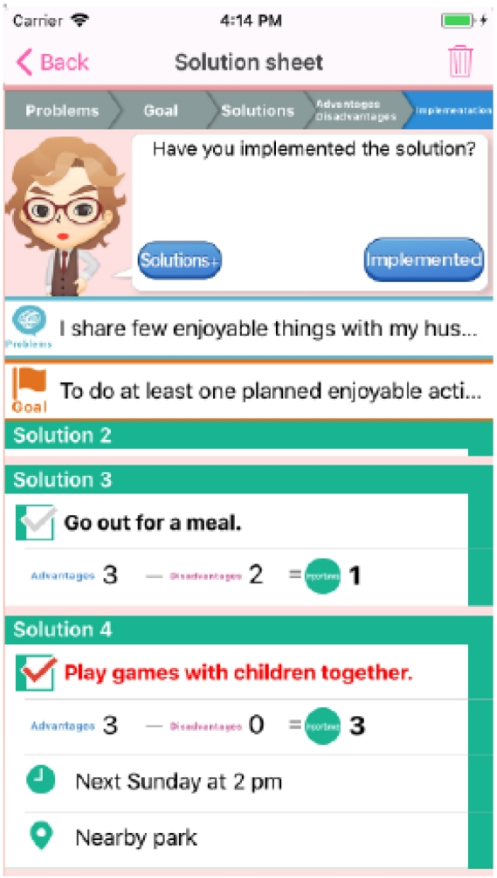


Fig. 2 Kaiketsu App
Application for smartphone based problem-solving treatment

190x285mm (300 x 300 DPI)

Fig. 3 Genki App
Application for smartphone based behavioral activation

190x285mm (300 x 300 DPI)

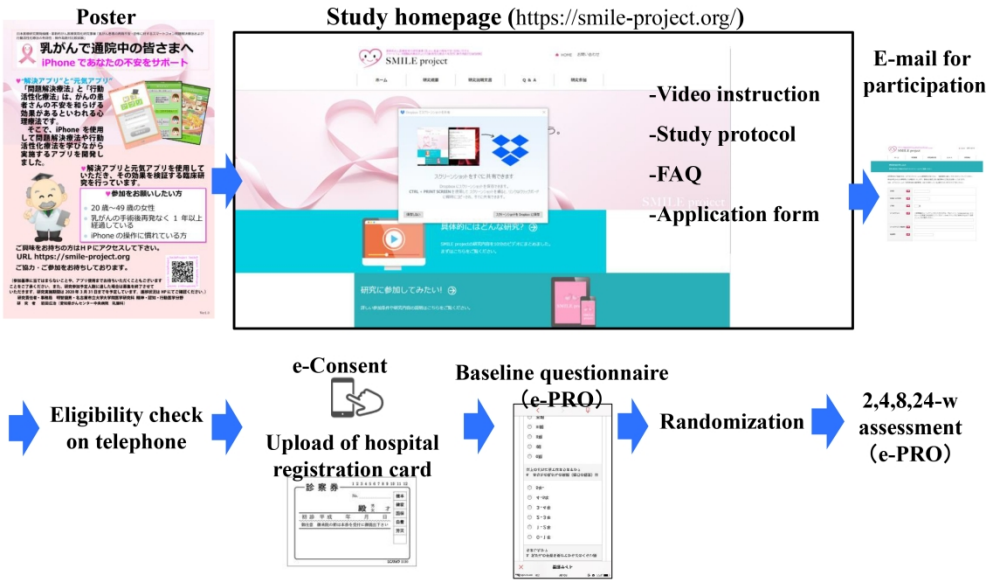


Fig. 4 Study management system
e-Consent: electric informed consent; e-PRO: electric patient reported outcome

285x190mm (300 x 300 DPI)

An appendix table

Details of sessions in smartphone problem-solving and behavioral activation therapies

Smartphone app	Details of each session
Problem-solving therapy (9 sessions)	1. Outline of problem-solving therapy 2. Introduction of 5 step of problem-solving 3. Example of problem-solving 4. First step (identification, definition, and breakdown of the problem) 5. Second step (establishing achievable goals) 6. Third step (generating solutions) 7. Fourth (evaluating and choosing the solution) and fifth step (implementing the chosen solution and evaluating the outcome after implementation) 8. Actual training 9. Concluding session
Behavioral activation therapy (2 sessions)	1. Outline and introduction of behavioral activation therapy including two types of activation (e.g., do pleasurable activity again and challenge new activity) and their actual training 2. Review of the session, learning knack of behavioral activation and concluding session

SMILE project

乳がん患者の再発不安・恐怖に対するスマートフォン問題解決療法および行動活性化療法の有効性のための無作為割付比較試験

メニュー

- ホーム
- 研究説明ビデオ
- 研究概要
- 研究説明文書
- Q & A
- 研究参加

ホーム

はじめに

このホームページは Smile project 研究の内容を説明しています。研究に参加を希望される方は、研究説明ビデオ、研究概要、研究説明文書をご覧ください。

研究説明文書

この試験は、公立大学法人　名古屋市立大学大学院　医学研究科長および名古屋市立大学病院長が設置する医学系研究倫理審査委員会（所在地：名古屋市瑞穂区瑞穂町字川澄１）において医学、歯学、薬学その他の医療又は臨床試験に関する専門家や専門以外の方々により倫理性や科学性が十分であるかどうかの審査を受け、実施することが承認されています。またこの委員会では、この試験が適正に実施されているか継続して審査を行います。なお、本委員会にかかわる規程等は、以下、ホームページよりご確認いただくことができます。

名古屋市立大学病院　臨床研究開発支援センター　ホームページ　“患者の皆様へ”　http://ncu-cr.jp/patient

１説明書の趣旨

【研究参加をお願いする理由】

皆様におかれましては、療養しながら様々な負担を抱えた日々を送っていらっしゃることと推察いたします。私たちのグループは、がんの患者さんによりよいケアを提供するための研究に取り組んでおります。がんの手術後再発なく過ごされていらっしゃる皆様において、再発に対して不安に思われていることを深く理解しております。現在、私たちの研究グループは、スマー

トフォンを用いて日常生活の困り事を解決し、活動の幅を広げることで、再発の不安をどれくらい和らげることができるのかを知るための研究を行っています。この支援方法は有用である可能性がありますが、まだ科学的に証明されていません。

以下に研究の内容について説明してありますので、よくお読みになった上で、ご協力いただける場合には、ウェブで同意をお願いいたします。操作が難しい場合、こちらから文書をダウンロードしていただき、書面として同意書にご署名をお願いいたします。

【研究目的】

多くのがんの患者さんが、治療後の再発の不安を抱えていらっしゃることが明らかになっています。がんの患者さんの不安や恐怖に対し、日常生活の困り事を解決していくこと（これを「問題解決療法」といいます）、楽しくやりがいのある活動を生活に取り入れること（これを「行動活性化療法」といいます）を通して気持ちを和らげることが有効であると言われています。また、近年、スマートフォンが普及し、生活のうえで身近なものになってきていることを踏まえ、私たちのグループはスマートフォンを用いた問題解決療法、行動活性化療法を開発いたしました。この研究は、スマートフォンを

用いてこれら支援を行うことによって、どの程度、精神的な苦痛を和らげることができるかを調べます。

【研究への協力について】

1）研究方法について

このスマートフォンを用いたアプリによる治療が、皆様にとって本当に有用であるかどうかを明らかにするために、コンピューターを使ってランダムに五分五分の確率で、２つのグループに分けて研究を行います。この研究を無作為割り付け対照試験といいます。この方法では患者さんの希望でもなく、医師が選択するのでもなく、誰の意志も入れずに決めることができます。この方法は世界中の臨床試験や医学研究で使われており、治療法に対する医師の先入観が入らずに、より客観的に治療法の効果を確かめることが出来ます。

今回、研究への参加に同意をいただけましたら、皆様は a）「すぐにスマホアプリを開始するグループ」または b）「２ヶ月（8 週間）後からスマホアプリ開始するグループ」のどちらかに割り付けられます。b）「２ヶ月後からスマホアプリ開始するグループ」に割り当てられた場合は、研究開始後 2 カ月（8 週間）たって皆様のご希望があれば、アプリを使用し参加して頂くことができます。

2）皆様に具体的にお願いしたいこと

①アンケート調査

研究に参加していただく皆様に対して、普段の治療やスマートフォンを用いた問題解決療法、行動活性化療法が行われる前後の状態を把握するために、アンケート調査を行います。これによって不安などの気持ちの状態、皆様が必要とする援助（これをニードといいます）、生活の質（クォリティー・オブ・ライフ）などを把握します。

a）「すぐにスマホアプリを開始するグループ」に割り付けられた方は、調査を 5 回実施させて頂く予定で、時期は研究に参加されてから同意時（第 0 週）、第 2 週、第 4 週、第 8 週、第 24 週になります。

b）「２ヶ月（8 週間）後からスマホアプリ開始するグループ」に割り付けられた方は、調査を 4 回実施させて頂く予定で、時期は研究に参加されてから同意時（第 0 週）、第 2 週、第 4 週、第 8 週になります。

この時期になりましたら、iPhone のウェブ上でアンケートにお答えください。（アンケートの入力が完了していない場合、研究事務局からメールやお電話をさせていただく予定ですのでご了承ください）。

また、a）「すぐにスマホアプリを開始するグループ」に割り付けられた方の中でご協力がいただける方に、8 週後の時点で、アプリの有用性をどれぐ

らい感じたか、またどのような点がよかったかなど、電話で聞き取りをさせていただく予定です。

②スマートフォンを用いた問題解決療法、行動活性化療法への参加

1 回目、同意時（第 0 週）のアンケート記入後、a）「すぐにスマホアプリを開始するグループ」に割り付けられた方は、スマートフォンを用いた問題解決療法、行動活性化療法をすぐに実施していただきます。スマートフォンを用いた問題解決療法、行動活性化療法は「解決アプリ」「元気アプリ」を使い、ご自分で進めていただきます（アプリは週におおよそ各 30 分程度かかります。アプリはたくさん実施していただいたほうがより効果的ですので、みなさんの自習を励ますために、事務局からメールを第 8 週までは毎週お送りいたします。）。b）「２ヶ月（8 週間）後からスマホアプリ開始するグループ」に割り付けられた方は、ご希望に応じて、２ヶ月（8 週間）後からアプリを使っていただきます。

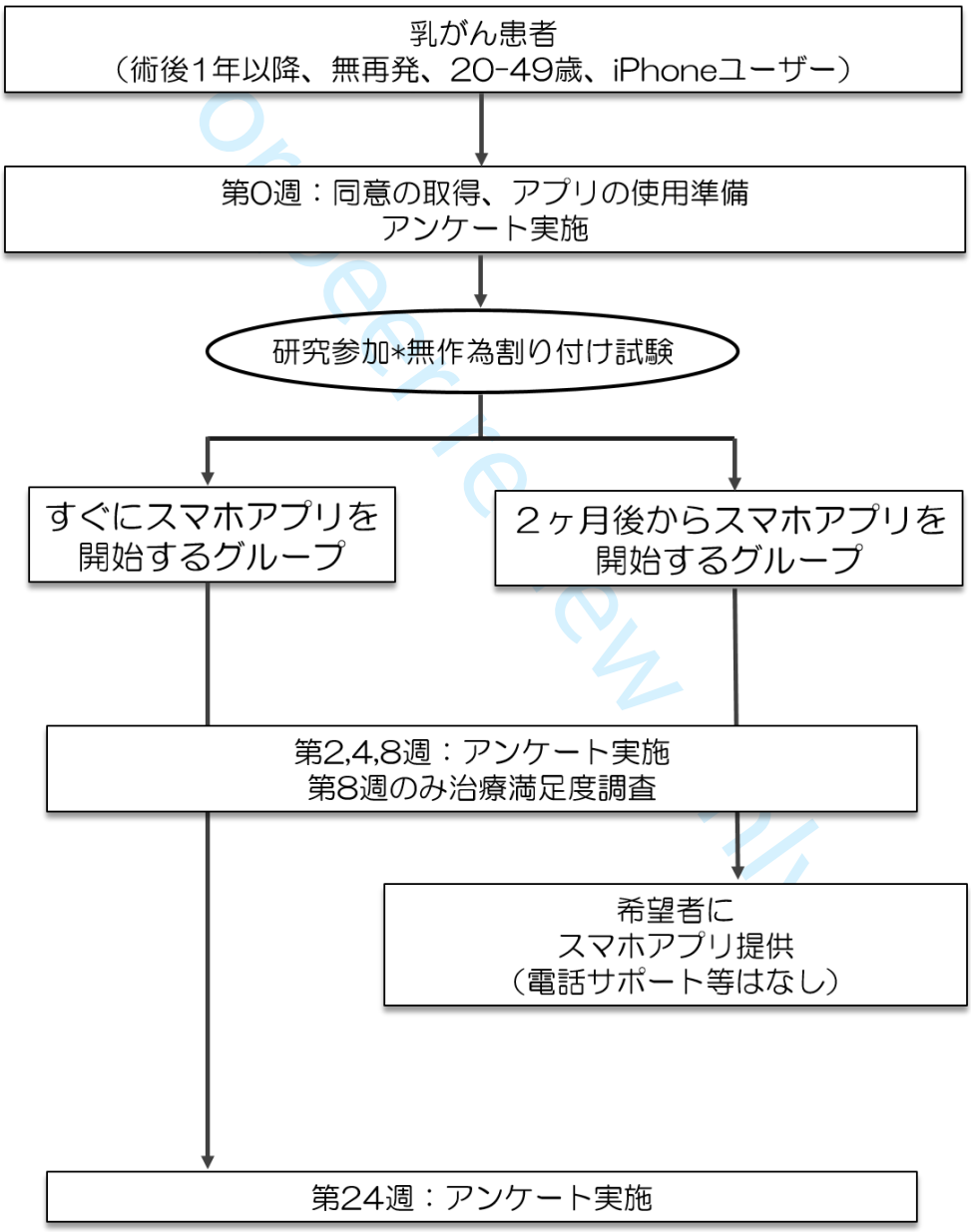
③アプリ内容についての調査

【a）「すぐにスマホアプリを開始するグループ」に割り付けられた方のみ】

研究が終了した時点（第 8 週）で、協力して頂ける方に、アプリを使ってみてよかった点や問題解決療法、行動活性化療法で役に立った部分とその理

由について調査をさせて頂きます。調査は電話で行わせて頂きます（10 分程度を予定しております）。

【研究の流れと研究参加基準】



以下のすべてに当てはまる方は、研究に参加いただけます。

1）同意するときに 20 歳以上 49 歳以下の女性

2）乳がん患者

3）再発や転移がない

4）同意するときに手術から 1 年以上経過していること

5）アンケートに記入・協力できる

6）iPhone または iPad を使用していること（iPad についてはネット環境下での使用をお願いできる方）

また、以下の条件に 1 つでもあてはまる方は、この研究に参加いただけません。

1）重い身体疾患（症状のために家事や軽作業ができない）や乳がん以外のがんをもっている、または、かかったことがある（完治を含む）

2）日本語の読み書きが難しい

3）現在、心療内科、精神科に受診している

4）問題解決療法、行動活性化療法、認知行動療法を経験したことがある

5）研究者が研究への参加を不適当であると判断させていただいた場合

	項目	第 0 週	第 2 週	第 4 週	第 8 週	第 24 週
研究者	説明と同意	○				
データセンター	割り付け	○				
参加者	アンケート	○	○	○	○	○(＊)
	治療満足度				○(＊)	
	アプリの内容調査				○(＊)(**)	

(＊)すぐにスマホアプリを開始するグループのみ

(**) 対象はご協力いただける一部の方のみ

【研究参加は自由意思に任されること】

本研究へのご協力は皆様個人の自由意思によるものです。いったん同意された後でも、理由を明確にすることなくいつでも同意を撤回することができます。不参加や途中撤回の場合でも、何ら不利益は生じません。

2 研究に参加した場合に予想される利益および不利益

本研究では、再発の不安や恐怖に対してスマートフォンを用いた問題解決療法、行動活性化療法を行います。研究に参加して頂くことによって、精神的な負担が軽減し、生活の質が改善する可能性があります。

また、本研究は、アンケートへの記入、メール、スマートフォンのアプリ操作が主で、皆様の身体に与える悪影響はございません。しかしながら、内面的なことに触れることで皆様に不快感を与えることがあるかもしれません。一方、これまでの私どもの同様の研究の経験からは、不利益はほとんどないと考えております。

3 健康被害等への補償

本研究は、ほぼ危険性は伴わないため、研究を行うことによる健康被害に対して補償や賠償保険などは準備しておりません。もし、身体状態や精神状態が悪化した場合には、お手数ですがかかりつけの医療機関でご相談いただければ幸いです。

4 研究の資金源等

本研究は以下の研究費の支援のもと行われています。

- 日本医療研究開発機構研究費「乳がん患者の再発不安・恐怖に対するスマートフォン行動活性化および問題解決療法の有効性-無作為割付比較試験（主任研究者　明智龍男）」
- 名古屋市立大学特別研究奨励費「乳がんサバイバーの再発不安・恐怖に対する Information and communication technology (ICT) を応用した問題解決療法の有用性に関する予備的検討（研究代表者　明智龍男）」
- 文部科学省科学研究費補助金基盤研究 B 「致死的疾患の再発・転移の不安、恐怖の評価法の確立および新規心理学的介入方法の開発（主任研究者　明智龍男）」
- 国立がん研究センター研究開発費「支持療法の開発および検証のための基盤整備（主任研究者　内富庸介）」
- 文部科学省科学研究費補助金若手研究 B 「がん罹患に伴う心理的成長を促すスマートフォンによる問題解決療法の開発と効果検証（主任研究者　今井文信）」

5　個人情報の保護

研究において得られたプライバシーに関する情報は厳重に守られます。皆様の名前などの個人を識別する情報は、この研究の結果の報告や発表に使用されることはございません。

6　研究計画等の開示

皆様が希望すれば、他の参加者の個人情報や本研究の独創性の確保に支障がない範囲内で、研究計画および研究の方法に関する資料を閲覧することができます。閲覧希望の場合は事務局までお問合せください。

7　研究結果及び記録の公表

個人情報が分からないようにした上で、本研究の結果を統計学的に分析し、結果及び臨床試験を通じて得られた皆様に係わる記録が、医学および看護学の発展のため学会や学術雑誌等で公表される予定であることをご了承下さい。なお、アプリによる治療経過における治療内容、アンケートの結果などすべてが分析の対象となります。研究の進み具合やその成果については、ご希望がありましたら説明いたします。

8　研究から生ずる知的所有権について

本研究によって特許が生じた場合は、名古屋市立大学に帰属するものといたします。

9　研究期間中のデータ等について

この研究で得られたアンケート（データ）の結果は、主にスマートフォンを用いた問題解決療法、行動活性化療法の介入前後の状態を比較するために

用います。これらデータ（要配慮個人情報）は、別に作成した対応表で名前や年齢などの個人情報と照合できるような形にいたします。なお前述の対応表は、名古屋市立大学大学院医学研究科精神・認知・行動医学分野内の金庫にて厳重に保管いたします。

10　研究終了後のデータ等について

この研究で得られたデータは、原則として研究終了後 5 年で、名古屋市立大学病院の機密書類として廃棄します。

将来、本データを別の医学・看護学の研究に用いる場合には、改めてその研究について倫理審査委員会に申請し、承認を得た上で実施いたします。

11　費用負担について

スマホアプリはすべて無料でご利用いただけます。ただし、ご利用の携帯電話会社にはアプリの使用時やデータの送受信にかかる通信料はお支払いいただく必要があります。アプリを使って頂くためにパケット定額サービスの加入をお勧めします。また、本研究へのご参加に関して、些少ながら謝礼（アマゾンギフト券を予定）をお送りさせていただきます。

研究組織

研究責任者

明智龍男　名古屋市立大学大学院医学研究科・精神・認知・行動医学　教授

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益子　友恵　　国立がん研究センター社会と健康研究センター健康支援研究部

研究参加

本研究への参加を希望される方は、必要事項をご記入いただき、参加に関する条件に該当しているかを確認の上「参加する」ボタンを 1 回押してください。

氏名	姓　　名
ふりがな	姓　　名
年齢	※20-49 歳がプルダウン等で選択できるようにしてはどうか
携帯番号	
メールアドレス 携帯電話のメールアドレスを入力される方は、予めドメイン「mail.sports-web.jp（仮）」からのメールを受信できる設定にしてください。 Gmail アドレスをご使用の方は必ず「迷惑メール」をご確認ください。	
メールアドレス （確認用）	
乳がん治療のため通院されている病院名	

- ☐ ホームページ上の研究説明ビデオおよび研究概要を確認した
- ☐ 申込時の年齢が 20 歳以上から 49 歳以下である
- ☐ 乳がんと診断されており、現在までに再発・転移はない
- ☐ 乳がんの手術後 1 年以上経過している
- ☐ iPhone または iPad を日常的に使用している

研究に参加する

（研究参加ボタンを押した後）

研究に申込みいただき、ありがとうございました。

参加受付のメールが登録いただいたメールアドレスに届きますので、ご確認をお願いいたします。後日、事務局から問い合わせの電話をさせていただきます。

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
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	5
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	5
Protocol version	#3	Date and version identifier	3
Funding	#4	Sources and types of financial, material, and other support	25
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	25
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	25

sponsor contact information			
Roles and responsibilities: sponsor and funder	#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	25
Roles and responsibilities: committees	#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)	13-14
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	6-8
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	**8**
Objectives	#7	Specific objectives or hypotheses	8
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, non-inferiority, exploratory)	8-9
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	10-11
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)	10-11
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-10

Interventions: modifications	#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)	15
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	10
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	15
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	16-20
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)	Fig 1
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	21-22
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	11
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8, 13
Allocation concealment	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed	8, 13

mechanism		envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8, 13
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13-14
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	8-9, 13-14
Data collection plan	#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	Table 1 16-20
Data collection plan: retention	#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	15
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	Table 1 13-14
Statistics: outcomes	#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	20-21
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	20-21
Statistics: analysis population and missing data	#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)	15-16 20-21

Data monitoring: formal committee	#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	13-14
Data monitoring: interim analysis	#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	19, 20
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13-14
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	22-23
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)	23
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13-14
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	25-26
Data access	#29	Statement of who will have access to the final trial dataset,	14

		and disclosure of contractual agreements that limit such access for investigators	
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	**20**
Dissemination policy: trial results	#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	22-23
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	22, 27
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	14
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	13
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

Note from the Editors: Instructions for reviewers of study protocols

Since launching in 2011, BMJ Open has published study protocols for planned or ongoing research studies. If data collection is complete, we will not consider the manuscript.

Publishing study protocols enables researchers and funding bodies to stay up to date in their fields by providing exposure to research activity that may not otherwise be widely publicised. This can help prevent unnecessary duplication of work and will hopefully enable collaboration. Publishing protocols in full also makes available more information than is currently required by trial registries and increases transparency, making it easier for others (editors, reviewers and readers) to see and understand any deviations from the protocol that occur during the conduct of the study.

The scientific integrity and the credibility of the study data depend substantially on the study design and methodology, which is why the study protocol requires a thorough peer-review.

BMJ Open will consider for publication protocols for any study design, including observational studies and systematic reviews.

Some things to keep in mind when reviewing the study protocol:

- Protocol papers should report planned or ongoing studies. The dates of the study should be included in the manuscript.
- Unfortunately we are unable to customize the reviewer report form for study protocols. As such, some of the items (i.e., those pertaining to results) on the form should be scored as Not Applicable (N/A).
- While some baseline data can be presented, there should be no results or conclusions present in the study protocol.
- For studies that are ongoing, it is generally the case that very few changes can be made to the methodology. As such, requests for revisions are generally clarifications for the rationale or details relating to the methods. If there is a major flaw in the study that would prevent a sound interpretation of the data, we would expect the study protocol to be rejected.