Effects of an internet-based cognitive behavioral therapy (iCBT) intervention on preventing major depressive episode among workers: A protocol for a randomized controlled trial

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Title Paper

Title: Effects of an internet-based cognitive behavioral therapy (iCBT) intervention on preventing major depressive episode among workers: A protocol for a randomized controlled trial

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Key words: Internet-based cognitive behavioral therapy, depression, prevention, workers, randomized controlled trial

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ABSTRACT

Introduction: The primary prevention of depressive disorder is an important strategy for global mental health. The aim of the study is to examine the effects of the internet-based cognitive behavioral therapy (iCBT) program on decreasing the risk of a major depressive episode (MDE) as defined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR), using a randomized controlled trial (RCT) design among workers employed in a private company in Japan.

Methods and analysis: All of the workers in four companies (n=20,000) will be recruited through an invitation e-mail. Participants who fulfilled the inclusion criteria will be randomly allocated to intervention or control groups (planned N=4,050 for each group). They will be allowed to complete the six lessons of the iCBT program within 10 weeks after the baseline survey. Those in the control group will receive the same iCBT after 12 months. The program includes several CBT skills: self-monitoring, cognitive restructuring, assertiveness, problem solving, and relaxation. The primary outcome is a new onset of DSM-IV-TR MDE during the 12-month follow-up, which will be assessed using the web version of the WHO Composite International Diagnostic Interview version 3.0 depression section.

Ethics and dissemination: The Research Ethics Review Board of Graduate School of Medicine, the University of Tokyo (No. 3083-(2)), approved the study procedures.
**Trial registration number:** The study protocol is registered at the UMIN Clinical Trials Registry (UMIN-CTR) (ID = UMIN000014146).

*Keywords:* Internet-based cognitive behavioral therapy, depression, prevention, workers, randomized controlled trial

**INTRODUCTION**

Depressive disorder is one of the most prevalent psychiatric disorders, affecting around 340 million people worldwide [1], and it is associated with a substantial deterioration in quality of life and economic loss in the community and the workplace [2, 3]. Thus, the primary prevention of depressive disorder is an important strategy for global mental health. In addition, stress has enormous socioeconomic implications for all spheres of employment in terms of absenteeism, staff turnover, lost productivity, poor morale, etc. [4, 5]. Although the burden of stress and depression on the workplace is substantial [6], few studies aiming to prevent psychosocial problems have been conducted.

Cognitive behavioral therapy (CBT) is an effective approach for preventing depressive disorder. Two previous meta-analyses have shown that CBT is an effective preventive measure for major depressive disorder. One meta-analysis reported that the risk of depressive disorder decreased
16% on average in the intervention group and summarized 15 various types of CBTs [7]. Another meta-analysis of RCTs with a CBT program, “Coping with Depression (CwD)” [8], has shown that the program can also prevent major depressive disorder and indicated a 38% decrease in the risk among participants in the program [9]. However, major limitations exist in the dissemination of these CBT interventions: The programs require that professionals be well trained in CBT [10-12]; time, cost, and stigma are other barriers to access to a CBT program [13].

An innovative way to deliver CBT-based treatment widely is using a computerized CBT (CCBT) and CCBT via the internet (iCBT). The CCBT and iCBT programs teach basic information and skills based on the same CBT principles as face-to-face CBT programs do with a highly structured format comprised of educational lessons, homework assignments, and supplementary resources [14]. Previous studies have shown a significant positive treatment effect of CCBT and iCBT programs on depression and anxiety in the clinical setting [15]. An iCBT program is particularly beneficial with its high anonymity [16] and high accessibility [17]. Recently, there have been increasing applications of iCBT for preventing depression. Using self-reported symptoms of depression as an outcome, one study of adolescents reported a significant prevention effect of iCBT programs, though it included only male participants [18]. In addition, one study of university students [19] and one community-based study [20] reported a significant effect of iCBT programs on improving depressive symptoms in non-clinical settings. However, one community-based study
failed to show a significant effect [21]. We also have reported that a six-session iCBT program improved symptoms of depression in a RCT in the workplace [22]. However, no previous RCT investigated a beneficial effect of an iCBT program on reducing the risk of depressive disorder, which was diagnosed according to standardized diagnostic criteria, such as the DSM-IV [23].

The present study conducts a twelve-month follow-up large-scale randomized controlled trial. An improved iCBT program, which is based on the results of the previous study [22], is used. The purposes of this randomized controlled study are as follows:

1) To decrease the risk of DSM-IV-defined major depressive episode (MDE) through the twelve-month follow-up among workers in Japan.

2) To examine the effects of the iCBT program on improving the symptoms of depression at three-, six-, and twelve-month follow-ups among workers who have subthreshold depressive symptoms in Japan.

3) To examine the effects of the iCBT program on improving work engagement and work performance at three-, six-, and twelve-month follow-ups among workers in Japan.

4) To examine the cost-effectiveness of the iCBT program.

METHOD AND ANALYSIS

Trial design

The study will be a two-arm, parallel-group, TAU-controlled, non-blinded randomized study. The
allocation ratio of the intervention group to the control group is 1 to 1. Participants will be randomly
allocated either to the intervention or to the control group after they have completed a baseline
online questionnaire survey. Online follow-up surveys will be conducted three, six, and twelve
months after the baseline. The study protocol was registered at the UMIN Clinical Trials Registry
(UMIN-CTR) (ID = UMIN000014146).

Participants

Working men and women will be selected according to the following criteria:

*Inclusion criteria*

1) Age 20-60 at study entry.

2) Men and women.

3) Currently employed full time by the business company.

4) Can access the Internet via a PC at home or at his/her workplace.

*Exclusion criteria*

1) Non-regular or part-time employees.

2) Sick leave for 15 or more days for a physical or mental condition in the past three months.

3) Current treatment for a mental health problem from a mental health professional.

4) A major depressive episode within the past month as ascertained by the web version of the
Japanese WHO-CIDI 3.0.

5) A lifetime history of bipolar disorder as ascertained by the web version of the Japanese WHO-CIDI 3.0.

Procedure

Figure 1 shows the participant flowchart of this trial. The clinical research coordinator (CRC) will send out invitations to 20,000 employees, of whom 9,000 will give the informed consent, of whom 8,100 will be eligible. These 8,100 will be randomized either to the intervention group (n=4,050) or to the control group (n=4,050). They will be allowed to complete the six lessons within 10 weeks after the baseline survey. Those in the control group can receive the iCBT after 12 months. We will send an invitation e-mail to all workers who belong to a company. The assessment of eligibility will be checked at the baseline survey. We prepared a website that includes a full explanation of the study. Before the baseline survey, participants will be invited to read the explanation on the website and asked to click an “agree” button to show their consent to participate in the study; then, they will proceed to the baseline questionnaire page. In order for the randomization and start of intervention to be as close as possible, CRC will endeavor to randomize the participants immediately after closing the application and sending an e-mail with the iCBT program course description as soon as possible.
Intervention program

The iCBT program called *Internet CBT Program: Useful Mental Health Solutions Series for Business* was a six-week, web-based training course that provided CBT-based stress management skills [22]. This program is structured in six lessons, with one lesson per week. About 30 minutes are needed to learn each lesson, including the homework. This program can be used anywhere the internet is available.

One of the unique features of the program was that training was provided along with a comic story of a psychologist and a client to facilitate the understanding of the participants. Several merits of using a comic story with comic characters have been acknowledged in research on education in school. First, it helps motivate individuals. It would be useful to keep participants motivated to stay in the program [24]. Second, it facilitates easy learning. A program with text combined with comic stories would be easier for learners to understand compared to a text-only program [24 25]. Third, it would foster interest. Using a comic story fosters learners’ interest in the program [25]. These merits might be applicable to education in the workplace because most Japanese people of working age are familiar with comics.

The present iCBT program was developed with two established CBT packages as its basis. One is the cognitive therapy program developed by Beck [26]. The other is the “Coping with Depression (CwD)” program developed by Lewinsohn [8]. Regarding the CBT components of the
program, self-monitoring skill, cognitive restructuring skill, assertiveness skill, problem-solving skill, and relaxation skill were included. At the end of each lesson, participants were asked to submit homework to facilitate their understanding, although it was only voluntary-based. Participants who submitted their homework received feedback from trained staff (i.e., clinical psychologists).

Table 1 shows the contents of the iCBT program. The program included self-monitoring skill (in lesson 2), cognitive restructuring skill (in lessons 3 and 4), assertiveness skill (in lesson 5), problem-solving skill (in lesson 6), and relaxation skill (in lesson 4). In this study, the cognitive restructuring method was adopted as the primary and main cognitive approach and has been shown to be effective in reducing depression [27]. Assertiveness and problem-solving training, as well as the relaxation skill, were chosen as supplementary behavioral approaches to enhance the effect of the program.

Table 1 Contents of the iCBT program.

<table>
<thead>
<tr>
<th>Lesson No.</th>
<th>Title</th>
<th>Contents</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Learning about stress.</td>
<td>Learning about psychological stress model modified for this iCBT program.</td>
</tr>
<tr>
<td>2</td>
<td>Knack for self case formulation based on a CB model.</td>
<td>Learning about cognitive behavioral model and how to do self-monitoring based on CBT.</td>
</tr>
<tr>
<td>3</td>
<td>Try cognitive restructuring part 1.</td>
<td>Learning about cognitive restructuring.</td>
</tr>
</tbody>
</table>
Lesson 1 Learning about stress

In this lesson, participants learn about a psychological stress model modified from [28]. A guiding character, clinical psychologist “Miss Rino”, speaks about the relationship between stressors and stress reactions. Homework in this lesson includes respondents self-checking their stressors and stress reactions to help them identify these factors/conditions.

Lesson 2 Knack for self-case formulation based on a CB model

In this lesson, participants learn about a cognitive behavioral (CB) model, especially the five-part model (“five-part” refers to five areas: situation, thoughts, emotions, behavior, and physical feelings) [29] and a self-case formulation based on this model. The case formulation is a method used to understand the problem of a client [30]. The case formulation is necessary for clients to choose an appropriate approach to change the vicious circles of these five areas. Miss Rino introduces a five-part CB model using a vignette of a worker with a work-related problem. Homework in this
Lesson 3 Try cognitive restructuring part 1

In this lesson, participants learn about Beck's cognitive model and acquired self-monitoring skills based on this model. The model postulates that an individual's mood and behavior are affected by his/her automatic thoughts, which are shaped by dysfunctional schemas [31]. The cognitive restructuring technique is one of the standard cognitive approaches of CBT utilized to change the automatic negative thought into actual thought [26]. Miss Rino gives a lecture on a cognitive ABC model (Activating/Actual event, Belief, and Consequence) [26 32 33] and on identifying the automatic thoughts that cause the negative mood. Homework in this lesson includes a self-monitoring exercise of participants' negative mood caused by an automatic thought in a particular situation selected by the participants.

Lesson 4 Try cognitive restructuring part 2

In this lesson, participants learn cognitive restructuring skills. Miss Rino teaches participants how to change the automatic negative thought into actual thought. In the latter half of the lesson, participants learn a relaxation technique using a breathing method. Relaxation techniques are often added to the CBT intervention for workers, and they have shown significant effects on improving
depression [34]. Homework in this lesson includes an exercise on cognitive restructuring. Based on the homework of Lesson 3, participants try to reconsider the rationale behind the automatic thought, seek alternative thinking, and replace automatic thought with rational thinking.

_Lesson 5 Knack for communication_

In this lesson, participants learn active listening and assertiveness skills. Active listening (AL) is a way of listening and responding to another person with an aim to improve mutual understanding [35].

AL is applied to non-therapeutic situations as a tool for better communication. Assertiveness is typically defined in terms of the legitimate and honest expression of one’s personal rights, feelings, beliefs, and interests without violating or denying the rights of others [36 37]. In order to communicate assertively, the DESC (Describe, Express, Specify and Choose or Consequence) script is used [38]. Assertiveness training can help employees change their job environments by teaching them to appropriately communicate their concerns to supervisors, coworkers, or subordinates [39].

Assertiveness training has often been used as a supplemental component of stress management interventions in workplace [40]. In this lesson, Miss Rino also teaches active listening and assertiveness skills based on the DESC script. Homework in this lesson includes an assertiveness exercise based on the DESC script.
Lesson 6 How to solve your problem effectively

In this lesson, participants learn a problem-solving technique based on the problem-solving therapy. Problem-solving therapy is a cognitive behavioral intervention that focuses on training adaptive problem-solving attitudes and skills [41]. A rational problem-solving style involves the deliberate and systematic application of four major problem-solving skills: 1) problem definition and formulation, 2) generation of alternative solutions, 3) decision making, and 4) solution implementation and verification [42]. Problem-solving training is often used in stress management intervention in the workplace [34 43]. In this lesson, Miss Rino teaches participants how to sort out the problem and make a list of solutions using problem-solving methods. Homework in this lesson includes a problem-solving exercise.

Intervention group

Participants will complete six weekly lessons and homework within the iCBT program. They will be allowed to complete the six lessons within 10 weeks after the baseline survey. The participants will be reminded by e-mail to complete each lesson and/or to submit homework if they had not already done so. Reminders will be sent from the research office to the participants every Monday.

Control group
Participants will be able to use an internal employee assistance program service as a treatment as usual (TAU).

Outcomes

Table 2 shows the overview of outcome measurements. Primary outcome will be assessed at the baseline, the six-month follow-up, and the twelve-month follow-up. All secondary outcomes, except for the time preference, will be assessed at the baseline, the three-month follow-up (end of acute phase treatment), the six-month follow-up, and the twelve-month follow-up. The time preference will be assessed at the baseline and the twelve-month follow-up.

Table 2 Overview of outcome measurements

<table>
<thead>
<tr>
<th>measurement</th>
<th>aim</th>
<th>Baseline (T1)</th>
<th>3-M F/U (T2)</th>
<th>6-M F/U (T3)</th>
<th>12-M F/U (T4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>the web-version of the Japanese WHO-CIDI 3.0 depression section</td>
<td>Duration before the onset of major depressive episode</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>BDI-II</td>
<td>Severity of depression</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>K6</td>
<td>Severity of psychological distress</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>HPQ</td>
<td>Work performance</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Sick leave days</td>
<td>Sick leave days in the past 3 months</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>UWES</td>
<td>Work engagement</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Time preference</td>
<td>Time preference</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>EQ-5D</td>
<td>Quality of Life</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Healthcare use</td>
<td>Healthcare use</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>

Note: BDI-II = Beck Depression Inventory II, K6 = Kessler psychological distress scale, HPQ = Health...
and Work Performance Questionnaire, UWES = Utrecht Work Engagement Scale.

Primary outcome

Incidence of MDE

The primary outcome measure is the onset of MDE during the six- and twelve-month follow-ups. The onset of MDE during the follow-up will be assessed using the web version of the Japanese WHO-CIDI 3.0 depression section [44 45] according to the DSM-IV-TR. The face-to-face version of WHO-CIDI 3.0 was translated into Japanese and its validity for diagnosing MDE was tested [46]. Questions and skip logics of the face-to-face version were used to develop the web version. The web version has been shown to have a good concordant with the clinical diagnosis of MDE [47] and to be reliable in a one-year test-retest survey [48]. A discrepancy in the onset information may occur between the two measurements at the six- and the twelve-month follow-ups. An incident case with MDE will be identified if a respondent reported an episode of MDE either at the six- or the twelve-month follow-up. An onset month of an episode of MDE will also be asked. When different onset months will be reported at the six- and the twelve-month follow-ups, information from the six-month follow-up will be used.

Secondary outcomes

Beck Depression Inventory-II (BDI-II)
The Beck Depression Inventory II (BDI-II) is a 21-item self-report inventory that measures depressive symptoms such as sadness, pessimism, suicidal thoughts or wishes, tiredness or fatigue, loss of energy, and loss of pleasure, among others [49 50]. Each item is scored on a scale ranging from 0 to 3, with a higher score indicating more serious depressive symptoms.

Kessler’s psychological distress scale (K6)

Psychological distress will be measured by the Japanese version of Kessler’s Psychological Distress Scale (K6) [51 52]. The K6 scale consists of six items assessing the frequency with which respondents have experienced symptoms of psychological distress during the past 30 days. The response options range from 0 (none of the time) to 4 (all of the time). The internal reliability and validity found in previous studies are acceptable [51].

Health and Productivity Questionnaire (HPQ)

The World Health Organization Health and Productivity Questionnaire (HPQ) is a self-report instrument designed to estimate the workplace costs of health problems in terms of self-reported sickness absence (absenteeism) and reduced job performance (presenteeism) [53]. Respondents will be asked to rate their overall work performance during the past 4 weeks. The item will be scored on an 11-point scale ranging from 0 (worst possible performance) to 10 (best possible performance). High
scores indicate a high degree of perceived work performance.

Sick leave days during past 3 month

Respondents will be asked to report the number of sick leave days they took during past three month.

Utrecht Work Engagement Scale (UWES)

Work engagement will be assessed using the short form of the Japanese version of the Utrecht Work Engagement Scale (UWES) [54]. The UWES consists of three subscales (i.e., vigor, dedication, absorption) comprising nine items. Items are scored on a 7-point scale ranging from 0 (never) to 6 (always). Examples of items are “At my job, I feel strong and vigorous” (vigor), “I am enthusiastic about my job” (dedication), and “I am immersed in my work” (absorption). A total score is calculated from all nine items.

Time preference (time discounting)

Time preference is obtained by following procedure [55 56]. The respondents will be asked to choose between two options, “A” and “B”. The respondent receives JPY 1 million (around USD 12,000) in a month when he/she chooses option A, while he/she receives a different amount in 13 months when he/she chooses option B. This question consists of nine choices (see Table 3). For
example, for the sixth choice, the respondents compare JPY 1 million today to JPY 1,020,000 (around USD 12,240) in 13 months. In this case, choosing option B instead of option A is the same as receiving 2% of the annual interest rate. The questionnaire is shown in Table 3, where the amount received under option A is specified as JPY 1 million and the imputed interest rate for option B changes from -5% to over 10%.

Table 3 Questionnaire to elicit time-discount rate.
Suppose you have two mutually-exclusive options to receive some money. You may choose Option “A”, to receive 1 million JPY in a month; or Option “B”, to receive a different amount in 13 months. Compare the amounts and delay until its receipt in Option “A” with Option “B” and indicate which option you would prefer for each pair of all nine choice pairs.

<table>
<thead>
<tr>
<th>Option A (Receipt in a month)</th>
<th>Option B (Receipt in 13 months)</th>
<th>Interest rate (Annual)</th>
<th>Circle A or B</th>
</tr>
</thead>
<tbody>
<tr>
<td>JPY 1 million</td>
<td>JPY 950,000</td>
<td>-5%</td>
<td>A B</td>
</tr>
<tr>
<td>JPY 1 million</td>
<td>JPY 1 million</td>
<td>0%</td>
<td>A B</td>
</tr>
<tr>
<td>JPY 1 million</td>
<td>JPY 1,001,000</td>
<td>0.10%</td>
<td>A B</td>
</tr>
<tr>
<td>JPY 1 million</td>
<td>JPY 1,005,000</td>
<td>0.50%</td>
<td>A B</td>
</tr>
<tr>
<td>JPY 1 million</td>
<td>JPY 1,010,000</td>
<td>1%</td>
<td>A B</td>
</tr>
<tr>
<td>JPY 1 million</td>
<td>JPY 1,020,000</td>
<td>2%</td>
<td>A B</td>
</tr>
<tr>
<td>JPY 1 million</td>
<td>JPY 1,060,000</td>
<td>6%</td>
<td>A B</td>
</tr>
<tr>
<td>JPY 1 million</td>
<td>JPY 1,100,000</td>
<td>10%</td>
<td>A B</td>
</tr>
<tr>
<td>JPY 1 million</td>
<td>Over JPY 1,100,000</td>
<td>Over 10%</td>
<td>A B</td>
</tr>
</tbody>
</table>

Quality of life

Health-related quality of life will be assessed with the EQ-5D [57]. The EQ-5D consists of five
items covering five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each of which is rated as causing “no problems” to “unable to”, and a visual analogue scale. The EQ-5D is a widely applied quality of life instrument, and its reliability and validity are well established [57].

**Key economic outcomes**

**Clinical endpoints**

In the cost-effectiveness analyses, the main outcome will be depression-free years gained.

Depression-free years will be assessed by calculating the difference in follow-up lengths and the duration of any major depressive episode (i.e., period of time in weeks that a person meets DSM-IV criteria). In the cost-utility analysis, quality-adjusted life years (QALYs) will be the clinical endpoint.

QALYs will be obtained from the EQ-5D.

**Costs**

The direct medical costs will be estimated from the questions about healthcare use. Indirect costs stemming from production losses due to absenteeism and presenteeism will be assessed with the HPQ.
Healthcare use

Respondents will be asked to report on their healthcare use at any time during past three months as follows:

1) Consultation with a general practitioner (if yes, the number of times).

2) History and number of hospitalizations (if yes, the number of days of hospitalization).

3) Use of medication of any kind.

4) Use of consultation with an industrial physician or the employee assistance program (if yes, the number of times).

Sample size calculation

A meta-analysis of CBT interventions using the “Coping with Depression (CwD)” program reported that the average effect size (incidence ratio, IR) for prevention of major depressive episode was 0.62 (95% CI: 0.43 to 0.91) at post-test [9]. A previous follow-up survey of employees in a company showed that the incidence of major depressive disorder was 2.8% during twelve months [48]. We applied a method proposed by Rubinstein and colleagues [58] to calculate a minimal sample size and a statistical power for a proportional hazard model analysis.

Thus, if we equally randomize 8,272 to an intervention group and control group (4,136 participants in each group), we will have 90% power to detect a treatment effect, assuming that IR =
0.62. However, these calculations ignore dropout. We expect that 75% will complete our
twelve-month follow-up, resulting in 3,102 respondents in each group at twelve months. In this
situation, we will have 80% power to detect the IR of 0.62.

Randomization

Participants who fulfill the inclusion criteria will be randomly allocated to intervention or control
groups. Stratified permuted-block randomization will be conducted as well. Participants will be
stratified into 16 strata according to two factors: K6 score (5 or greater or less than 5) in the baseline
survey and the eight workplaces to which they belong. A stratified permuted-block random table will
be generated by an independent biostatistician. Enrollment will be conducted by a CRC, and
assignment will be conducted by an independent research assistant. The stratified permuted-block
random table will be password protected and blinded to the researcher. Only the research assistant
will be able to access it during the work of random allocation.

Statistical methods

Clinical efficacy

A survival analysis will be conducted to test for the effectiveness of the intervention on the time to
the onset of MDE while controlling for censoring effects due to the differential length of the
follow-up or the completion of the follow-up without the onset of MDE. The length of follow-up for each participant will be represented by either the number of months between the baseline and the onset of MDE or the end of the twelve-month follow-up period (six-month follow-up if a respondent dropped out at twelve-month follow-up), whichever comes first. The cumulative incidence of MDE at six- and twelve-month follow-up as well as event-free survivals in every follow-up month will be estimated by the Kaplan-Meier method, and the statistical significance of the difference between the cumulative proportions of having MDE at the six- and the twelve-month follow-ups in the intervention and control groups will be tested. A log-rank test will be conducted to test the difference in the survival probabilities between the intervention and control groups. A single covariate Cox discrete time hazard model will be also used to test the difference and to estimate the hazard ratio (HR) and the 95% confidence intervals (CIs) of having MDE in the intervention group compared to the control group. The intervention effect will be also estimated, adjusting for dependent censoring using the inverse probability of the censoring weighted (IPCW) method for conducting sensitivity analysis [59]. A similar analysis will be also conducted using an alternative case definition, i.e., having a moderate level of depression (a BDI-II score of 20 or above).

For secondary outcomes, a mixed model for repeated measures conditional growth model analyses will be conducted using a group (intervention and control) * time (baseline, three-, six- and twelve-month follow-ups) interaction as an indicator of intervention effect. An intention to treat
(ITT) analysis will be conducted as well. Effect sizes and the 95% CIs will be calculated using Cohen’s d among those who completed the questionnaire at baseline and at a follow-up. The values of 0.2, 0.5, and 0.8 are generally interpreted as being suggestive of small, medium, and large effects, respectively [60]. In addition, the number needed to treat (NNT) to reduce depressive symptoms or psychological distress to achieve improvement from subthreshold depression will be calculated.

Referencing the cutoff scores of BDI-II and K6 of previous studies [49 61], all statistical analyses will be conducted using the SPSS Statistics 21.0.

Subgroup analysis

The effectiveness of the program may differ according to the initial severity of depression. We will therefore use, as one stratification factor, high/low subthreshold depression (i.e., participants who scored 5 or more in the K6) at baseline survey and will analyze the results according to a priori-defined subgroups (selective intervention effect).

Economic analyses

In the cost-effectiveness analyses, the incremental cost-effectiveness ratio (ICER) will be stated as costs per depression-free months gained, whereas the ICER in the cost-utility analyses will represent the costs per quality-adjusted life month gained. Bootstrapping will be used to test the robustness of
the ICERs and to quantify the uncertainty around the ratios that will be graphically represented on a
cost-effectiveness plane.

ETHICS AND DISSEMINATION

Ethical and safety considerations

The Research Ethics Review Board of Graduate School of Medicine/Faculty of Medicine, the
University of Tokyo, approved the study procedures (No. 3083-(2)). We have prepared a website
which contains a full explanation of the study. Before the baseline survey, participants will be invited
to read the explanation on the website and asked to click an “agree” button to show their consent to
participate in the study. Then, they will proceed to a baseline questionnaire page. Written consent is
not required by the Ethical Guidelines for Biomedical Research Involving Human Subjects, Japan;
the Research Ethics Review Board of Graduate School of Medicine/Faculty of Medicine the
University of Tokyo, has approved this procedure to obtain the participants’ consent.

Data confidentiality

The survey data will be temporarily stored on the server placed at the Department of
Mental Health, Graduate School of Medicine, the University of Tokyo. After the survey,
the collected data will be moved to a password-locked stand-alone PC. The collected data will be stored as linkable anonymizing data. The data will be accessible only by the CRC.

**Dissemination of research findings**

The main findings of this study will be disseminated via publications in peer-reviewed international journals. Presentations of study findings will also be taken at relevant research conferences, and local academic symposia and seminars.
Acknowledgements

We appreciate the help of the following persons in completing this project: Takayuki Narumi, Jun Naoi, Keisuke Kito, Chinatsu Narumi, Hayato Mori, Sayaka Horii, Mitsuyasu Mizusaki, Chihiro Hoshino, Kie Fujii, Aya Matsumoto, and Izumi Unezawa. Thanks are also due to Dr. Takashi Fukuda for his advice of economic evaluation.

Competing interests

KI is employed part-time by Chugai Pharmaceutical Company and Medical Care Toranomon as a clinical psychologist.

TAF has received lecture fees from Eli Lilly, Meiji, Mochida, MSD, Pfizer and Tanabe-Mitsubishi, and consultancy fees from Sekisui and Takeda Science Foundation.

He is diplomate of the Academy of Cognitive Therapy. He has received royalties from Igaku-Shoin, Seiwa-Shoten and Nihon Bunka Kagaku-sha. The Japanese Ministry of Education, Science, and Technology, the Japanese Ministry of Health, Labor and Welfare, and the Japan Foundation for Neuroscience and Mental Health have funded his research projects.

YM has received lecture fees from Union of Japanese Scientists and Engineers, EPS Co., Ltd., and statcom Co., Ltd., and consultancy fees from Zeria pharmaceutical Co., Ltd., Ono pharmaceutical Co., Ltd., Mebix Co., Ltd. He has received royalties from Igaku-Shoin and Ewanami-Shoten.

AS works for Hitachi Systems, Ltd. as a part-time consultant. He is on the advisory board for Junpukai Health Care Center and Ds's Mental Health Labo. He has received royalties from Baifukan, Kawashima-shoten, Seishin-shobou, and Seiwa-Shoten.

KK has received lecture fees from Astellas, Novartis, Eli Lilly, Otsuka, Dainippon-Sumitomo, and Yoshitomi pharmaceutical companies. He has received collaborative research grants from Astellas, Hitachi Co, and Hitachi Medical, and research grants from Yoshitomi, Dainippon-Sumitomo, Astellas, and GSK.
Funding

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Authors' contributions

Conceived and designed the experiments: KI NK TAF YM KK. Contributed reagents/materials/analysis tools: KI NK. Wrote the paper: KI NK TAF AS. All authors read and approved the final paper.
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Epub Date].


change assessed with the Beck Depression Inventory-II in Japanese patients with
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10.1016/j.psychres.2004.03.014[published Online First: Epub Date].


Baseline survey (T1)
Participants will be recruited from one company (N=20,000)

Exclusion criteria
1. Having MDD during past 1 month.
2. Having lifetime bipolar disorder.
3. Having sick leave days of 15 days or more in total due to own health problems during the past 3 months.
4. Going to hospital during the past 1 month.

Random assignment

Assigned to intervention
At 3-month follow-up (T2)
At 6-month follow-up (T3)
At 12-month follow-up (T4)

Assigned to control
At 3-month follow-up (T2)
At 6-month follow-up (T3)
At 12-month follow-up (T4)

Figure 1 participant flowchart.
Effects of an internet-based cognitive behavioral therapy (iCBT) intervention on preventing major depressive episode among workers: A protocol for a randomized controlled trial

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<th>BMJ Open</th>
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<tr>
<td>Article Type:</td>
<td>Protocol</td>
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<tr>
<td>Date Submitted by the Author:</td>
<td>06-Apr-2015</td>
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<td>Complete List of Authors:</td>
<td>Imamura, Kotaro; University of Tokyo, Kawakami, Norito; The University of Tokyo, Department of Mental Health Furukawa, Toshiaki; Kyoto University, Graduate School of Medicine and School of Public Health Matsuyama, Yutaka; Univ Tokyo, Shimazu, Akihito; The University of Tokyo, Department of Mental Health Kasai, Kiyoto; The University of Tokyo,</td>
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<td>Keywords:</td>
<td>OCCUPATIONAL &amp; INDUSTRIAL MEDICINE, Depression &amp; mood disorders &lt; PSYCHIATRY, PREVENTIVE MEDICINE</td>
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</table>
Title page

Title: Effects of an internet-based cognitive behavioral therapy (iCBT) intervention on preventing major depressive episode among workers: A protocol for a randomized controlled trial

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Key words: Internet-based cognitive behavioral therapy, depression, prevention, workers, randomized controlled trial

Word count: 4,107 words
ADMINISTRATIVE INFORMATION

Title
Effects of an internet-based cognitive behavioral therapy (iCBT) intervention on preventing major depressive episode among workers: A protocol for a randomized controlled trial

Trial registration
The study protocol is registered at the UMIN Clinical Trials Registry (UMIN-CTR) (ID = UMIN000014146).
https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&reptno=R00001646&type=summary&language=E

Protocol version
This protocol was newly registered at 3 Jun 2014. First revision was conducted due to revise the target sample size at 16 Aug. 2014. Second revision was conducted due to revise the anticipated trial start date at 23 Feb. 2015.

Funding
The present study is supported by the Grant-in-Aid for Young Scientists (B) 2014 (No. 26860433) from the Japan Society for the Promotion of Science. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Roles and responsibilities
Principal investigator (PI) will be Norito Kawakami (MD, PhD, MPH, psychiatric epidemiologist). Co-PIs will be Kotaro Imamura (PhD, MPH, clinical psychologist), Akihito Shimazu (PhD, clinical psychologist), Toshi A. Furukawa (MD, PhD, psychiatrist), Yutaka Mtsuyama (PhD, biostatistician), and Kiyoyo Kasai (MD, PhD, psychiatrist). Clinical research coordinator (CRC) will be Kotaro Imamura.

KI will be at the Data coordinating center to be located within the Department of Mental Health, Graduate School of Medicine, The University of Tokyo. NK will be responsible for the statistical analyses. YM will consult with NK regarding the design and conduct of the study, what statistical analyses should be done and how to interpret the results, and the reporting of the results for publication.
ABSTRACT

Introduction The aim of this study is to examine the effects of an internet-based cognitive behavioral therapy (iCBT) program on decreasing the risk of a major depressive episode (MDE) among workers employed in a private corporate group in Japan, using a randomized controlled trial (RCT) design.

Methods and analysis All of the workers in a corporate group (n = 20,000) will be recruited through an invitation e-mail. Participants who fulfill the inclusion criteria will be randomly allocated to intervention or control groups (planned N = 4,050 for each group). They will be allowed to complete the six lessons of the iCBT program within 10 weeks after the baseline survey. Those in the control group will receive the same iCBT after 12 months. The program includes several CBT skills: self-monitoring, cognitive restructuring, assertiveness, problem solving, and relaxation. The primary outcome measure is no new onset of MDE (using DSM-IV-TR/DSM-5 criteria) during the 12-month follow-up. Assessment will use the web version of the WHO Composite International Diagnostic Interview version 3.0 depression section.

Ethics and dissemination The Research Ethics Review Board of Graduate School of Medicine, the University of Tokyo (No. 3083-(2)), approved the study procedures.

Trial registration number The study protocol is registered at the UMIN Clinical Trials Registry (UMIN-CTR) (ID = UMIN000014146).
Keywords: Internet-based cognitive behavioral therapy, depression, prevention, workers, randomized controlled trial
INTRODUCTION

Depressive disorder is one of the most prevalent psychiatric disorders, affecting around 340 million people worldwide[1], and it is associated with a substantial deterioration in quality of life and economic loss in the community and the workplace[2, 3]. Thus, the primary prevention of depressive disorder is an important strategy for global mental health. In addition, stress has enormous socioeconomic implications for all spheres of employment in terms of absenteeism, staff turnover, lost productivity, poor morale, etc.[4, 5]. Although the burden of stress and depression on the workplace is substantial[6], few studies aiming to prevent psychosocial problems have been conducted.

Two previous meta-analyses have shown that cognitive behavior therapy (CBT) is an effective preventive measure for major depressive disorder. One meta-analysis reported that the risk of depressive disorder decreased 16% on average in the intervention group and summarized 15 various types of CBTs[7]. Another meta-analysis of randomized controlled trials (RCTs) with a CBT program, “Coping with Depression (CwD)”[8], showed that the program can also prevent major depressive disorder and indicated a 38% decrease in the risk among participants in the program[9]. However, major limitations exist in the dissemination of these CBT interventions: The programs require that professionals be well trained in CBT[10-12]; time, cost, and stigma are other barriers to access to a CBT program[13].
An innovative way to deliver CBT-based treatment widely is by using computerized CBT (CCBT) and CCBT via the internet (iCBT). Both CCBT and iCBT programs teach basic information and skills based on the same CBT principles as face-to-face CBT programs, with a highly structured format comprised of educational lessons, homework assignments, and supplementary resources[14].

Previous studies have shown a significant positive treatment effect of CCBT and iCBT programs on depression and anxiety in the clinical setting[15]. An iCBT program is particularly beneficial with its high anonymity[16] and high accessibility[17]. Recently, there have been increasing applications of iCBT for preventing depression. Using self-reported symptoms of depression as an outcome, one study of adolescents reported a significant prevention effect of iCBT programs, though it included only male participants[18]. In addition, one study of university students[19] and one community-based study[20] reported a significant effect of iCBT programs on improving depressive symptoms in non-clinical settings. However, one community-based study failed to show a significant effect[21]. We also have reported that a six-session iCBT program successfully improved symptoms of depression in a RCT in the workplace[22]. However, a search of the literature revealed only one previous RCT (conducted by the authors)[23], which investigated the effect of an iCBT program on reducing the risk of major depressive episode (MDE) diagnosed according to DSM-IV diagnostic criteria[24]. The control group was also provided with a treatment program during the follow-up.[23] Thus, evidence for the effect of an iCBT on reducing risk of MDE is still very
A previous follow-up survey of employees in a company showed that the incidence of DSM-IV major depressive disorder was 2.8% during 12 months in Japan [25]. If we equally randomize about 8,000 participants to intervention and control groups (4,000 in each group), the total number of incidence will be 146 (55 and 91 in the intervention and control groups, respectively), assuming that IR = 0.62 (see sample size calculation in method and analysis for details). Since the number of participants will be large, it would not be possible to conduct face-to-face or even telephone interviews to ascertain the occurrence of MDE during the follow-up; it is a feasible strategy to use the web-based self-report version of a standard structured interview, such as WHO-Composite International Diagnostic Interview (CIDI) 3.0 depression section [26 27], which has been shown to have a good concordant with the clinical diagnosis of MDE [28] and an acceptable one-year test-retest reproducibility [25]. While a self-report assessment of MDE is clearly a major limitation, only such an instrument is feasible for a large-scale trial to reduce the risk of MDE diagnosed strictly following DSM-IV/DSM-5 criteria, which cannot be made by a symptom checklist.

Objectives

The present study is a twelve-month follow-up large-scale randomized controlled trial. An improved iCBT program, which was based on the results of the previous study[22], will be used. The purposes of this randomized controlled study are as follows: 1) to decrease the risk of
DSM-IV/DSM-5-defined MDE through the 12-month follow-up among workers in Japan; 2) to examine the effects of the iCBT program on improving the symptoms of depression at three-, six-, and twelve-month follow-ups among workers who have subthreshold depressive symptoms in Japan; 3) to examine the effects of the iCBT program on improving work engagement and work performance at three-, six-, and twelve-month follow-ups among workers in Japan; and 4) to examine the cost-effectiveness of the iCBT program. We expect that: 1) the iCBT program will reduce the risk of MDE during the 12-month follow-up; 2) it will improve symptoms of depression at three-, six-, and 12-month follow-ups among workers who have subthreshold depressive symptoms at baseline; and, 3) it will improve work engagement and work performance at three-, six-, and twelve-month follow-ups, and 4) the program will be cost-effective.

### Trial design

The study will be a two-arm, parallel-group, TAU-controlled, non-blinded randomized study. The allocation ratio of the intervention group to the control group is 1 to 1. Participants will be randomly allocated either to the intervention or to the control group after they have completed a baseline online questionnaire survey. Online follow-up surveys will be conducted three, six, and twelve months after the baseline. The study protocol was registered at the UMIN Clinical Trials Registry (UMIN-CTR) (ID = UMIN000014146). This protocol manuscript was reported according to the SPIRIT guideline checklist.
METHOD AND ANALYSIS

Participants

Working men and women will be selected according to the following criteria:

Inclusion criteria

1) Age 20-60 at study entry.

2) Currently employed full time by the business company.

3) Can access the Internet via a PC at home or at his/her workplace, since the server software used in this study allows access only from a PC, but not from mobile devices such as smartphones.

Exclusion criteria

1) Non-regular or part-time employees.

2) Sick leave for 15 or more days for a physical or mental condition in the past three months.

3) Current treatment for a mental health problem from a mental health professional.

4) A major depressive episode within the past month as ascertained by the web version of the Japanese WHO-CIDI 3.0.

5) A lifetime history of bipolar disorder as ascertained by the web version of the Japanese WHO-CIDI 3.0.

Procedure

Figure 1 shows the participant flowchart of this trial. Our previous RCT reported that 47.5% of
employees who received invitation e-mails completed a baseline survey and 10% of them had to be
excluded[22]. For this study, the clinical research coordinator (CRC) will send out invitations to
20,000 employees, of whom 9,000 are expected to give the informed consent, and 8,100 are
expected to be eligible. These 8,100 will be randomized either to the intervention group (n = 4,050)
or to the control group (n = 4,050). They will be allowed to complete the six lessons within 10 weeks
after the baseline survey. Those in the control group can receive the iCBT after 12 months. An
invitation e-mail to all workers in a corporate group will direct them to a website that includes a full
explanation of the study. After reading the explanation of the study on the website they will be asked
to click an “agree” button to give their consent to participate in the study; then, they will proceed to
the baseline questionnaire page. If a candidate clicks a “disagree” button, the website page will close.
In order for the randomization and start of intervention to be as close as possible, the CRC will
endeavor to randomize the participants immediately after closing the application and send an e-mail
with the iCBT program course description as soon as possible. A computer system for automating
the randomization of candidates on a first-come, first-served basis is not available.

Intervention program

The iCBT program called Internet CBT Program: Useful Mental Health Solutions Series for
Business is a six-week, web-based training course that provides CBT-based stress management
skills[22]. This program is structured in six lessons, with one lesson per week. About 30 minutes are
needed for each lesson, including the homework. This program can be used anywhere the internet is available.

One of the unique features of the program is that training is provided along with a Manga (Japanese comic) story of a psychologist and a client to facilitate the understanding of the participants. Several merits of using a comic story with Manga characters have been acknowledged in research on education in school. First, it helps motivate participants to stay in the program[29]. Second, it facilitates easy learning. A program with text combined with comic stories is easier for learners to understand compared to a text-only program[29-30]. Third, using a comic story fosters learners’ interest in the program[30]. These merits might be applicable to education in the workplace because most Japanese people of working age are familiar with comics.

The present iCBT program was developed with two established CBT packages as its basis. One is the cognitive therapy program developed by Beck[31]. The other is the “Coping with Depression (CwD)” program developed by Lewinsohn[8]. The CBT skill components included in the program are: self-monitoring, cognitive restructuring, assertiveness, problem-solving, and relaxation. The behavioral activation technique, a main component of the CwD, is not included in the present RCT in order to be consistent with the previous RCT[22-23]. At the end of each lesson, participants will be asked to submit homework on a voluntary basis, to receive feedback from trained staff (e.g., clinical psychologists) to facilitate their understanding. Feedback will be sent to the participants.
within two days after their submission.

Table 1 shows the contents of the iCBT program. The program includes self-monitoring skills (in lesson 2), cognitive restructuring skills (in lessons 3 and 4), assertiveness skills (in lesson 5), problem-solving skills (in lesson 6), and relaxation skills (in lesson 4). In this study, the cognitive restructuring method was adopted as the primary and main cognitive approach, as it previously had been shown to be effective in reducing depression[32]. Assertiveness and problem-solving training, as well as training in relaxation, were chosen as supplementary behavioral approaches to enhance the effect of the program.

Table 1 Contents of the iCBT program.

<table>
<thead>
<tr>
<th>Lesson No.</th>
<th>Title</th>
<th>Contents</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Learning about stress.</td>
<td>Learning about psychological stress model modified for this iCBT program.</td>
</tr>
<tr>
<td>2</td>
<td>Knack for self-case formulation based on a CB model.</td>
<td>Learning about cognitive behavioral model and how to do self-monitoring based on CBT.</td>
</tr>
<tr>
<td>3</td>
<td>Try cognitive restructuring part 1.</td>
<td>Learning about cognitive restructuring.</td>
</tr>
<tr>
<td>4</td>
<td>Try cognitive restructuring part 2.</td>
<td>Learning about cognitive restructuring and relaxation using breathing method.</td>
</tr>
<tr>
<td>5</td>
<td>Knack for communication.</td>
<td>Learning about active listening and assertiveness.</td>
</tr>
<tr>
<td>6</td>
<td>How to solve your problem effectively.</td>
<td>Learning about problem-solving methods.</td>
</tr>
</tbody>
</table>
Lesson 1: Learning about stress

In this lesson, participants learn about a psychological stress model[33]. A guiding character, clinical psychologist, Miss Rino, speaks about the relationship between stressors and stress reactions.

Homework in this lesson includes respondents self-checking their stressors and stress reactions to help them identify these factors/conditions.

Lesson 2: Knack for self-case formulation based on a CB model

In this lesson, participants learn about a cognitive behavioral (CB) model, especially the five-part model (“five-part” refers to five areas: situation, thoughts, emotions, behavior, and physical feelings)[34] and a self-case formulation based on this model. Case formulation is a method used to understand the problem of a client[35]. Case formulation is necessary for clients to choose an appropriate approach to change the vicious circles of these five areas. Miss Rino introduces a five-part CB model using a vignette of a worker with a work-related problem. Homework in this lesson includes self-monitoring using the five-part model.

Lesson 3: Try cognitive restructuring part 1

In this lesson, participants learn about Beck's cognitive model and acquired self-monitoring skills based on this model. The model postulates that an individual's mood and behavior are affected by his/her automatic thoughts, which are shaped by dysfunctional schemas[36]. The cognitive restructuring technique is one of the standard cognitive approaches of CBT utilized to change the
 automatic negative thought into actual, realistic, and flexible thought[31]. Miss Rino gives a lecture
on a cognitive ABC model (Activating/Actual event, Belief, and Consequence)[31, 37, 38] and on
identifying the automatic thoughts that cause a negative mood. Homework in this lesson includes a
self-monitoring exercise of participants’ negative mood caused by an automatic thought in a
particular situation selected by the participants.

Lesson 4: Try cognitive restructuring part 2

In this lesson, participants learn cognitive restructuring skills. Miss Rino teaches participants how to
change an automatic negative thought into an actual thought. In the latter half of the lesson,
participants learn a relaxation technique using a breathing method. Relaxation techniques are often
added to the CBT intervention for workers, and they have shown significant effects on improving
depression[39]. Homework in this lesson includes an exercise on cognitive restructuring. Based on
the homework of Lesson 3, participants try to reconsider the rationale behind the automatic thought,
seek alternative thinking, and replace automatic thought with rational thinking.

Lesson 5: Knack for communication

In this lesson, participants learn active listening and assertiveness skills. Active listening (AL) is a
way of listening and responding to another person with an aim to improve mutual understanding[40].
Active listening is applied to non-therapeutic situations as a tool for better communication.
Assertiveness is typically defined as the legitimate and honest expression of one’s personal rights,
feelings, beliefs, and interests without violating or denying the rights of others[41-42]. In order to communicate assertively, the DESC (Describe, Express, Specify, and Choose or Consequence) script is used[43]. Assertiveness training can help employees change their job environments by teaching them to appropriately communicate their concerns to supervisors, coworkers, or subordinates[44]. Assertiveness training has often been used as a supplemental component of stress management interventions in the workplace[45]. In this lesson, Miss Rino also teaches active listening and assertiveness skills based on the DESC script. Homework in this lesson includes an assertiveness exercise based on the DESC script.

Lesson 6: How to solve your problem effectively

In this lesson, participants learn a problem-solving technique based on problem-solving therapy. Problem-solving therapy is a cognitive behavioral intervention that focuses on training adaptive problem-solving attitudes and skills[46]. A rational problem-solving style involves the deliberate and systematic application of four major problem-solving skills: 1) problem definition and formulation, 2) generation of alternative solutions, 3) decision making, and 4) solution implementation and verification[47]. Problem-solving training is often used in stress management intervention in the workplace[39, 48]. In this lesson, Miss Rino teaches participants how to sort out the problem and make a list of solutions using problem-solving methods. Homework in this lesson includes a problem-solving exercise.
1 Intervention group

2 Participants in the intervention group will complete six weekly lessons and homework within the
3 iCBT program. They will be allowed to complete the six lessons and submit their homework within
4 10 weeks after the baseline survey. The participants will be reminded by e-mail to complete each
5 lesson and/or to submit homework if they had not already done so. Reminders will be sent from the
6 research office to the participants every Monday.

7 Control group

8 Participants in the control group will be able to use an internal employee assistance program service,
9 such as consulting with a physician or a psychologist and group, or online education/training
10 programs for promoting mental health, as a treatment as usual (TAU). These programs contained few
11 descriptions of CBT knowledge and skills.

12 Outcomes

13 Table 2 shows an overview of outcome measures. The primary outcome measure will be assessed at
14 the baseline, the six-month follow-up, and the twelve-month follow-up. All secondary outcomes,
15 except for the time preference, will be assessed at the baseline, the three-month follow-up (end of
16 acute phase treatment), the six-month follow-up, and the twelve-month follow-up. The time
17 preference will be assessed at the baseline and the twelve-month follow-up. Non-respondents will
18 receive reminded reminder e-mail at least two times from the research center for each of the
follow-up surveys, at three-, six-, and twelve-months.

Table 2 Overview of outcome measures

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Aim</th>
<th>Baseline (T1)</th>
<th>3-M F/U (T2)</th>
<th>6-M F/U (T3)</th>
<th>12-M F/U (T4)</th>
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<tbody>
<tr>
<td>The web-version of the Japanese WHO-CIDI 3.0 depression section</td>
<td>Duration before the onset of major depressive episode</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>BDI-II</td>
<td>Severity of depression</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>K6</td>
<td>Severity of psychological distress</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>HPQ</td>
<td>Work performance</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Sick leave days</td>
<td>Sick leave days in the past 3 months</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>UWES</td>
<td>Work engagement</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Time preference</td>
<td>Time preference</td>
<td>x</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>EQ-5D</td>
<td>Quality of Life</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Healthcare use</td>
<td>Healthcare use</td>
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</tr>
</tbody>
</table>

Note: BDI-II = Beck Depression Inventory II, K6 = Kessler psychological distress scale, HPQ = Health and Work Performance Questionnaire, UWES = Utrecht Work Engagement Scale.

Primary outcome

Incidence of MDE

The primary outcome measure is the onset of MDE during the twelve-month follow-up. To collect accurate information of the onset of MDE, assessments will be conducted at the six- and twelve-month follow-ups. The onset of MDE during the follow-up will be assessed using the web version of the Japanese WHO-CIDI 3.0 depression section[26-27] according DSM-IV-TR criteria.
The face-to-face version of WHO-CIDI 3.0 was translated into Japanese and proved to be valid for diagnosing MDE[49]. The web version asks respondents the same set of questions and uses the skip logics of the depression section, and a diagnosis of MDE is automatically produced by a computer program using an algorithm specific to WHO-CIDI 3.0. The web version has been shown to have a good concordance with the clinical diagnosis of MDE[28] and to be reliable in a one-year test-retest survey[25]. While the WHO CIDI3.0 was originally designed to produce a diagnosis according to DSM-IV-TR criteria, the instrument can also produce a diagnosis of MDE based on DSM-5 criteria[50].

Since respondents will be asked to report any episode of MDE, along with the month of onset, at both the six- and twelve-month follow-up, there is possibility of discrepancy in the reported onset information. In the case of such discrepancy, the reported onset at the six-month follow-up will be used for the purposes of this study.

Secondary outcomes

*Beck Depression Inventory-II (BDI-II)*

The Beck Depression Inventory II (BDI-II) is a 21-item self-report inventory that measures depressive symptoms such as sadness, pessimism, suicidal thoughts or wishes, tiredness or fatigue, loss of energy, and loss of pleasure, among others[51-52]. Each item is scored on a scale ranging
from 0 to 3, with a higher score indicating more serious depressive symptoms.

*Kessler’s psychological distress scale (K6)*

Psychological distress will be measured by the Japanese version of Kessler’s Psychological Distress Scale (K6)[53-54]. The K6 scale consists of six items assessing the frequency with which respondents have experienced symptoms of psychological distress during the past 30 days. The response options range from 0 (none of the time) to 4 (all of the time). The internal reliability and validity found in previous studies are acceptable[53].

*Health and Productivity Questionnaire (HPQ)*

The World Health Organization Health and Productivity Questionnaire (HPQ) is a self-report instrument designed to estimate the workplace costs of health problems in terms of self-reported sickness absence (absenteeism) and reduced job performance (presenteeism)[55]. Previous studies have documented significant associations (r = 0.61 to 0.87) of HPQ work hours assessments with payroll records[55] and job performance assessments with supervisor ratings (r = 0.52)[56], as well as other administrative records (area under the curve, 0.58 to 0.72)[27]. Respondents will be asked to rate their overall work performance during the past 4 weeks. The item will be scored on an 11-point scale ranging from 0 (worst possible performance) to 10 (best possible performance). High scores indicate a high degree of perceived work performance.

*Sick leave days during past 3 month*
Respondents will be asked to report the number of sick leave days they took during past three months.

**Utrecht Work Engagement Scale (UWES)**

Work engagement will be assessed using the short form of the Japanese version of the Utrecht Work Engagement Scale (UWES)[57]. The UWES consists of three subscales (i.e., vigor, dedication, absorption) comprising nine items. Items are scored on a 7-point scale ranging from 0 (never) to 6 (always). Examples of items are “At my job, I feel strong and vigorous” (vigor), “I am enthusiastic about my job” (dedication), and “I am immersed in my work” (absorption). A total score is calculated from all nine items.

**Time preference (time discounting)**

Time preference (time discounting) is one’s relative valuation for having a good currently compared with its valuation at a later date. Time preference may moderate the effect of an iCBT program.

Among others[58], in the present study, time preference is assessed by the following procedure[59-60]. The respondents will be asked to choose between two options, A and B. The respondent receives JPY 1 million (around USD 12,000) in a month when he/she chooses option A, while he/she receives a different amount in 13 months when he/she chooses option B. This question consists of nine choices (see Table 3). For example, for the sixth choice, the respondents compare JPY 1 million today to JPY 1,020,000 (around USD 12,240) in 13 months. In this case, choosing option B instead of option A is the same as receiving a 2% annual increase. The questionnaire is
shown in Table 3, where the amount received under option A is specified as JPY 1 million and the 
imputed interest rate for option B changes from -5% to over 10%.

Table 3 Questionnaire to elicit time-discount rate.

Suppose you have two mutually-exclusive options to receive some money. You may choose Option 
“A”, to receive 1 million JPY in a month; or Option “B”, to receive a different amount in 13 months. 
Compare the amounts and delay until its receipt in Option “A” with Option “B” and indicate which 
option you would prefer for each pair of all nine choice pairs.

<table>
<thead>
<tr>
<th>Option A (Receipt in a month)</th>
<th>Option B (Receipt in 13 months)</th>
<th>Interest rate (Annual)</th>
<th>Circle A or B</th>
</tr>
</thead>
<tbody>
<tr>
<td>JPY 1 million</td>
<td>JPY 950,000</td>
<td>-5%</td>
<td>A</td>
</tr>
<tr>
<td>JPY 1 million</td>
<td>JPY 1 million</td>
<td>0%</td>
<td>A</td>
</tr>
<tr>
<td>JPY 1 million</td>
<td>JPY 1,001,000</td>
<td>0.10%</td>
<td>A</td>
</tr>
<tr>
<td>JPY 1 million</td>
<td>JPY 1,005,000</td>
<td>0.50%</td>
<td>A</td>
</tr>
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<td>JPY 1 million</td>
<td>JPY 1,010,000</td>
<td>1%</td>
<td>A</td>
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<td>JPY 1 million</td>
<td>JPY 1,020,000</td>
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<td>JPY 1 million</td>
<td>JPY 1,060,000</td>
<td>6%</td>
<td>A</td>
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<tr>
<td>JPY 1 million</td>
<td>JPY 1,100,000</td>
<td>10%</td>
<td>A</td>
</tr>
<tr>
<td>JPY 1 million</td>
<td>Over JPY 1,100,000</td>
<td>Over 10%</td>
<td>A</td>
</tr>
</tbody>
</table>

Quality of life

Health-related quality of life will be assessed with the EQ-5D\[61\]. The EQ-5D consists of five items 
covering five dimensions (mobility, self-care, usual activities, pain/discomfort, and 
anxiety/depression), each of which is rated as causing “no problems” to “unable to,” and a visual 
analogue scale. The EQ-5D is a widely applied quality of life instrument, and its reliability and 
validity are well established\[61\].
Key economic outcomes

Clinical endpoints

A cost-effectiveness analysis will be based on the main outcome of depression-free years gained. Depression-free years will be assessed by calculating the difference in follow-up lengths and the duration of any major depressive episode (i.e., period of time in weeks that a person meets DSM-IV criteria). In the cost-utility analysis, quality-adjusted life years (QALYs) will be the clinical endpoint. QALYs will be obtained from the EQ-5D.

Costs

Direct medical costs will be estimated from the questions about healthcare use. Indirect costs stemming from production losses due to absenteeism and presenteeism will be assessed with the World Health Organization Health and Productivity Questionnaire (HPQ)[55].

Healthcare use

Respondents will be asked to report on their healthcare use at any time during past three month as follows: 1) consultation with a general practitioner (if yes, the number of times); 2) history and number of hospitalizations (if yes, the number of days of hospitalization); 3) use of medication of any kind; and, 4) use of consultation with an industrial physician or the employee assistance program.
Sample size calculation

A meta-analysis of CBT interventions using the “Coping with Depression (CwD)” program reported that the average effect size (incidence ratio, IR) for prevention of major depressive episode was 0.62 (95% CI: 0.43 to 0.91) at post-test[9]. A follow-up survey of employees in a company showed that the incidence of major depressive disorder was 2.8% during twelve months[25]. We applied a method proposed by Rubinstein and colleagues[62] to calculate a minimal sample size and a statistical power for a proportional hazard model analysis. Thus, if we equally randomize 8,272 to an intervention group and control group (4,136 participants in each group), we will have 90% power to detect a treatment effect, assuming that IR = 0.62. However, these calculations ignore dropout. We expect that 75% will complete our twelve-month follow-up, resulting in 3,102 respondents in each group at twelve months. In this situation, we will have 80% power to detect the IR of 0.62.

On the other hand, a previous systematic review has shown that the incidence of major depressive disorder was greater in subjects with subthreshold depressive symptoms than in subjects without subthreshold depressive symptoms[63]. By stratifying participants according to the K6, we will conduct subgroup analyses targeting the high risk group.

Randomization

Participants who fulfill the inclusion criteria will be randomly allocated to intervention or control...
groups. Stratified permuted-block randomization will be conducted as well. Participants will be stratified into 16 strata according to two factors: K6 score (5 or greater or less than 5) in the baseline survey and the eight workplaces to which they belong. The intervention effect may vary according to the severity of psychological distress at baseline. In addition to the analysis of the whole sample (to examine the universal intervention effect), we will also analyze data by a priori defined subgroups (to examine the selective intervention effect). A stratified permuted-block random table will be generated by an independent biostatistician. Enrollment will be conducted by a CRC, and assignment will be conducted by an independent research assistant. The stratified permuted-block random table will be password protected and blinded to the researcher. Only the research assistant will be able to access it during the work of random allocation.

Statistical methods

Clinical efficacy

A survival analysis will be conducted to test for the effectiveness of the intervention by comparing the survival time not having MDE between the intervention and control groups. The survival time of each participant was calculated as months from baseline to the onset of MDE or the termination of the observation. The length of follow-up for each participant will be represented by either the number of months between the baseline and the onset of MDE or the end of the twelve-month follow-up period (six-month follow-up if a respondent dropped out at twelve-month follow-up),
whichever comes first. The cumulative incidence of MDE at six- and twelve-month follow-up as well as event-free survivals in every follow-up month will be estimated by the Kaplan-Meier method, and the statistical significance of the difference between the cumulative proportions of having MDE at the six- and the twelve-month follow-ups in the intervention and control groups will be tested. A log-rank test will be conducted to test the difference in the survival probabilities between the intervention and control groups. A single covariate Cox discrete time hazard model will be used to test the difference and to estimate the hazard ratio (HR) and the 95% confidence intervals (CIs) of having MDE in the intervention group compared to the control group. The intervention effect also will be estimated, adjusting for dependent censoring using the inverse probability of censoring weighted (IPCW) method for conducting a sensitivity analysis[64]. A similar analysis also will be conducted using an alternative case definition, such as having a moderate level of depression (a BDI-II score of 20 or above).

For secondary outcomes (i.e., symptoms of depression), a mixed model for repeated measures conditional growth model analysis will be conducted using a group (intervention and control) * time (baseline, three-, six- and twelve-month follow-ups) interaction as an indicator of intervention effect. An intention to treat (ITT) analysis will be conducted as well, using the mixed model for repeated measures conditional growth model analysis. Effect sizes and 95% CIs will be calculated using
Cohen’s $d$ among those who completed the questionnaire at baseline and at a follow-up. The values
of 0.2, 0.5, and 0.8 are generally interpreted as being suggestive of small, medium, and large effects,
respectively[65]. In addition, the number needed to treat (NNT) to reduce depressive symptoms or
psychological distress to achieve improvement from subthreshold depression will be calculated.

Referencing the cutoff scores of BDI-II and K6 of previous studies[51, 66], all statistical analyses
will be conducted using the SPSS Statistics 21.0.

Subgroup analysis

The effectiveness of the program may differ according to the initial severity of depression. We will
therefore use, as one stratification factor, high/low subthreshold depression (i.e., participants who
scored 5 or more in the K6) at baseline survey and will analyze the results according to
a priori-defined subgroups (selective intervention effect).

Economic analysis

In the cost-effectiveness analysis, the incremental cost-effectiveness ratio (ICER) will be stated as
costs per depression-free months gained, whereas the ICER in the cost-utility analysis will represent
the costs per quality-adjusted life month gained. Bootstrapping will be used to test the robustness of
the ICERs and to quantify the uncertainty around the ratios that will be graphically represented on a
cost-effectiveness plane.

Data Monitoring
1. A Data and Safety Monitoring Board (DSMB) will be set up, including an independent chair and at least two independent members. The DSMB will meet every three months after the first client is randomized. The purpose of the meetings will be to review the report prepared by the CRC. The CRC will prepare DSMB reports to monitor recruitment progress and data collection (e.g., percentage completing each follow-up).
ETHICS AND DISSEMINATION

Ethical and safety considerations

The Research Ethics Review Board of Graduate School of Medicine/Faculty of Medicine, the University of Tokyo, approved the study procedures (No. 3083-(2)). We have prepared a website that contains a full explanation of the study. Before the baseline survey, participants will be invited to read the explanation on the website and asked to click an “agree” button to show their consent to participate in the study. Then, they will proceed to a baseline questionnaire page. Candidates will be fully informed that their participation is totally voluntary, that even after voluntarily participating they can withdraw from the study without stating the reason, and that neither participation nor withdrawal will cause any advantage or disadvantage to them. Written consent is not required by the Ethical Guidelines for Biomedical Research Involving Human Subjects, Japan; the Research Ethics Review Board of Graduate School of Medicine/Faculty of Medicine the University of Tokyo, has approved this procedure to obtain the participants’ consent.

Data confidentiality

The survey data will be temporarily stored on a server placed at the Department of Mental Health, Graduate School of Medicine, the University of Tokyo. After the survey, the collected data will be moved to a password-locked stand-alone PC. The collected data will be stored as linkable anonymizing data. The data will be accessible only by the CRC.
Dissemination of research findings

The main findings of this study will be disseminated via publications in peer-reviewed international journals. Presentations of study findings will also be offered at relevant research conferences, and local academic symposia and seminars.

Strengths and limitations

The greatest strength of this study design is its focus on the effect of the iCBT program on preventing the onset of MDE using a large-scale RCT design in a healthy working population. The present study also is intended to add evidence for the effect of CBT programs on positive health outcomes (e.g., work engagement and work performance) and economic evaluation of iCBT on the primary prevention strategy among healthy workers.

One of the major weaknesses of this study is that MDE will be measured by self-report, which may be affected by the perception of the participants or by situational factors at work. The validity of the web-based CIDI depression section has been established partially but needs further clarification and refinement. The other limitation is that the participants will be recruited from one corporate group in Japan. Most of them have their own PCs in their offices or homes. The participants may also be assumed to have experience with using a PC and studying in online programs. Therefore, generalization of the findings to populations that do not share the characteristics of the participants may be limited.
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Authors' contributions

Conceived and designed the experiments: KI NK TAF YM KK. Contributed reagents/materials/analysis tools: KI NK. Wrote the paper: KI NK TAF AS. All authors read and approved the final paper.

Competing interests

KI is employed part-time by Chugai Pharmaceutical Company and Medical Care Toranomon as a clinical psychologist.

NK has received lecture fees from Meiji, Otsuka, EAP Consulting, Fujitsu Software Technologies, Japan Productivity Center, Occupational Health Foundation, Japan Housing Finance Agency, Aishin-Seiki, and Japan Dental Association, and consultancy fees from Sekisui Chemicals, Junpukai Health Care Center, and Osaka Chamber of Commerce and Industry. He has received royalties from

2. TAF has received lecture fees from Eli Lilly, Meiji, Mochida, MSD, Pfizer and Tanabe-Mitsubishi, and consultancy fees from Sekisui and Takeda Science Foundation. He is diplomate of the Academy of Cognitive Therapy. He has received royalties from Igaku-Shoin, Seiya-Shoten and Nihon Bunka Kagaku-sha. The Japanese Ministry of Education, Science, and Technology, the Japanese Ministry of Health, Labor and Welfare, and the Japan Foundation for Neuroscience and Mental Health have funded his research projects.

3. YM has received lecture fees from Union of Japanese Scientists and Engineers, EPS Co., Ltd., and statcom Co., Ltd., and consultancy fees from Zeria pharmaceutical Co., Ltd., Ono pharmaceutical Co., Ltd., Mebix Co., Ltd. He has received royalties from Igaku-Shoin and Ewanami-Shoten.

4. AS works for Hitachi Systems, Ltd. as a part-time consultant. He is on the advisory board for Junpukai Health Care Center and Ds’s Mental Health Labo. He has received royalties from Baifuukan, Kawashima-shoten, Seishin-shobou, and Seiwa-Shoten.

5. KK has received lecture fees from Astellas, Novartis, Eli Lilly, Otsuka, Dainippon-Sumitomo, and Yoshitomi pharmaceutical companies. He has received collaborative research grants from Astellas,
Hitachi Co, and Hitachi Medical, and research grants from Yoshitomi, Dainippon-Sumitomo, Astellas, and GSK.

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**Data sharing statement**

No additional data are available.
1
2 Figure 1 participant flowchart.
3
4
5
REFERENCES


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10.1037/0033-2909.112.1.155[published Online First: Epub Date].

First: Epub Date].
Figure 1 participant flowchart.
190x254mm (300 x 300 DPI)
# SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents

<table>
<thead>
<tr>
<th>Section/item</th>
<th>Item No</th>
<th>Description</th>
<th>Reported on page No</th>
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<tbody>
<tr>
<td><strong>Administrative information</strong></td>
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<tr>
<td>Title</td>
<td>1</td>
<td>Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym</td>
<td>p.2</td>
</tr>
<tr>
<td>Trial registration</td>
<td>2a</td>
<td>Trial identifier and registry name. If not yet registered, name of intended registry</td>
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<td></td>
<td>2b</td>
<td>All items from the World Health Organization Trial Registration Data Set</td>
<td>N/A</td>
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<tr>
<td>Protocol version</td>
<td>3</td>
<td>Date and version identifier</td>
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<tr>
<td>Funding</td>
<td>4</td>
<td>Sources and types of financial, material, and other support</td>
<td>p.2</td>
</tr>
<tr>
<td>Roles and responsibilities</td>
<td>5a</td>
<td>Names, affiliations, and roles of protocol contributors</td>
<td>p.2</td>
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<td>5b</td>
<td>Name and contact information for the trial sponsor</td>
<td>p.2</td>
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<tr>
<td></td>
<td>5c</td>
<td>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</td>
<td>p.2</td>
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<tr>
<td></td>
<td>5d</td>
<td>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)</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Introduction</strong></td>
<td></td>
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<tr>
<td>Background and rationale</td>
<td>6a</td>
<td>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</td>
<td>pp.5-7</td>
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<tr>
<td></td>
<td>6b</td>
<td>Explanation for choice of comparators</td>
<td>N/A</td>
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<tr>
<td>Objectives</td>
<td>7</td>
<td>Specific objectives or hypotheses</td>
<td>pp.7-8</td>
</tr>
<tr>
<td>Trial design</td>
<td>8</td>
<td>Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)</td>
<td>p.8</td>
</tr>
</tbody>
</table>

**Methods: Participants, interventions, and outcomes**
Study setting 9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained pp.9-10

Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) p.9

Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered pp.10-16

11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) N/A

11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) p.16

11d Relevant concomitant care and interventions that are permitted or prohibited during the trial N/A

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 pp.16-23

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) pp.9-10

Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations p.23

Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size pp.9-10

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation 16a Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions pp.23-24
<table>
<thead>
<tr>
<th>Topic</th>
<th>Subtopic</th>
<th>Description</th>
<th>Page(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment</td>
<td>Mechanism</td>
<td>Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned</td>
<td>pp.23-24</td>
</tr>
<tr>
<td>Implementation</td>
<td></td>
<td>Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions</td>
<td>pp.23-24</td>
</tr>
<tr>
<td>Blinding (masking)</td>
<td></td>
<td>Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how</td>
<td>pp.23-24</td>
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<td>If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant’s allocated intervention during the trial</td>
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</table>

**Methods: Data collection, management, and analysis**

<table>
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<th>Topic</th>
<th>Subtopic</th>
<th>Description</th>
<th>Page(s)</th>
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<tbody>
<tr>
<td>Data collection methods</td>
<td></td>
<td>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</td>
<td>pp.9-10</td>
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<tr>
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<td>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</td>
<td>pp.16-17</td>
</tr>
<tr>
<td>Data management</td>
<td></td>
<td>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</td>
<td>pp.26-27</td>
</tr>
<tr>
<td>Statistical methods</td>
<td></td>
<td>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</td>
<td>pp.24-25</td>
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<td>Methods for any additional analyses (eg, subgroup and adjusted analyses)</td>
<td>pp.25-26</td>
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<td>Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)</td>
<td>pp.24-26</td>
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**Methods: Monitoring**

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<th>Topic</th>
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<tbody>
<tr>
<td>Data monitoring</td>
<td></td>
<td>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</td>
<td>pp.26-27</td>
</tr>
</tbody>
</table>
21b Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial

Harms 22 Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct

Auditing 23 Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval 24 Plans for seeking research ethics committee/institutional review board (REC/IRB) approval

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)

Consent or assent 26a Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)

26b Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable

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

Declaration of interests 28 Financial and other competing interests for principal investigators for the overall trial and each study site

Access to data 29 Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators

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

Dissemination policy 31a Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions

31b Authorship eligibility guidelines and any intended use of professional writers

31c Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
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*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license."
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