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Four 2×2 factorial trials of smartphone CBT to reduce subthreshold depression and to prevent new depressive episodes among adults in the community–RESiLIENT trial (Resilience Enhancement with Smartphone in LIving ENvironmenTs): a master protocol

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ABSTRACT

Introduction The health burden due to depression is ever increasing in the world. Prevention is a key to reducing this burden. Guided internet cognitive–behavioural therapies (iCBT) appear promising but there is room for improvement because we do not yet know which of various iCBT skills are more efficacious than others, and for whom. In addition, there has been no platform for iCBT that can accommodate ongoing evolution of internet technologies.

Methods and analysis Based on our decade-long experiences in developing smartphone CBT apps and examining them in randomised controlled trials, we have developed the Resilience Training App Version 2. This app now covers five CBT skills: cognitive restructuring, behavioural activation, problem-solving, assertion training and behaviour therapy for insomnia. The current study is designed as a master protocol including four 2×2 factorial trials using this app (1) to elucidate specific efficacies of each CBT skill, (2) to identify participants' characteristics that enable matching between skills and individuals, and (3) to allow future inclusion of new skills. We will recruit 3520 participants with subthreshold depression and ca 1700 participants without subthreshold depression, to examine the short-term efficacies of CBT skills to reduce depressive symptoms in the former and to explore the long-term efficacies in preventing depression in the total sample. The primary outcome for the short-term efficacies is the change in depressive symptoms as measured with the Patient Health Questionnaire-9 at week 6, and that for the long-term efficacies is the incidence of major depressive episodes as assessed by the computerised Composite International Diagnostic Interview by week 50.

Ethics and dissemination The trial has been approved by the Ethics Committee of Kyoto University Graduate School of Medicine (C1556).

Trial registration number UMIN000047124.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This trial aims to examine specific efficacies of various internet cognitive–behavioural therapy (iCBT) skills and to evaluate interactions of these skills with participants' characteristics to enable optimal matching of iCBT skills and individuals.
⇒ The trial is designed as a master protocol involving four 2×2 factorial trials with common intervention arms, thus allowing efficient use of the sample.
⇒ The trial can be expanded as a platform trial to accommodate new developments in the smartphone CBT app.
⇒ The trial uses remote recruitment and informed consent procedures using the internet to allow accelerated recruitment.

INTRODUCTION

In 1984, a report by the US National Institute of Mental Health concluded that prevention of depression is impossible.[1] However, research over the next 30 years has shown that depression prevention is possible[2] and cost-effective.[3] In the meantime, however, health losses due to common mental disorders are continuing to increase and depression remains the largest source of disabilities due to mental health worldwide.[4 5] Subthreshold depression, that is, a depressive state falling short of meeting the diagnostic threshold for major depression, is more prevalent than major depression itself and leads to major losses in well-being and productivity.[6] Prevention of depression usually takes the form of

indicated prevention, preventing subthreshold states to develop into full-blown episodes.[2] To maintain and improve the mental health of the entire population, it is necessary to prevent the transition from a subdepressive state to a clinically depressive level, to reduce depression in those who are currently depressed and to maintain the euthymic state in those who have once improved.[7]

Our recently published systematic reviews have shown that various psychotherapies are effective not only in treating but also in preventing depression, with cognitive–behavioural therapy (CBT)-based interventions having the strongest evidence base in both respects.[2 8 9] CBT typically includes cognitive and behavioural skill components such as cognitive restructuring (CR), behavioural activation (BA), problem-solving (PS), assertion training (AT), behaviour therapy for insomnia (BI) and relaxation. However, classic face-to-face CBT is not widespread enough to meet the actual clinical, let alone preventive, needs, because it requires a lot of human, financial and time resources. On the other hand, since the 2000s, research on internet CBT (iCBT) using information and communication technology has seen much progress, and it is now well established that guided iCBT is as effective as standard face-to-face treatment and both are superior to usual care in treating clinical depression[10 11] and subclinical depression.[11–13] Evidence is also emerging that they may be able to prevent new depression onset among participants with subthreshold depression.[12 14]

However, there is much room for improvement for these promising interventions. First, various iCBT packages shown to be effective in randomised controlled trials consist of different combinations of CBT skills and we do not yet know if all their components are necessary or if more efficient and less time-consuming combinations may be possible for individuals, both in the treatment and prevention of depression. Second, the internet and smartphone technologies are in constant evolution but no system has yet been developed to accommodate ongoing innovations in digital interventions.

We have been developing a series of smartphone CBT apps in the past decade. Our original smartphone CBT 'Kokoro App' ('Kokoro' means mind in Japanese) included CR and BA, and its efficacy and safety have been demonstrated in a randomised controlled trial involving 164 drug-refractory depressed patients.[15] We then developed new iCBT modules of PS and AT. Using PS and BA significantly reduced fear of cancer recurrence and depression among 447 breast cancer survivors in a randomised controlled trial.[16] Putting all these components together, we have developed the 'Resilience Training App' which targets subclinical distress in the general population, promotes their resilience and well-being, and aims to prevent the future incidence of clinical depression. Using this Resilience Training App Version 1, we recently completed a fully factorial trial to examine the specific efficacy of CR, BA, PS, AT and self-monitoring among 1093 college students with subthreshold depression: after 2 months, the students saw moderate to large reductions in their depression and anxiety on average and we were unable to detect skill-specific efficacies.[17] However, when we conducted a component network meta-analysis of iCBT packages to treat depression in 76 trials (18 178 participants), BA proved the most efficacious, followed by BI, PS and AT.[18]

Based on these results, we have now added an iCBT module for BI in Version 2 of the Resilience Training App, and we hereby plan the RESiLIENT Study (Resilience Enhancement with Smartphone in LIving ENvironmenTs), a master protocol of four 2×2 factorial randomised trials, to elucidate the following clinical questions:

1. The Resilience Training App Version 2 includes CR, BA, PS, AT and BI. By examining their various combinations in factorial trials, we aim to estimate the specific efficacies of these various CBT skills.
2. We further plan to examine interactions between these CBT skills and individuals' baseline characteristics to enable matching between interventions and individuals.
3. The trial is designed as a platform trial in which new versions of the existing CBT modules or a completely new module may be later added to allow randomised comparisons.

METHODS

This protocol has been written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials guideline,[19] the Consolidated Standards of Reporting Trials statement for randomised trials of non-pharmacological treatments,[20] and the Japanese Ethical Guidelines for Medical and Biological Research Involving Human Subjects (23 March 2021) and its Guidance (16 April 2021). This report is based on the protocol version 1.0.2, approved on 28 July 2022 by Kyoto University Graduate School of Medicine Ethics Committee (approval number C1556). The trial has been registered in UMIN-CTR (UMIN000047124).

Overall design

The RESiLIENT trial is a platform trial involving four 2×2 factorial trials examining the efficacy of five smartphone CBT skills. Analysis 1 will focus on the acute intervention effects at week 6 among participants with the Patient Health Questionnaire-9 (PHQ-9) scores of 5 or more at week 0. Analysis 2 will focus on the long-term prophylactic effects at week 50 among all participants. The trial will be powered for analysis 1 but will remain exploratory for analysis 2. The recruitment started on 1 September 2022 and is scheduled to complete by 31 March 2024, with the last follow-up planned to complete by 30 April 2024.

Participants

Study settings

Participants will be recruited in the following four fields. The potential participants will access the internet web

Table 1 Contents of the interventions and controls

		Chapter 1	Chapter 2	Chapter 3	Chapter 4	Chapter 5	Chapter 6
1	BA	4 basic lessons for BA	2 advanced lessons for BA	1 advanced lesson for BA	1 advanced lesson for BA	BA in everyday life	To sum up and to continue
2	CR	4 basic lessons for CR	2 advanced lessons for CR	1 advanced lesson for CR	1 advanced lesson for CR	CR in everyday life	To sum up and to continue
3	PS	4 basic lessons for PS	2 advanced lessons for PS	2 advanced lessons for PS	1 advanced lesson for PS	PS in everyday life	To sum up and to continue
4	AT	5 basic lessons for AT	2 advanced lessons for AT	1 advanced lesson for AT	1 advanced lesson for AT	AT in everyday life	To sum up and to continue
5	BI	5 basic lessons for BI	1 advanced lesson for BI	1 advanced lesson for BI	1 advanced lesson for BI	BI in everyday life	To sum up and to continue
6	BA+CR	4 basic lessons for BA	4 advanced lessons for BA	4 basic lessons for CR	4 advanced lessons for CR	BA and CR in everyday life	To sum up and to continue
7	BA+PS	4 basic lessons for BA	4 advanced lessons for BA	4 basic lessons for PS	5 advanced lessons for PS	BA and PS in everyday life	To sum up and to continue
8	BA+AT	4 basic lessons for BA	4 advanced lessons for BA	5 basic lessons for AT	4 advanced lessons for AT	BA and AT in everyday life	To sum up and to continue
9	BA+BI	4 basic lessons for BA	4 advanced lessons for BA	5 basic lessons for BI	3 advanced lessons for BI	BA and BI in everyday life	To sum up and to continue
10	Self-check	–	–	–	–	–	To sum up and to continue
11	Health information	Physical exercise	Nutrition	Oral health	–	–	To sum up and to continue
12	Delayed treatment	–	–	–	–	–	To sum up and to continue

All the participants will receive weekly encouragement emails, except for groups 11 and 12.
AT, assertion training; BA, behavioural activation; BI, behaviour therapy for insomnia; CR, cognitive restructuring; PS, problem-solving.

page for the trial to apply for the study (the Participant timeline section).

1. Health insurance societies
   There are several types of public health insurance schemes together constituting the universal healthcare in Japan. We will collaborate with three large associations from them, namely, National Federation of Health Insurance Societies covering employees and their families in large corporations (ca 30 million insured), Japan Health Insurance Association covering employees and their families of small-to-middle-sized corporations (ca 35 million insured), and National Civil Engineering Health Insurance Societies covering civil engineering and construction workers and their families (ca 0.2 million insured).
2. Business companies and corporations
3. Community and local governments
4. Direct-to-consumer advertisements

Eligibility criteria

Inclusion criteria

1. People of any sex, aged 18 years or older at the time of providing informed consent.
2. In possession of their own smartphone (either iOS or Android).
3. Written informed consent for participation in the trial.
4. Completion of all the baseline questionnaires within 1 week after providing informed consent.

Exclusion criteria

1. Cannot read or write Japanese.
2. Receiving treatment from mental health professionals at the time of screening.
3. Screening PHQ-9 total scores of (1) 15 or higher, or (2) between 10 and 14, inclusive, and scoring 2 or 3 on its item 9.[17 21]

Interventions and controls

The participants will be randomised equally to one of the following nine intervention arms and the three control arms.

Interventions

The intervention arms include:

1. BA
2. CR
3. PS
4. AT
5. BI
6. BA+CR
7. BA+PS
8. BA+AT
9. BA+BI

BA consists of psychoeducation about pleasurable activities according to the principle 'When your body moves, so does your mind'. It provides a worksheet of a personal experiment to test out a new activity and also a gamified 'action marathon' to promote such personal experiments.

CR consists of psychoeducation of the cognitive–behavioural model and cognitive restructuring. The participant learns how to monitor their reactions to

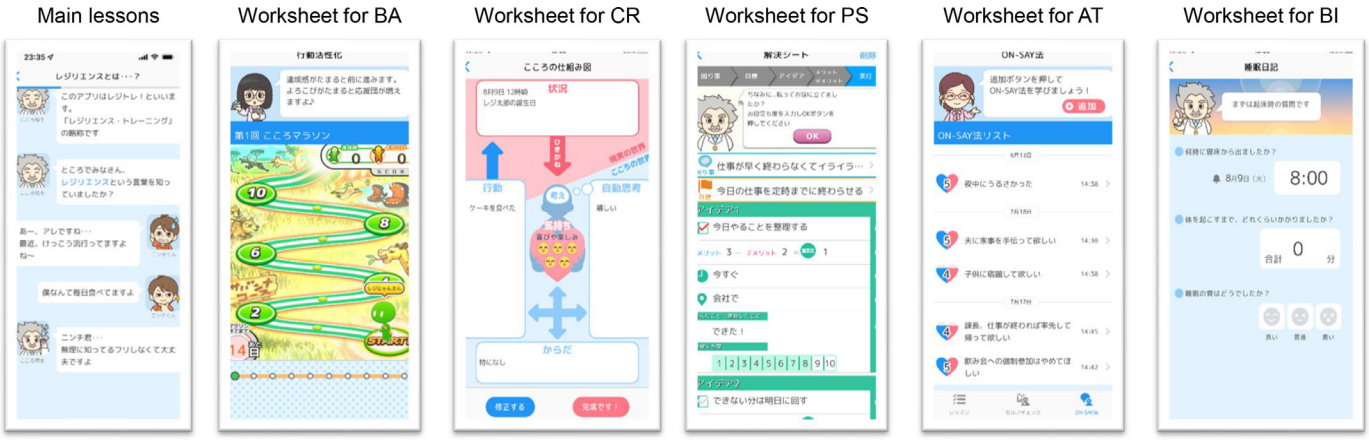

Figure 1 Sample screenshots from the Resilience Training App (copyright by Toshi A Furukawa, Masaru Horikoshi and Tatsuo Akechi). AT, assertion training; BA, behavioural activation; BI, behaviour therapy for insomnia; CR, cognitive restructuring; PS, problem-solving.

situations in terms of feelings, thoughts, body reactions and behaviours by filling in mind maps. The participant uses these mind maps to apply cognitive restructuring and find alternative thoughts. In order to help the participant broaden their thoughts, CR provides three tools, each of which guides them to alternative thoughts through interactions with the app characters.

PS teaches the participants how to break down the issue at hand, to specify a concrete and achievable objective for it, to brainstorm possible solutions, to compare their advantages and disadvantages, and finally to choose the most desirable action and act on it. A worksheet to guide the participants through this process is provided.

AT consists of psychoeducation of assertive communication in contrast to aggressive or passive communication. The participant learns how to express their true feelings and wishes without hurting others or sacrificing themselves. They fill in worksheets to construct appropriate lines in response to their own real-life interactions.

BI teaches the mechanisms of healthy sleep, invites the participant to keep daily sleep records, based on which the participant will start applying sleep restriction and stimulus control techniques, the two proven behavioural skills to increase sleep efficiency.

Each component consists of seven to nine lessons, divided into two to four chapters as appropriate (table 1), as well as worksheets to practise the skill (figure 1). The participants are expected to complete one chapter per week and can only move on to the next chapter after a week has passed since they started the previous chapter and after they have completed one worksheet. The participants receive weekly encouragement emails, templated but tailored in accordance with each participant's progress by the trial coordinators in the management team (the coordinators have no CBT background and hence are forbidden to provide any therapeutic contents) and are prompted to fill in PHQ-9 every week.

The reason why we emphasise and use BA in arms 6–9 and how we will analyse them will be explained in the Statistical methods section below.

Controls

In psychotherapy trials, there is no gold standard control condition like the pill placebo in pharmacotherapy trials. Psychotherapy controls must be designed in accordance with the participants' needs, the available resources and the clinical questions of the study,[22] and may produce different effect size estimates.[23] In the RESiLIENT trial, we therefore will use three different control conditions with different levels of stringency.

1. Weekly self-checks
2. Health information
3. Delayed intervention

In the weekly self-check arm, the participants will receive weekly encouragement emails and monitor their moods through the weekly PHQ-9 up to week 6 (as in the intervention arms) and then the monthly PHQ-9 thereafter up to week 50. This arm is intended as an attention control to match the attention provided through encouragement emails and self-checks but lacking in active interventions.

In the health information arm, the participants will receive URL of websites containing tips for healthy life (physical activities, nutrition and oral health, none of which focuses on mental health) for the initial 3 weeks and will be asked to answer quizzes for comprehension. They will be asked to fill in self-reports at weeks 3 and 6 (without encouragement emails), and then follow-up evaluations thereafter up to week 50. This arm is intended as a placebo intervention.

In the delayed treatment arm, the participants will be placed on the wait list and be asked to fill in self-reports at weeks 3 and 6. They will then be randomised to 1 of the 11 arms (#1 through #11) at week 6, if they so wish then, and will follow respective programmes thereafter.

Concomitant interventions

All the participants, in the active or control arms, are free to seek whatever mental health interventions they wish through the 50 weeks. The received professional interventions, either pharmacotherapy or psychotherapy, will be monitored and recorded at weeks 6 and 50.

New interventions

The RESiLIENT trial is designed as a platform trial to accommodate any new psychosocial intervention. In order to examine a new skill (X), two new arms will be added, namely X and BA+X, to allow a new 2×2 factorial trial, using the BA and the control condition in common with the foregoing factorial trials. However, for the new factorial trial, we will use only those who were concurrently randomised as the new intervention arms X and BA+X. The necessary sample size for the new factorial trial will be calculated de novo, when the addition is planned, and the addition must be approved by the Ethics Committee.

Measures

Primary outcomes

The primary outcome is the change in PHQ-9 from baseline to week 6 (analysis 1).

Secondary outcomes

The secondary outcomes include:

1. Incidence of a major depressive episode by week 50 (analysis 2).
2. Changes in PHQ-9 from baseline to weeks 1, 2, 3, 4, 5; 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50.
3. Changes in the Generalized Anxiety Disorder-7 (GAD-7) from baseline to weeks 3, 6, 26 and 50, as anxiety usually coexists with depression and we aim to examine what effects the intervention components, while mainly targeting depression, may have on anxiety. We also aim to monitor broad psychopathology of common mental disorders encompassing depression, anxiety and insomnia as well as positive mental health which are deteriorated in common mental disorders.
4. Changes in the Insomnia Severity Index (ISI) from baseline to weeks 3, 6, 26 and 50.
5. Changes in the Short Warwick Edinburgh Mental Well-Being Scale (SWEMWBS) from baseline to weeks 3, 6, 26 and 50.
6. Changes in the CBT Skills Scale from baseline to weeks 6, 26 and 50.
7. Changes in the Work and Social Adjustment Scale (WSAS), the Utrecht Work Engagement Scale (UWES), the Health and Work Performance Questionnaire (HPQ) and the EuroQOL-5D-5L (EQ-5D-5L) from baseline to weeks 6 and 50.
8. The Client Satisfaction Questionnaire-3 (CSQ-3), adherence to smartphone CBT, co-interventions, safety information at weeks 6 and 50.
9. Medical expenditures and absenteeism among those participating through their health insurance societies by week 50.

Baseline and outcome variables

We will measure the following baseline variables as potential prognostic factors (characteristics that predict the outcome regardless of the intervention) and effect modifiers (characteristics that predict the differences in outcomes between the interventions) for iCBT efficacy.

1. Demographic variables
   - Age
   - Sex
   - Marital status
   - Number of cohabitants
   - Socioeconomic status of the residential area (as estimated by the zip code)
   - Education
   - Employment
   - Physical conditions and illnesses, including past and current treatments
   - Physical disability
   - Mental health conditions, including past and current treatments
   - Alcohol use and CAGE questionnaire[24 25]
2. Psychosocial variables
   - Short form of the Big-5 questionnaire[26–28]
   - Adverse Childhood Experiences (ACE)[29 30]
   - Assessment of Signal Cases (ASC)-Life difficulties[31]
   - ASC-Social support[31]
   - CBT Skills Scale[32]
   - Readiness for smartphone CBT

ASC-Motivation[31]

Familiarity with smartphone usage

3. Clinical variables
   - PHQ-9[21]
   - GAD-7[33]
   - ISI[34]
   - Past and current major depressive episodes according to the major depression section of the computerised WHO Composite International Diagnostic Interview (CIDI)[35 36]
   - WSAS[37]
   - HPQ[38 39]
   - UWES[40]
   - EQ-5D-5L[41 42]
   - SWEMWBS[43 44]
   - Co-interventions
   - CSQ-3[45]
   - Adherence to smartphone CBT
   - Safety information
   - Health insurance data (claims data, absenteeism) among those participating through their health insurance societies

Table 2 shows the overall schedule of baseline and outcome measurements.

Instruments

Adverse Childhood Experiences

The ACE is one of the established and frequently used questionnaires to assess childhood maltreatment including psychological and physical abuse during childhood and other adverse environments. Each relevant experience is rated as having been present or not.[29] The reliability and validity of its Japanese version have been established.[30]

Table 2 Measurement schedule

	Questionnaire part I at landing page	Questionnaire part II on smartphone app (week 0)	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Weeks 10, 14, 18, 22	Week 26	Weeks 30, 34, 38, 42, 46	Week 50
Allowances (days)	–		+6	+6	+6	+6	+6	+14	+14	+14	+14	+28
PHQ-9	○	○	Δ	Δ	○	Δ	Δ	○	○	○	○	○
GAD-7		○			○			○		○		○
ISI		○			○			○		○		○
SWEMWBS		○			○			○		○		○
CIDI		○										○
Baseline characteristics		○										
ASC-Motivation		○			○							
ICT usage		○										
ACE		○										
Short Big-5		○										
ASC-Life difficulties		○										
ASC-Social support		○										
CBT skills	○							○		○		○
WSAS		○						○				○
UWES		□						□				□
HPQ		□						□				□
EQ-5D-5L		○						○				○
Co-interventions								○				○
CSQ-3								○				○

○: to be administered to all participants; □: only to those currently employed; and Δ: all participants except for groups 10 and 11.
.ACE, Adverse Childhood Experiences; ASC, Assessment of Signal Cases; CBT, cognitive–behavioural therapy; CIDI, Composite International Diagnostic Interview; CSQ-3, Customer Satisfaction Questionnaire-3; EQ-5D-5L, EuroQOL-5D-5L; GAD-7, Generalized Anxiety Disorder-7; HPQ, Health and Work Performance Questionnaire; ICT, information and communication technologies; ISI, Insomnia Severity Index; PHQ-9, Patient Health Questionnaire-9; SWEMWBS, Short Warwick Edinburgh Mental Well-Being Scale; UWES, Utrecht Work Engagement Scale; WSAS, Work and Social Adjustment Scale.

Assessment of Signal Cases

The ASC is designed to measure factors shown to influence the course of the treatment including social support, life difficulties and motivation.[31] Each subscale contains six to seven items, each rated on a 5-point scale for the past week. The validity and reliability of the original version have been ascertained.[31] The Japanese version was developed through back-translation and its reliability will be examined in this current study.

CBT Skills Scale

In order to measure specific cognitive or behavioural skills, we have developed the short versions based on the following established questionnaires: CR,[46] BA,[47 48] assertiveness,[49] PS[50] and sleep hygiene.[51] Each item is rated on a Likert scale between 0=barely true of me through 3=mostly true of me, and the average of the score items constitutes the score for each skill. The reliability and validity of the CBT Skills Scale have been ascertained.[32]

Composite International Diagnostic Interview

To determine the Diagnostic and Statistical Manual of Mental Disorders, 4th Ed. (DSM-IV) major depressive disorder diagnosis during the lifetime and the previous 12 months, we will use the self-administered Japanese WHO-CIDI 3.0 depression section.[52 53] The self-administered version has been demonstrated to be reliable in a 1-year test–retest survey[36] and to have good concordance with the clinical diagnosis of major depressive episode.[54]

Client Satisfaction Questionnaire-3

The CSQ-3 is the short version of the longer, 8-item and 18-item version to measure client satisfaction with psychotherapies. Its reliability and validity have been established.[45]

EuroQOL-5D-5L

The EQ-5D is one of the most frequently and well-established instruments to describe and value health in the five domains of mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each item was rated in three levels in its original version but has now been expanded to five levels to enhance the scale's sensitivity.[41] The population norms for the Japanese have been established.[42]

Generalized Anxiety Disorder-7

The GAD-7, which consists of seven questions that depict anxiety, tension and worry, was created to gauge the severity of generalised anxiety. Each item is given a value ranging from 0=not at all to 3=almost every day, with the total score falling between 0 and 21. Its validity and reliability have been proven.[33] The PHQ-9 and GAD-7 have been recommended and used as part of a standardised battery to measure health outcomes for depression and anxiety.[55 56]

Health and Work Performance Questionnaire

We will employ one item from the WHO HPQ's presenteeism subscale. The reliability and validity of the original scale have been established.[38 57] The reliability and validity of the one-item version have been ascertained.[39]

Insomnia Severity Index

The ISI was developed and validated as a brief screening measure of insomnia and as an outcome measure in treatment research. It has adequate reliability and validity to quantify perceived insomnia severity[34] and has been used extensively in insomnia research. The reliability and validity of the Japanese version have been confirmed.[58]

Personal Health Questionnaire-9

The PHQ-9 comprises the nine DSM-5 diagnostic criteria items for a major depressive episode.[21] Each item is given a value ranging from 0=not at all to 3=almost every day, with the overall score falling between 0 and 27. Both the original PHQ-9 and its Japanese version have satisfactory validity and reliability.[59 60] The PHQ-9 and GAD-7 have been recommended and used as part of a standardised battery to measure health outcomes for depression and anxiety.[55 56]

Short form of the Big-5 questionnaire

There are several validated scales to measure personality traits according to the five-factor model. We will use the Big-Five Scale of Personality Trait Adjectives,[26] which is widely used in Japan, in its abridged form. The short version's validity and reliability have been established.[27 28] Each of the five personality traits—neuroticism, extraversion, openness, agreeableness and conscientiousness—is assessed using five to seven related adjectives, each of which is rated on a 5-point Likert scale from 0=untrue of me to 4=true of me.

Short Warwick Edinburgh Mental Well-Being Scale

The SWEMWBS is a short seven-item version of the Warwick Edinburgh Mental Well-Being Scale, developed to measure positive mental well-being at the general population level.[43] The scale is based on a conceptual framework that mental well-being consists of two key dimensions of hedonia and eudaimonia. Each item is rated on a 5-point Likert scale between 1=none of the time and 5=all of the time. The reliability and validity of the SWEMWBS have been well confirmed.[61] The Japanese version has been developed using the standard back-translation method.[62]

Utrecht Work Engagement Scale

Engagement in work has been conceptualised in three dimensions of vigour (high levels of energy while working), dedication (sense of significance and enthusiasm) and absorption (sense of concentration and engrossment). We will use the ultra-short, three-item version of the widely used UWES. The reliability and validity of the scale, including its Japanese version, have been confirmed.[40]

Work and Social Adjustment Scale

We will measure the impairments in social functioning in the domains of work, home management, social leisure activities, private leisure activities and close relationships, each rated on a 9-point Likert scale between 0=not at all through 8=very severely. The reliability and validity of the scale have been established for the original[37] as well as the Japanese version.[63]

Participant timeline

Figure 2 shows the participant timeline.

Statistical methods

The 2×2 factorial design

The RESiLIENT trial is a master protocol for the following four 2×2 factorial trials, each of which is to be analysed independently.

	Randomisation for BA	
Randomisation for CR	BA+, CR+	BA–, CR+
	BA+, CR–	BA–, CR–

	Randomisation for BA	
Randomisation for PS	BA+, PS+	BA–, PS+
	BA+, PS–	BA–, PS–

	Randomisation for BA	
Randomisation for AT	BA+, AT+	BA–, AT+
	BA+, AT–	BA–, AT–

	Randomisation for BA	
Randomisation for BI	BA+, BI+	BA–, BI+
	BA+, BI–	BA–, BI–

The four factorial trials will use the BA arm and the control arm in common. We will use the no treatment arm for the primary analysis, and use the self-check arm and the health information arm as sensitivity analyses using increasingly stringent comparisons.

We use the factorial design for the following reasons. First, the factorial design can increase the statistical power to examine the efficacy of the included skills. Second, in the factorial design, we can test the interaction between the iCBT skills.[64–66] We anticipate that the optimal iCBT packages would likely include two or three skills. While the available studies indicate that there probably are no important interactions among various iCBT skills,[17 18] it would be informative to have tested the interactions when we eventually propose combinations of iCBT skills.

We test out the combinations of various skills with BA for the following reasons. First, BA was the most efficacious and the only statistically significant component in the individual patient data component network meta-analysis of iCBT components and delivery methods.[18] Second, BA alone has often been shown to be as efficacious as the more complex CBT packages in the network meta-analysis of various psychotherapies for depression.[8 67] Third, in trials that aimed at increasing scalability of CBT interventions, the active interventions often included BA.[68] Lastly, the foregoing studies that used different versions of the Resilience Training App included BA when they successfully differentiated the intervention from the control condition[15 16] or suggested that BA may be the most efficacious though not statistically significantly so among the included components in the fully factorial trial examining CR, BA, PS and AT.[17]

Statistical analyses

All analyses will be conducted with the intention-to-treat sample.

Analysis 1

For the factorial trial, we will use the mixed-effects repeated-measures analysis (MMRM) to estimate the mean difference in change scores on PHQ-9 for each component: the model will include treatments, visit (as categorical) and treatment-by-visit interaction as fixed effects, adjusted for the baseline PHQ-9 scores, employment status, age and sex. The primary outcome is the change in PHQ-9 scores from baseline to week 6. We will use the unstructured variance–covariance matrix for the MMRM to account the within-participant correlations: in case of non-convergence, we will use the Toeplitz, heterogeneous compound asymmetry, autoregressive (1), compound symmetry, and variance components models in this order. No adjustment for multiple testing will be applied in examination of statistical significance of the main effects and the conventional threshold for statistical significance ($p<0.05$, two sided) will be used, because conventionally, the multiple hypotheses have been tested independently in these trial designs assuming as if the tested interventions could have been assessed in separate trials.[64 65 69 70] We will assess the interaction between the treatments in a sensitivity analysis. Previous research has not been suggestive of interactions among iCBT components,[17 18 71] but when we identify a strong interaction, we will interpret the results considering the interaction. We will use the delayed treatment arm for the primary comparison but the health information and the self-check arms as sensitivity analyses.

We will examine the influence of baseline characteristics as prognostic factors by entering them as covariates and as effect modifiers by entering their interaction with treatment in the above MMRM.

We will use a similar MMRM model for GAD-7, ISI and SWEMWBS at week 6. For CBT skills, WSAS, UWES, HPQ and EQ-5D-5L, which are measured only at baseline and at week 6, their change scores will be assessed using the analysis of covariance: missing baseline values will be imputed through multiple imputation. For CSQ-3, which is measured only at week 6, its endpoint score will be

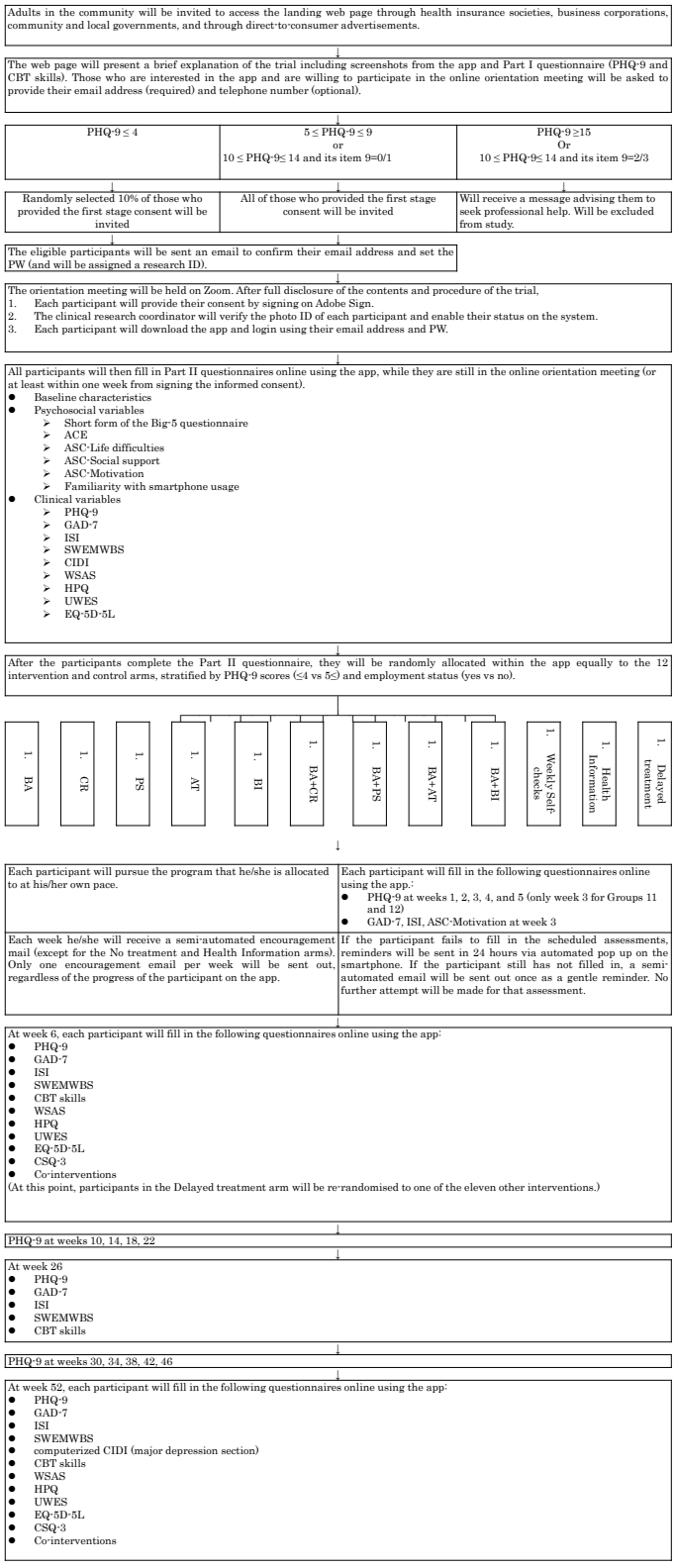

Figure 2 Participant timeline. ACE, Adverse Childhood Experiences; ASC, Assessment of Signal Cases; AT, assertion training; BA, behavioural activation; BI, behaviour therapy for insomnia; CBT, cognitive–behavioural therapy; CIDI, Composite International Diagnostic Interview; CR, cognitive restructuring; CSQ-3, Client Satisfaction Questionnaire-3; EQ-5D-5L, EuroQOL-5D-5L; GAD-7, Generalized Anxiety Disorder-7; HPQ, Health and Work Performance Questionnaire; ISI, Insomnia Severity Index; PHQ-9, Patient Health Questionnaire-9; PS, problem-solving; PW, password; SWEMWBS, Short Warwick Edinburgh Mental Well-Being Scale; UWES, Utrecht Work Engagement Scale; WSAS, Work and Social Adjustment Scale.

assessed using the analysis of variance: missing baseline values will be imputed through multiple imputation.

Analysis 2

An exploratory analysis will be conducted to compare the incidence of a major depressive episode between the proposed optimal skill(s) against the control conditions through the time-to-event analysis (Kaplan-Meier survival analysis) among those with or without baseline subthreshold depression and who did not have a major depressive episode at baseline. The influence of baseline characteristics on the time-to-event will be explored by using Cox proportional hazard analysis if the proportional hazard assumption is met.

Preplanned secondary analyses

The following secondary analyses are preplanned, to make the analyses more sensitive to changes in respective scales (SWEMWBS for well-being and ISI for insomnia) by limiting the participants to those with potentials for improvement and minimising ceiling or floor effects:

1. Efficacy of various components on SWEMWBS among those with reduced well-being at baseline (defined as scoring 20 or less on the SWEMWBS).[44 61]
2. Efficacy of the BI component on sleep parameters among those with substantive insomnia at baseline (defined as scoring 8 or more on the ISI).[34] The primary outcome of this secondary analysis will be the ISI but will include other sleep parameters such as sleep efficiency, total sleep, sleep latency, etc.

Interim analysis

No interim analysis is planned.

Sample size

The RESiLIENT trial will be powered for each factorial trial for its primary outcome of the analysis 1, that is, PHQ-9 at week 6 among those with the baseline PHQ-9 scores of 5 or more. The Fun the Learn, Act and Think through Technology trial has shown a standardised mean difference of 0.3–0.4 for the earlier version of the Resilience Training App using the combination of BA+CR over the waiting list control among patients with drug-refractory depression.[15] In order to detect a standardised mean difference of 0.2 at alpha=0.05 and beta=0.10, each factorial trial in the current master protocol would need in total 1053 participants (FactorialPowerPlan, http://methodology.psu.edu), hence 264 in each arm. Altogether the RESiLIENT trial will require 264×12=3168 participants with baseline PHQ-9 scores of 5 or more. The Healthy Campus Trial (HCT) had 5% dropout rates for its eighth week outcome.[17] We may expect somewhat higher dropout rates in the RESiLIENT trial, which targets the general adult population in the community. Assuming a 10% dropout rate, the required sample size will be 3520.

We will include all participants with any baseline PHQ-9 scores for analysis 2, but the power for analysis 2 may be low due to the low event rates among the participants. The post hoc power calculation will be conducted for the expected 20% reduction in terms of HR.[2] In the HCT participants, which used the same recruitment procedure and entered all those with PHQ-9 scores of 5 or more but entered only a random one-tenth of those scoring 4 or less, the latter were approximately half of the former: we therefore anticipate approximately 5200 participants altogether for the RESiLIENT trial.

Allocation and blinding

We will use permuted block randomisation, stratified by PHQ-9 scores (≤4 vs 5≤) and employment status (yes vs no). The block size will be known to the study statistician only, who will generate the random sequence by using SAS PROC PLAN.

The above sequence will be implemented in the app and participants will be allocated to 1 of the 12 intervention or control arms automatically by the app when they complete the part I questionnaires.

Neither the participants nor the trial management team will be blinded to the interventions. However, the trial statistician will be blinded to the interventions until after they sign off the completed statistical reports.

Data collection and management

All the data will be entered into the web or the smartphone app by the participants. The data will be transferred securely to the server using the Secure Socket Layer. The server program behind the web and the smartphone app has built-in automated checks for the inappropriate or missing data entries.

The trial management team will send out encouragement emails weekly (up to week 6) and at weeks 26 and 50, to compliment the participants' progress and also to prompt their responses to the questionnaires. The encouragement emails will not contain any CBT-specific instructions. The trial management team will be based at Kyoto University Department of Health Promotion and Human Behavior.

Data monitoring

The trial management team will submit a report to the independent Data and Safety Monitoring Board (DSMB) every 6 months after enrolment of the first participant. The report will contain information on the number of participants enrolled, their follow-up status and serious adverse events. Based on this report, the DSMB will provide recommendations to the Steering Committee.

The Steering Committee will discontinue the trial when they receive a recommendation or an instruction to the effect from the DSMB or the overseeing Ethics Committee.

Harms

All the serious adverse events (defined as those leading to death, life-threatening, necessitating hospitalisation or leading to permanent serious disabilities) will be handled according to the standard operationalised procedure #10 by Kyoto University Graduate School of Medicine (http://www.ec.med.kyoto-u.ac.jp/doc/SOP10.pdf).

In addition, when any rise in suicidality (defined as scoring 10 or more on the total PHQ-9 scores and scoring 2 or more on item 9 of PHQ-9 for 2 consecutive weeks) is noted, the participant will receive an email recommending visiting the consultation services listed by the Japanese Ministry of Health, Labour and Welfare for the general public (https://kokoro.mhlw.go.jp/agency/) or other mental health professionals.

Ethics

The protocol has been approved by the Kyoto University Graduate School of Medicine Ethics Committee (approval number C1556). Any amendment to the protocol will be reviewed by the Ethics Committee.

Consent

The participant will provide written informed consent through Adobe Sign after full disclosure of the purpose and procedures of the study based on the written materials as well as through the online orientation meeting.

Confidentiality and access to data

All the participants will be assigned a research ID upon registration and their data will be managed by this ID. No personally identifiable information will be collected except for the email address and telephone number (optional), which will be linked to the research ID. The correspondence table between the email address and the research ID as well as the signed forms will be stored in a separate server different from the main server for the trial data. Only the trial management team will have access to the correspondence table, while the Steering Committee members will have access to the full trial data including the research ID without the correspondence table.

Ancillary and post-trial care

No ancillary or post-trial care is planned.

Patient and public involvement

People with lived experiences and members from the general community have joined the Steering Committee after the study protocol had been semifinalised and the funding had been secured. Since then they have participated in the improvement and finalisation of the smartphone apps as well as the contents and quantity of questionnaires, and also in the preparation of the materials to be shared with the potential participants in the orientation meeting for informed consent.

They will continue to serve in the Steering Committee throughout the current trial and will provide advice as needed on the conduct of the trial as well as possible future additions/modifications to the study.

DISCUSSION

This protocol paper described the study protocol for the master trial involving four 2×2 factorial trials examining five CBT skills (CR, BA, PS, AT and BI) implemented on the smartphone platform among 5200 participants with or without baseline subthreshold depression. We plan to recruit 3520 adults with subthreshold depression to examine the acute phase effectiveness to reduce depressive symptoms, and further ca 1700 adults without subthreshold depression to examine the long-term effectiveness to prevent depression among those with or without baseline subthreshold depression but without baseline major depressive episode.

The trial has several novel design and implementation features. First, it aims to elucidate specific efficacy of the included CBT skills by way of the factorial experiments. The factorial design also enables examination of interactions among the CBT skills. Second, it is a master protocol to conduct four factorial trials simultaneously and makes efficient use of the study participants across the planned four factorial trials. Third, the master protocol allows room for addition of a new arm in the course of the trial if necessary. Fourth, it uses remote recruitment and informed consent procedures taking full advantage of the internet. We expect that this will allow us to recruit a fairly large sample within relatively short periods. Fifth, the large sample size will allow exploration of prognostic factors and effect modifiers to match individual characteristics with each CBT skill. Lastly, we believe that the patient and public involvement in the preparatory phases of this study has not only made the study more relevant to their needs but also increased its feasibility.

Given the novelty and scale of the study, we anticipate the following difficulties. First, the smartphone app and the backend server system controlling the smartphone app for this study are bound to be complex and sophisticated, due to the multiplicities of the interventions and the complexities of the study design. We have dedicated months and years to develop the platform, have pilot tested it before the start of the enrolment and plan to implement the initial phase 3–6 months where we only slowly recruit the participants to adjust remaining glitches in the system if any and to ascertain that the interventions and assessments are delivered as planned. Second, we can never be sure of the success of the recruitment. Our past experiences suggest that we may have to advertise our study to some 200 000 people to ensure the sample size of 5200 eligible participants. At the time of the writing of this protocol paper (July 2022), the total population accessible to our collaborators sums up to 400 000. Should this turn out to be insufficient, we will seek additional collaborators.

In conclusion, we expect our study to provide valuable information on the specific efficacies of individual CBT skills, the prognostic factors and effect modifiers for them to enable matching between individual characteristics and CBT components, and finally to build more efficient and effective smartphone CBT apps to promote mental health and reduce depression burden in the general population.

Ethics and dissemination

The protocol has been approved by the Kyoto University Graduate School of Medicine Ethics Committee (approval number C1556).

We will disseminate the results from the study in scientific meetings and in scientific journals. The main results will be posted in UMIN-CTR and on the home page of the trial.

The deidentified data will be uploaded to UMIN-ICDR ((http://www.umin.ac.jp/icdr/index-j.html) after the main results have been published, in order to enable secondary use of the data in the interest of public health and medicine.

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Contributors TAF conceived the study. TAF, HN, PC and JW designed the study, in repeated consultations with AT, MS, YL, RT, MH, TA, NKawakami, TN, NKondo, SF, HC and RCK. TAF drafted the first manuscript, while HN, PC, JW, AT, MS, YL, RT, MH, TA, NKawakami, TN, NKondo, SF, HC and RCK made critical contributions to the manuscript. All the authors have seen the final manuscript and approved it for submission.

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Competing interests TAF, MH and TA jointly possess intellectual properties of the Resilience Training App. TAF reports personal fees from Boehringer-Ingelheim, DT Axis, Kyoto University Original, Shionogi and SONY, and a grant from Shionogi, outside the submitted work; In addition, TAF has patents 2020-548587 and 2022-082495 pending, and intellectual properties for Kokoro-app licensed to Mitsubishi-Tanabe. AT received lecture fees from Sumitomo Dainippon Pharma, Eisai, Janssen Pharmaceutical, Meiji-Seika Pharma, Mitsubishi Tanabe Pharma, Otsuka, and Takeda Pharmaceutical. MS reports personal fee from SONY outside the submitted work. TA has received lecture fees from Chugai, Daiichi-Sankyo, Dainippon-Sumitomo, Eizai, Janssen, Kyowa, Lilly, MSD, Meiji-Seika Pharma, Mochida, Nipro, Nihon-Zoki, Otsuka, Pfizer, Takeda and Viatris; and royalties from Igaku-shoin, outside the submitted work. TA has patents (2019-01749 and 2020-135195&2022-069057) pending. NKa reports personal fees from Junpukai Foundation, Riken Institute, JAXA, Sekisui Chemical Co and SB@Work, outside the submitted work; and Department of Digital Mental Health is an endowment department, supported with an unrestricted grant from 15 enterprises (https://dmh.m.u-tokyo.ac.jp/c). TN reports personal fees from Pfizer, MSD, Ohtsuka, Chuga, Dentsu, Takeda, Janssen, Boehringer Ingelheim, Eli Lilly, Mitsubishi Tanabe, Novartis, Allergan, Maruho, Novo Nordisk, TOA EIYO; and research grants from I&H Co, Cocokarafine Group Co and Konica Minolta, all outside the submitted work. HN received a research fund from GlaxoSmithKline and consulting fees from Kyowa Kirin, GlaxoSmithKline, Ono Pharmaceutical, Sony, Terumo, outside the submitted work. JMSW reports research funding from Boehringer-Ingelheim, GSK, Intercept, UCB, all outside the current work. All the other coauthors declare no conflicts of interests.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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