BMJ Open

Effects of two types of smartphone-based stress management programs on depression and anxiety among hospital nurses in Vietnam: a protocol for three-arm randomized controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-025138
Article Type:	Protocol
Date Submitted by the Author:	01-Jul-2018
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Keywords:	MENTAL HEALTH, OCCUPATIONAL & INDUSTRIAL MEDICINE, PUBLIC HEALTH

Title: Effects of two types of smartphone-based stress management programs on depression and anxiety among hospital nurses in Vietnam: a protocol for three-arm randomized controlled trial

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Word count: 4,565

ABSTRACT

Introduction: Due to an increasing demand to health care in low- and middle-income countries in Asia, it is important to develop a strategy to manage work-related stress in health care settings, particularly among nurses in these countries. The purposes of this three-arm randomized controlled trial (RCT) is to examine the effects of newly developed smartphone-based Internet cognitive behavioral therapy (iCBT) programs on preventing depressive and anxiety symptoms as primary outcomes at 3- and 6-month follow-ups among hospital nurses in Vietnam.

Methods and analysis: The target study population will be healthy registered nurses working in a large general hospital (which employs approximately about 2,000 nurses) in Vietnam. They will be invited to participate in this study. Participants who fulfil the eligibility criteria will be randomly allocated to the intervention group A (n = 360), the intervention group B (n = 360), or a control group (n = 360). Two types of smartphone-based six-module stress management programs (A and B) will be developed. Participants in the intervention groups will be required to complete the program A or B within 10 weeks after the baseline survey. The primary outcomes are depressive and anxiety symptoms, measured by using the Depression Anxiety and Stress Scales (DASS) at 3- and 6-month follow-up.

Ethics and dissemination: The study procedures have been approved by the Research Ethics Review Board of Graduate School of Medicine/Faculty of Medicine, the University of Tokyo (no 11991) and the Ethical review board for Biomedical research of Hanoi University of Public Health (no 346/2018/YTCC-HD3). If a significant effect of the intervention programs will be found in the RCT, the programs will be provided to all nurses in the hospital including the control group.

Trial registration: The study protocol is registered at the UMIN Clinical Trials Registry (UMINCTR; ID=UMIN000033139). Registration date is 1st July 2018.

URL: https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000037796

Key words: iCBT, depression, anxiety, prevention, nurse

STRENGTH AND LIMITATION OF THIS STUDY

- This randomized controlled trial will first test the effectiveness of fully automated smartphone-based stress management programs on improving subthreshold depressive symptoms and other work-related outcomes among healthy nurses in Vietnam.
- This study will contribute to scaling up the primary prevention of depression and anxiety among nurses in low- and middle-income countries in Asia.
- A major weakness of this study is that all outcomes will be measured by self-report, which may be affected by the perception or situational factors at work of the participants.

INTRODUCTION

Nurses can suffer from various work-related stress from various sources such as workload, leadership/management style, professional conflict, emotional cost of caring, lack of reward, and shift working [1]. In addition, the lack of stress management skills and/or organizational factors at work may contribute to difficulty in coping with stress [2 3]. This often leads to severe psychological distress (e.g., depression and anxiety) [4], burnout [5], other health problems [6 7], and deterioration in quality of life and service provision [8]. A shortage of nurses, population aging, and various demands from service users (i.e., patients and families) have increased pressure and stress on nurses and other healthcare professionals [9-11]. Previous reports showed that deficits in the number of health service providers are very large in low- and middle-income countries in Southeast Asia [12 13], where, despite the rapidly increasing quantitative and qualitative demands to medical care in the rapidly aging society, there is a severe shortage of nurses, and many nurses lack the clinical skills to adequately respond to health-care demands [13]. Work-related stress has been increasing among nurses in Vietnam [14] and other Southeast Asian countries [15-18]. Moreover, work stress could also affect the quality of health care service in these countries [19]. It is important to manage work-related stress in health care settings, particularly among nurses, focusing on Southeast Asian countries such as Vietnam.

For the working population, stress management based on cognitive behavioral therapy (CBT) has been shown to reduce depression/anxiety symptoms among workers [20]. A recent meta-analysis reported that programs combining CBT and coping flexibility showed the highest effect size (d = 1.45 at 4 months' follow-up) in the workplace [21]. Other meta-analyses showed a similar effect of programs using CBT and relaxation on improving work-related stress among workers [22 23]. In the healthcare worker setting, CBT interventions have been shown to be effective. For instance, CBT, either with or without relaxation, showed a significant improving effect on stress symptoms among healthcare workers (standardized mean difference [SMD] = -0.38) and especially nurses (SMD = -0.34) at 6-month follow-up [2]. Computerized CBT delivered via the Internet (iCBT) and other web-based interventions including cognitive behavioral techniques holds promise as a cost-effective method to make CBT accessible to individual workers [24]. These iCBT programs provide basic information and skills on the basis of CBT principles as face-to-face CBT programs do, sometimes with a structured format that comprises educational lessons, homework assignments, and supplementary resources. A recent literature review stated that the benefits of web-based intervention in the workplace include fewer constraints with regard to time and location, the potential to access a larger target group, and protection of participant anonymity—thereby reducing possible stigma with regard to seeking help for stress [24]. Internet CBT interventions showed a small-to-moderate effect on increasing psychological well-being including reduction of psychological distress (g = 0.37) and

effective work such as engagement and productivity (g = 0.25) at post intervention period, compared with the control condition [25]. Another meta-analysis that examined the intervention effect at post intervention period and follow-up period (around 5 months) showed that eHealth interventions had a significant effect on improving mental health condition at both post intervention (g = 0.24) and follow-up (g = 0.23) among employees [26]. In addition, one randomized controlled trial (RCT) reported that web-based stress management programs including cognitive behavioral techniques reduced perceived work-related stress among nurses in the U.S. [27]. Internet CBT interventions might be useful to reduce work-related stress among nurses in low- and middle-income countries. However, evidence obtained for other sector workers in high income countries was not extended to nurses in low- and middle-income countries in Asia. It is necessary to develop low-cost iCBT interventions for improving work stress and promoting mental health of nurses in low- and middle-income countries and test its effectiveness.

An important challenge in applying web-based interventions is low adherence. Previous systematic reviews reported that adherence to complete web-based psychological intervention program in the workplace was approximately 40%, while the adherence rates varied considerably [25]. To enhance adherence, tailoring the web-based intervention program might be beneficial. A useful strategy to promote adherence to eHealth interventions is incorporating tailoring [28]. For instance, a previous RCT showed that the attrition and adherence rate of an individually-tailored iCBT program appeared favorable compared to studies that applied non-tailored iCBT programs [29]. Even programs that are not fully tailored, but that allow participants to choose a module from multiple options based on their preference may be useful, while a typical iCBT program provides multiple modules in a fixed sequential order. A comparison of the effects of these types of iCBT programs on outcomes and adherence has not been well studied before. Comparative effectiveness of these types of iCBT programs may depend on the culture of the target country and the target population. The other approach that becomes popular is to use smartphones as media for iCBT. Many smartphone Apps for stress management use evidence-based strategies [30]. However, only a small number of such programs have been evaluated with a RCT, with very limited evidence in the working population [31].

Objectives

Two types of smartphone-based iCBT programs for primary prevention of depression and anxiety with a similar number of modules and content will be developed for hospital nurses in Vietnam. The objectives of this study, using a three-arm RCT design, are to examine the effects of these intervention programs on improving depressive and anxiety symptoms as primary outcomes, work engagement, work performance, stress symptoms, psychosocial work environment, and health-related QOL as secondary outcomes at 3- and 6-month follow-ups, and to examine whether

a free-choice sequence multi-module stress management program (i.e., partially tailored) results in better adherence than similar modules completed in a fixed sequential order. We chose Vietnam as a target country because of the degree of resources and challenges: improved mobile access to the Internet; and on the other hand, increasing demands to medical service due to a rapidly aging population and an increasing number of cases of burnout among nurses.

METHODS AND ANALYSIS

Trial design

The study will be a three-arm including two different intervention groups, parallel-group, treatment as usual (TAU)-controlled, non-blinded randomized study. The allocation ratio of the intervention groups to the control group is 1:1:1. Participants will be recruited from a large general hospital in Hanoi, Vietnam, and randomly allocated to one of three groups after they have completed a baseline questionnaire survey. Follow-up surveys will be conducted 3 and 6 months after the baseline. The study protocol was registered at the UMIN Clinical Trials Registry (UMIN-CTR; ID=UMIN000033139). The study procedures have been approved by the Research Ethics Review Board of Graduate School of Medicine/Faculty of Medicine, the University of Tokyo (no 11991) and the Ethical review board for Biomedical research of Hanoi University of Public Health (no 346/2018/YTCC-HD3). This protocol manuscript was reported according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guideline checklist [32].

Participants

The target population of this RCT will be healthy nurses (i.e., primary prevention). Registered nurses working in a large general hospital (which employs approximately about 2,000 nurses) in Vietnam will be invited to participate and selected according to the following criteria:

Inclusion criteria

1. Currently employed full-time as registered nurse.
2. Can access the internet via a mobile device such as a smartphone.

Exclusion criteria

1. Plan to change or quit the job in the next 6 months.
2. Assistant nurses and helpers.
3. Non-regular or part-time employed.
4. Sick leave for 15 or more days for a physical or mental condition in the past 3 months.
5. Current treatment for a mental health problem from a mental health professional.

Procedure

Figure 1 shows the participant flow chart of this trial. Our preliminary research reported that about 60% of the nurses in the hospital have their own smartphone. In addition, a previous RCT reported that about 10% of participants had to be excluded according to two exclusion criteria, which were having sick leave for 15 or more days for own health problems in the past 3 months and receiving medical treatment for a mental health problem during the past month [33].

For this study, the clinical research coordinator (CRC) will send out invitations to 2,000 nurses, of whom 1,200 are expected to have their own smartphone and give informed consent, and 1,080 are

expected to be eligible. These 1,080 will be randomized to either one intervention group (n = 360), the other intervention group (n = 360), or the control group (n = 360). Participants in the two intervention groups will be required to complete the intervention programs within 10 weeks after the baseline survey.

An invitation letter to all nurses will include a full explanation of the study and information for the eligibility criteria. After reading the explanation of the study, they will be asked to give their written consent to participate in the study and to answer the questions according to the eligibility criteria. Then, they will be asked to return it to CRC within a week.

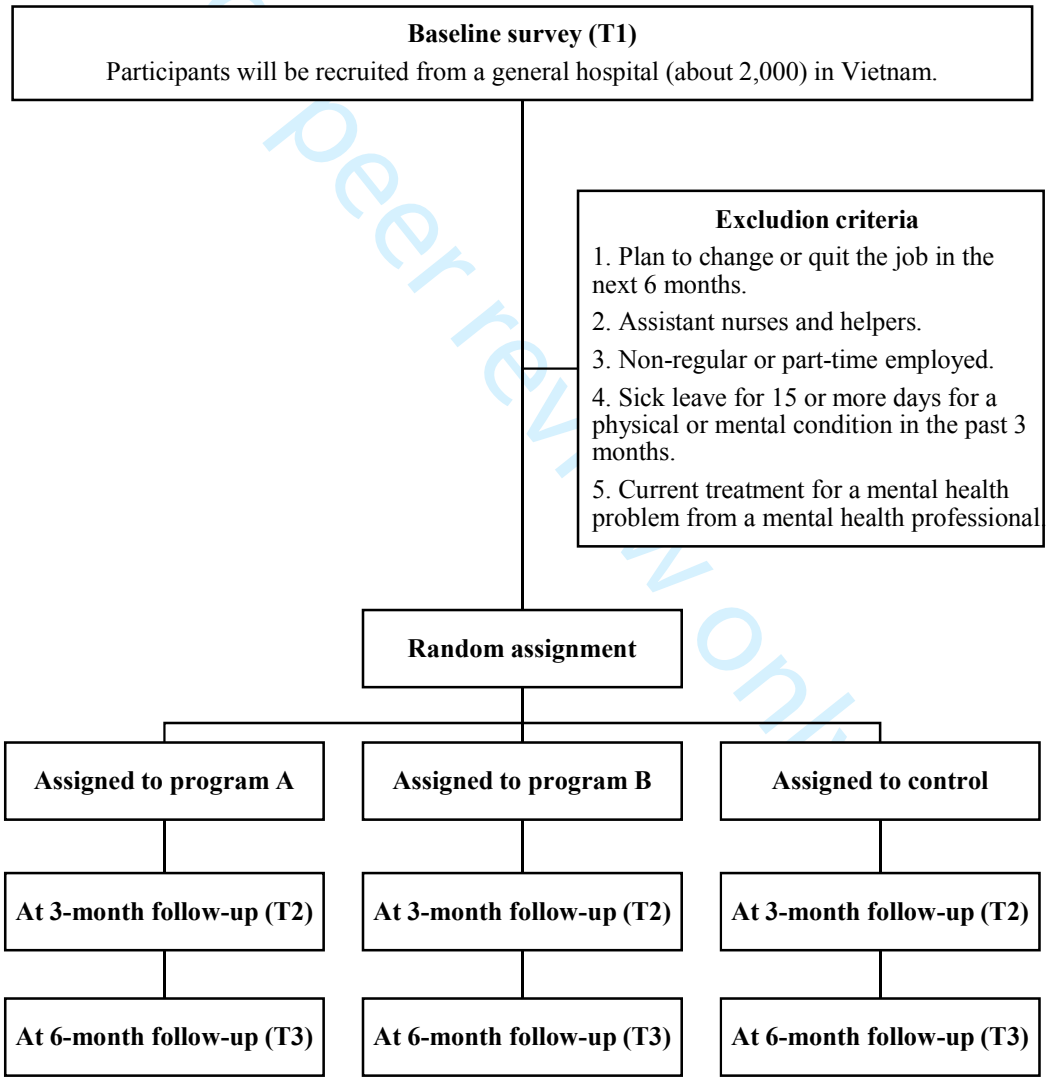

Figure 1 participant flowchart.

Intervention programs

In this study, two smartphone-based six-module stress management programs will be used. One (program A) is a free-choice, multi-module stress management program in which respondents are allowed to select one module per week based on their preference. The other (program B) is a fixed-order, multi-module stress management program in which respondents are required to study modules in a fixed order one per week. For both programs, it will take about 15 minutes to complete each module.

Program A includes 6 modules that provide six evidence-based stress management skills. This program is developed based on a previous web-based stress management program aimed to improve psychological distress of office workers [34], but further modified based on an intensive hearing from and discussion with nurses in Vietnam, e.g., replacing one module (on physical activity for stress management) with another (self-compassion). Participants may choose one module per week according to their preference. The program includes behavioral activation (Module 1), cognitive restructuring (Module 2), problem-solving (Module 3), assertiveness (Module 4), self-compassion (Module 5), and job crafting (Module 6).

Program B also includes 6 modules that provides CBT-based stress management skills, developed based on a previous iCBT program that successfully improved depression of office workers [33]. The 6 modules are pre-ordered, with one module accessible per week, from the Module 1 to Module 6. The program has two already established CBT packages as its basis. One is the cognitive therapy program developed by Beck [35]. The other is the 'Coping with Depression' program developed by Lewinsohn [36]. The program includes transactional model of stress and coping (Module 1), self-case formulation based on cognitive behavioral model (Module 2), behavioral activation skills (Module 3), cognitive restructuring skills (Modules 4 and 5), problem-solving skills (Module 6) and relaxation skills (Module 5). The program is modified so that the content fits the working situation and work culture of nurses in Vietnam. For instance, case stories are modified reflecting major stressors (i.e., job overload) of these nurses.

Table 1 shows the stress management techniques included in Program A and Program B. Behavioral activation, cognitive restructuring, and problem solving techniques are included in both Program A and Program B. Assertiveness, self-compassion, and job crafting techniques are only included in Program A. The transactional model of stress and coping, self-case formulation based on cognitive behavioral model, and relaxation techniques are only included in Program B. Details of each of the components are as follows.

Table 1 Contents of the free-choice (Program A) and fixed-order (Program B) stress management programs

Techniques for stress management	Program A (Module No.)	Program B (Module No.)
Transactional model of stress and coping	Not included	Module 1
Self-case formulation based on cognitive behavioral model	Not included	Module 2
Behavioral activation	Module 1	Module 3
Cognitive restructuring	Module 2	Modules 4 and 5
Relaxation	Not included	Module 5
Problem solving	Module 3	Module 6
Assertiveness	Module 4	Not included
Self-compassion	Module 5	Not included
Job crafting	Module 6	Not included

Transactional model of stress and coping (Module 1 in Program B)

Transactional stress model is defined as perceptions that demands exceed coping strategies [37]. According to this model, an individual's reaction to stressors is determined, in part, by their own appraisal of the stressor. In keeping with this model, stress will be defined as the psychological response to a situation or stimuli whereby an individual appraises the situation or stressor as exceeding their capabilities or resources. In this module, participants learn about the relationship between stressors and stress reactions.

Self-case formulation based on cognitive behavioral model (Module 2 in Program B)

In this module, 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) [38] and a self-case formulation based on this model. Case formulation is a method used to understand the problem of a client [39]. Case formulation is necessary for clients to choose an appropriate approach to change the vicious circles of these five areas.

Behavioral activation (Module 1 in Program A and Module 3 in Program B)

Behavioral activation is one of the most readily applied techniques in the CBT and it is a process to increase pleasurable and rewarding activities using behavioral strategies such as activity scheduling [40]. This module/program provides a behavioral activation technique on enhancing participants' liveliness. Participants learn about a theory of behavioral activation and how to plan an activity schedule for increasing pleasant activities.

Cognitive restructuring (Module 2 in Program A and Modules 4 and 5 in Program B)

The cognitive restructuring technique is one of the standard cognitive approaches of CBT utilized to change an automatic negative thought into an actual, realistic and flexible thought [35]. This module gives a lecture on a cognitive ABC model (Activating/Actual event, Belief, and Consequence) [35 41 42] and on identifying the automatic thoughts that cause a negative mood. Participants learn cognitive restructuring skills to change an automatic negative thought into an actual thought.

Relaxation (Module 5 in Program B)

Relaxation techniques are often added to the CBT intervention for workers, and they have shown significant effects on improving depression [22]. In the latter half of the Module 5, Participants learn a relaxation technique using a breathing method.

Problem solving (Module 3 in Program A and Module 6 in Program B)

Problem solving technique is a CB intervention that focuses on training adaptive problem-solving attitudes and skills [43]. 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 [44]. In this module, participants learn problem-solving skills to sort out the problem and make a list of solutions.

Assertiveness (Module 4 in Program A)

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 [45 46]. In order to communicate assertively, the DESC (Describe, Express, Specify, and Choose or Consequence) script is used [47]. In this module, participants learn assertiveness skills to appropriately communicate their concerns to supervisors, coworkers or subordinates, based on the DESC script.

Self-compassion (Module 5 in Program A)

Self-compassion describes a positive and caring attitude of a person toward her- or himself in the face of failures and individual shortcomings [48]. As a result of this caring attitude, individuals high in self-compassion are assumed to experience higher individual well-being. There are three interrelated elements that determine the self-compassionate reactions to negative events and experiences: self-kindness, sense of common humanity, and mindfulness [48 49]. In this module, participants learn a concept of self-compassion and how to express compassion toward themselves.

Job crafting (Module 6 in Program A)

Job crafting is defined as "the physical and cognitive change individuals make in the task or relational boundaries of their work" [50] and consists of the following three components: changing the job's boundaries (task crafting), changing the relational boundaries (relational crafting), and changing the cognitive task boundaries (cognitive crafting) [50]. In this module, participants learn about the concept of job crafting and how to craft their own job.

Intervention groups

Participants in the intervention groups will be required to complete Program A or B within 10 weeks after the baseline survey. The participants will be reminded by email to complete the program if they have not already done. Reminders will be sent from the research office. Before the start of the intervention program, participants in the intervention groups download the Apps and view an introduction module that provides general explanations of the programs. The introduction module is common for the two intervention programs with brief explanations about the psychological stress model, self-assessment of their own mood using Kessler's Psychological Distress Scale (K6) [51], and an introduction of the two intervention programs. Participants can contact CRC if they have a trouble downloading or using the Apps. After 3 months from baseline survey, the intervention programs will be closed by CRC.

Control group

Participants in the control group do not receive any intervention programs during the intervention and follow-up period (6 months). Participants both in the intervention group and the control group will be able to use an internal employee assistance program service. Participants in the control group will be provided a chance to use the intervention programs after their 6-month follow-up.

Outcomes

Table 2 shows an overview of the outcome measures. All outcome measures will be assessed at the baseline, the 3-month (the end of the intervention period) and 6-month follow-ups. Non-respondents will receive reminder email from the research center for each of the follow-up surveys.

Table 2 Overview of outcome measurements

Measurement	Aim	Baseline (T1)	3-M F/U (T2)	6-M F/U (T3)
Primary outcomes				
DASS	Severity of depression	x	x	x
DASS	Severity of anxiety	x	x	x
Secondary outcomes				
UWES	Work engagement	x	x	x
HPQ	Sickness absence (absenteeism) and reduced job performance (presenteeism)	x	x	x
DASS	Severity of stress symptoms	x	x	x
JCQ	Psychosocial work environment	x	x	x
EQ-5D	Health-related quality of life	x	x	x

Note: DASS = Depression Anxiety and Stress Scales, UWES = Utrecht Work Engagement Scale, HPQ = Health and Work Performance Questionnaire, JCQ = Job Content Questionnaire.

Primary outcomes

Depression and anxiety

The Depression Anxiety and Stress Scales (DASS) is a widely used screening tool to assess symptoms of depression, anxiety, and stress in community settings [52]. The DASS comprises three subscales (i.e., depression, anxiety, and stress) The depression subscale measures dysphoria, hopelessness, devaluation of life, among others. The anxiety subscale measures autonomic arousal, skeletal musculature symptoms, situational anxiety, among others. The stress scale measures difficulty relaxation, nervous arousal, easily upset/agitated, among others. The short 21-item version (seven items in each of three subscales) has been developed [53]. Items are scored on a 4-point scale ranging from 0 (*did not apply to me at all*) to 3 (*applied to me very much, or most of the time*). In order to yield equivalent scores to the full version of DASS (42-item), the total score of each scale is multiplied by 2 and ranges from 0 to 42 [53]. The Vietnamese version has been developed and tested, and its reliability and validity have been confirmed [54]. The depression scale and the anxiety scale will be used to assess the depression and anxiety symptoms as primary outcomes in this study.

Secondary outcomes

Work engagement

Work engagement will be assessed using the short form of the Utrecht Work Engagement Scale (UWES) [55]. 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*). A total score is calculated from all nine items. The Vietnamese version will be developed and validated before the study.

Sick leave days and self-reported work performance

The WHO 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 (presentism) [56]. 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. The Vietnamese version will be developed and validated before the study.

Stress symptoms

Stress symptoms will be assessed with the stress scales of DASS [52-54]. The details of DASS refer to above.

Psychosocial work environment

The Job Content Questionnaire (JCQ) will be used to assess psychological job demands, control, and support by coworkers and supervisors [57]. The JCQ consists of a five-item psychological demand scale, a nine-item decision latitude scale, a four-item supervisor support scale, and a 4-item coworker support scale. All the items were scored on a 4-point Likert scale, ranging from 1 (*strongly disagree*) to 4 (*strongly agree*). The Vietnamese version will be developed and validated before the study.

Health-related quality of life

Health-related quality of life will be assessed with the EQ-5D-5L [58]. The EQ-5D-5L 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. It is a widely applied quality of life instrument, and its reliability and validity are well established [58]. The Vietnamese version has been developed and tested for its reliability and validity [59].

Improvement of knowledge and self-efficacy.

Respondents will be asked to rate their improvement of knowledge and self-efficacy regarding the two intervention programs. Knowledge improvement will be assessed by asking participants, ''How much knowledge do you have about…,'' and self-efficacy improvement will be assessed by asking

respondents ‘‘How confident are you that you can do….’’ Both items were scored on 5-point scale ranging from 0 (*none*) to 4 (*enough*). This scale is originally developed and has not been validated yet.

Process evaluation

Program satisfaction and usage

Participants in the intervention groups will be asked to rate their satisfaction with the intervention program at the end of the intervention period. The usage of the intervention programs will be collected from the records of the Apps system.

Contamination of information

To evaluate contamination of information among participants, participants will be asked at follow-up survey; “During the past 3 months, have you gotten to know information on stress management from your colleagues who used any smartphone-based stress management programs?”, with a response option, yes/no. This scale will be originally developed.

Demographic characteristics

Demographic data, such as age, gender, marital status, occupation, education, chronic disease, and overtime hours during the past month also will be collected.

Sample size calculation

A required sample size was calculated for one of the outcome variables, i.e., depressive symptoms assessed by DASS. Previous meta-analyses of web-based psychological intervention on improving workers mental health in the workplace yielded effect sizes of 0.23 to 0.37 [25 26]. To detect a small effect size (i.e., 0.25) or more at an alpha error rate of 0.05 and a beta error rate of 0.10, the estimated sample size was 338 participants in each group. The statistical power was calculated using the G*Power 3 program [60 61].

Randomization

Participants who fulfil the inclusion criteria will be randomly allocated to each three-arm (two intervention groups or control groups). Stratified permuted-block randomization will be conducted as well. Participants will be stratified into two strata according to the depression subscale score of DASS (10 or greater or less than 10) in the baseline survey [54]. 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 mixed model for repeated measures conditional growth model analysis will be conducted using a group (intervention and control) × time (baseline, 3-month, and 6-month follow-ups) interaction as an indicator of intervention effect. An intention-to-treat principle will be applied as well. 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 [62]. All statistical analyses will be conducted using the SPSS Statistics V.22.0 (IBM Corp., USA).

Subgroup analysis

The effectiveness of the program may differ according to the initial severity of depression. We will therefore use the stratification factor (i.e., participants who scored 10 or more in DASS depression subscale at the baseline survey) and analyze the results according to a priori-defined subgroups (selective intervention effect).

Data monitoring

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 3 months after the first participant 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

Written informed consent will be obtained from all participants included in this study after full disclosure and explanation of the purpose and procedures of the study. Candidates will be informed that their participation is totally voluntary, that even after voluntarily participating they can withdraw from the study at any time without stating the reason, and that neither participation nor withdrawal will cause any advantage or disadvantage to them.

We expect no adverse health effect from this intervention, except possibly for deterioration in depressive/anxiety symptoms. We will provide the emergency phone call number and e-mail address at the central office. The CRC (TTran), who is a registered nurse, will then deal with the emergency call or e-mail first by herself, and then consult with the clinical supervisors (NK) to provide appropriate care.

Data confidentiality

Participants will complete a baseline/follow-up questionnaire with a sealed envelope and submit it to the research center. After the survey, the collected data will be entered into a password-locked stand-alone PC by the CRC. 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. If the significant effect of the intervention programs will be found in this RCT, these programs could be available for all nurses in Vietnam in the future.

Strengths and limitations

The greatest strength of this study is its focus on the effect of the fully automated web-based smartphone application intervention programs on improving subthreshold depressive symptoms among Vietnamese nurses using a RCT design. This study is also intended to add evidence for the effect of e-stress management programs on positive health outcomes (e.g., work engagement and work performance) among healthy nurses. To our knowledge, the present study will first demonstrate that the fully automated smartphone-based stress management programs would be effective on improving subthreshold depressive symptoms and other positive health outcomes among healthy nurses in Vietnam, a middle income country in Southeast Asia, using a well designed study protocol. This study will contribute to future development of strategies in the primary prevention of depression and promotion of positive mental health among nurses in the low- and middle-income

countries.

Another strength of this study is to contribute the creation of a new option for mental health service. This RCT will demonstrate the effectiveness of several types of e-stress management programs that were developed in this project in a low- and middle-income country context. These programs will provide hospital nurses in Vietnam with an opportunity to have access to a low-cost mental health service.

One of the major weaknesses of this study is that all outcomes will be measured by self-report, which may be affected by the perception of the participants or by situational factors at work. The other limitation is that the participants will be recruited from one general hospital in Vietnam. Therefore, generalization of the findings to populations that do not share the characteristics of the participants may be limited.

ACKNOWLEDGEMENT

Authors' contribution

KI, TTran, HN, KK, AS, TB, AN, QN, KN, GN, XT, TTruong, MZ, HM, YS, NS, AT, and NK conceived and designed the experiments. KI, TTran, HN, KK, AS, YS, NS, and NK contributed reagents/materials/analysis tools. KI, TTran, HN, HM, and NK wrote the paper. All authors read and approved the final paper.

Funding statement

This research was supported by AMED under Grant Number JP17jk0110014. The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interest

NK reports grants from Infocom Corp, Fujitsu Ltd, Fujitsu Software Technologies, and TAK Ltd, personal fees from Occupational Health Foundation, Japan Dental Association, Sekisui Chemicals, Junpukai Health Care Center, Osaka Chamber of Commerce and Industry, outside the submitted work. The other authors declare that they have no competing interests.

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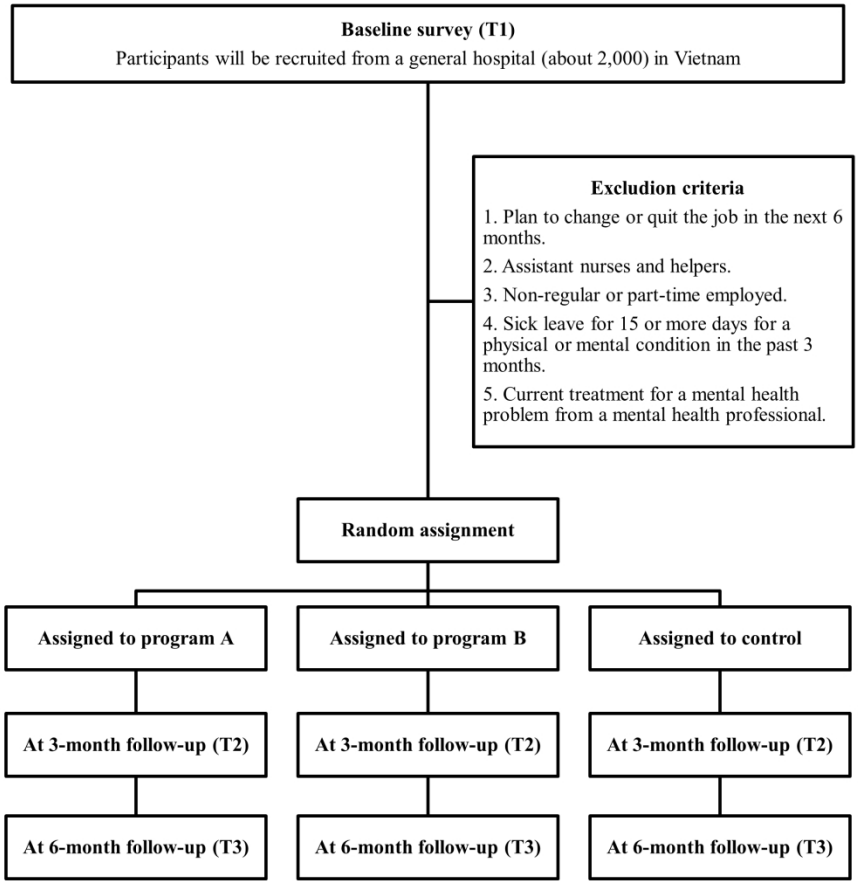

Figure 1 Participant flowchart.

190x254mm (300 x 300 DPI)

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-2, 18
	5b	Name and contact information for the trial sponsor	2
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	16

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	N/A
Objectives	7	Specific objectives or hypotheses	5-6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
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	7-8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12
	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	13-15
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)	7-8

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	_____15_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____7-8_____
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	_____15-16___
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____15-16___
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____15-16___
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____N/A_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____N/A_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_____12_____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_____12_____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	17
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	16
	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	N/A
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	17
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17
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)	N/A

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	17
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
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	17
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	N/A
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	17
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

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

BMJ Open

Effects of two types of smartphone-based stress management programs on depressive and anxiety symptoms among hospital nurses in Vietnam: a protocol for three-arm randomized controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-025138.R1
Article Type:	Protocol
Date Submitted by the Author:	07-Jan-2019
Complete List of Authors:	Imamura, Kotaro; The University of Tokyo, Department of Mental Health Tran, Thuy; Hanoi University of Public Health, Department of Occupational Health and Safety Nguyen, Huong; Hanoi University of Public Health, Faculty of Social Sciences - Behavior and Health Education Kuribayashi, Kazuto; The University of Tokyo, Department of Psychiatric Nursing Sakuraya, Asuka; The University of Tokyo, Department of Mental Health Nguyen, Anh; Bach Mai Hospital, General Director Bui, Thu; Bach Mai Hospital, Nursing Office Nguyen, Quynh; Hanoi University of Public Health, Department of Occupational Health and Safety Nguyen, Kien; Hanoi University of Public Health, Faculty of Social Sciences - Behavior and Health Education Nguyen, Giang; Bach Mai Hospital, Nursing Office Tran, Xuyen; Bach Mai Hospital, Nursing Office Truong, Tien; Hanoi University of Public Health, Faculty of Social Sciences - Behavior and Health Education Zhang, Melvyn; National University of Singapore, Psychological Medicine Minas, Harry; The University of Melbourne, Melbourne School of Population and Global Health Sekiya, Yuki; The University of Tokyo, Department of Mental Health Sasaki, Natsu; The University of Tokyo, Department of Mental Health Tsutsumi, Akizumi; Kitasato University, Department of Public Health Kawakami, Norito; The University of Tokyo, Department of Mental Health
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Occupational and environmental medicine, Public health
Keywords:	MENTAL HEALTH, OCCUPATIONAL & INDUSTRIAL MEDICINE, PUBLIC HEALTH

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Word count: 4,565

ABSTRACT

Introduction: Due to an increasing demand for health care in low- and middle-income countries in Asia, it is important to develop a strategy to manage work-related stress in health care settings, particularly among nurses in these countries. The purpose of this three-arm randomized controlled trial (RCT) is to examine the effects of a newly developed smartphone-based multi-module stress management programs on reducing severity of depressive and anxiety symptoms as primary outcomes at 3- and 7-month follow-up among hospital nurses in Vietnam.

Methods and analysis: The target study population will be registered nurses working in a large general hospital (which employs approximately about 2,000 nurses) in Vietnam. They will be invited to participate in this study. Participants who fulfil the eligibility criteria will be randomly allocated to the a free-choice, multi-module stress management (intervention group A, n = 360), the Internet cognitive behavioral therapy (iCBT), i.e., fixed-order, stress management (intervention group B, n = 360), or a treatment as usual control group (n = 360). Two types (free-choice and fixed sequential order) of smartphone-based six-module stress management programs will be developed. Participants in the intervention groups will be required to complete one of the programs within 10 weeks after the baseline survey. The primary outcomes are depressive and anxiety symptoms, measured by using the Depression Anxiety and Stress Scales (DASS) at 3- and 7-month follow-up.

Ethics and dissemination: The study procedures have been approved by the Research Ethics Review Board of Graduate School of Medicine/Faculty of Medicine, the University of Tokyo (no 11991) and the Ethical Review Board for Biomedical research of Hanoi University of Public Health (no 346/2018/YTCC-HD3). If a significant effect of the intervention programs will be found in the RCT, the programs will be made available to all nurses in the hospital including the control group. If the positive effects are found in this RCT, the e-stress management programs will be disseminated to all nurses in Vietnam.

Trial registration: The study protocol is registered at the UMIN Clinical Trials Registry (UMINCTR; ID=UMIN000033139). Registration date is 1st July 2018.

URL: https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000037796

Key words: iCBT, depression, anxiety, prevention, nurse

STRENGTH AND LIMITATION OF THIS STUDY

- This will be the first randomized controlled trial to test the effectiveness of fully automated smartphone-based stress management programs on improving depressive and anxiety symptoms and work-related outcomes among nurses in Vietnam.
- This study also intends to add evidence for the effect of e-stress management programs on positive health and work-related outcomes (e.g., work engagement and work performance) among nurses.

- A limitation of this study is that all outcomes will be measured by self-report, which may be affected by the perceptions or situational factors at work of the participants.

INTRODUCTION

Nurses can suffer from various work-related stresses related to factors such as workload, leadership/management style, professional conflict, emotional cost of caring, lack of reward, and shift work [1]. In addition, lack of stress management skills and/or organizational factors at work may contribute to difficulty in coping with stress [2 3]. This often leads to severe psychological distress (e.g., depression and anxiety) [4], burnout [5], other health problems [6 7], and deterioration in quality of life and service provision [8]. A shortage of nurses, population aging, and demands from service users (i.e., patients and families) have increased pressure and stress on nurses and other healthcare professionals [9-11]. Previous reports showed that deficits in the number of health service providers are very large in low- and middle-income countries in Southeast Asia [12 13], where, despite the rapidly increasing quantitative and qualitative demands to medical care in the rapidly aging society, there is a severe shortage of nurses, and many nurses lack the clinical skills to adequately respond to health-care demands [13]. Work-related stress has been increasing among nurses in Vietnam [14] and other Southeast Asian countries [15-18]. Moreover, work stress could also affect the quality of health care service in these countries [19]. It is important to manage work-related stress in health care settings, particularly among nurses, focusing on Southeast Asian countries such as Vietnam.

For the working population, stress management based on cognitive behavioral therapy (CBT) has been shown to reduce depression/anxiety symptoms among workers [20]. A recent meta-analysis reported that programs combining CBT and coping flexibility showed the highest effect size (d = 1.45 at 4 months' follow-up) in the workplace [21]. Other meta-analyses showed a similar effect of programs using CBT and relaxation on improving work-related stress among workers [22 23]. In the healthcare worker setting, CBT interventions have been shown to be effective. For instance, CBT, either with or without relaxation, showed a significant improving effect on stress symptoms among healthcare workers (standardized mean difference [SMD] = -0.38) and especially nurses (SMD = -0.34) at 6-month follow-up [2]. Computerized CBT delivered via the Internet (iCBT) and other web-based interventions including cognitive behavioral techniques holds promise as a cost-effective method to make CBT accessible to individual workers [24]. These iCBT programs provide basic information and skills on the basis of CBT principles as face-to-face CBT programs do, sometimes with a structured format that comprises educational lessons, homework assignments, and supplementary resources. A recent literature review stated that the benefits of web-based intervention in the workplace include fewer constraints with regard to time and location, the potential to access a larger target group, and protection of participant privacy—thereby reducing possible stigma with regard to seeking help for stress [24]. Internet CBT interventions showed a small-to-moderate effect on increasing psychological well-being including reduction of psychological distress (g = 0.37) and effective work outcomes such as engagement and productivity (g = 0.25) at post intervention period, compared with the control condition [25]. Another meta-analysis that examined the intervention effect at post intervention period

and follow-up period (around 5 months) showed that eHealth interventions had a significant effect on improving mental health condition at both post intervention (g = 0.24) and follow-up (g = 0.23) among employees [26]. In addition, one randomized controlled trial (RCT) reported that web-based stress management programs including cognitive behavioral techniques reduced perceived work-related stress among nurses in the U.S. [27]. Internet CBT interventions might be effective in reducing work-related stress among nurses in low- and middle-income countries. However, evidence obtained for other sector workers in high income countries was not extended to nurses in low- and middle-income countries in Asia. It is necessary to develop low-cost iCBT interventions for improving work stress and promoting mental health of nurses in low- and middle-income countries and test its effectiveness. An important challenge in applying web-based interventions is low adherence. Previous systematic reviews reported that completion of web-based psychological intervention programs in the workplace was approximately 40%, while the adherence rates varied considerably [25]. A useful strategy to promote adherence to eHealth interventions is incorporating tailoring [28]. For instance, a previous RCT showed that the attrition and adherence rate of an individually-tailored iCBT program appeared favorable compared to studies that applied non-tailored iCBT programs [29]. Even programs that are not fully tailored, but that allow participants to choose a module from multiple options based on their preference may be useful, while a typical iCBT program provides multiple modules in a fixed sequential order. A comparison of the effects of these different types of iCBT programs on adherence and outcomes has not been well studied before. Comparative effectiveness of these types of iCBT programs may depend on the culture of the target country and the target population. The other approach that has become popular is to use smartphones as media for iCBT. Many smartphone apps for stress management use evidence-based strategies [30]. However, only a small number of such programs have been evaluated with a RCT, with very limited evidence in the working population [31].

Objectives

Two types of smartphone-based multi-module stress management intervention programs for reduction in symptoms of depression and anxiety with a similar number of modules and content will be developed for hospital nurses in Vietnam. The objectives of this study, using a three-arm RCT design, are:

- to examine the effects of these intervention programs on improving depressive and anxiety symptoms as primary outcomes, and on work engagement, work performance, stress symptoms, psychosocial work environment, and health-related quality of life (QOL) as secondary outcomes at 3- and 7-month follow-up; and
- to examine whether a free-choice sequence (i.e., partially tailored) program results in better adherence than completion of similar modules in a fixed sequential order.

We chose Vietnam as a target country because of the degree of resources and challenges, improved

mobile access to the Internet, the increasing demands on medical services due to a rapidly aging population, and an increasing number of cases of burnout among nurses.

The hypotheses of this study are;

H1: The newly developed smartphone-based multi-module stress management intervention programs will significantly improve the primary outcomes (i.e., depressive and anxiety symptoms) among participants in the intervention groups compared with participants in the control group.

H2: The newly developed smartphone-based multi-module stress management intervention programs will significantly improve the secondary outcomes (i.e. work engagement, work performance, stress symptoms, psychosocial work environment, and health-related QOL) among participants in the intervention groups compared with participants in the control group.

H3: Participants will show significantly better adherence (i.e., completion rate of the program) to the free-choice program than the fixed-sequence program.

METHODS AND ANALYSIS

Trial design

The study will be a three-arm (including two different intervention groups), parallel-group, treatment as usual (TAU)-controlled, non-blinded randomized study. The allocation ratio of the intervention groups to the control group is 1:1:1. Participants will be recruited from a large general hospital in Hanoi, Vietnam, and randomly allocated to one of three groups after they have completed a baseline questionnaire survey. Follow-up surveys will be conducted 3 and 7 months after the baseline. The study protocol was registered at the UMIN Clinical Trials Registry (UMIN-CTR; ID=UMIN000033139). The study procedures have been approved by the Research Ethics Review Board of Graduate School of Medicine/Faculty of Medicine, the University of Tokyo (no 11991) and the Ethical Review Board for Biomedical research of Hanoi University of Public Health (no 346/2018/YTCC-HD3). This protocol manuscript is written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guideline checklist [32].

Participants

The target population of this RCT will be registered nurses working in a large general hospital (which employs approximately 2,000 nurses) in Vietnam who will be invited to participate and selected according to the following criteria:

Inclusion criteria

1. Currently employed full-time as registered nurse.
2. Can access the internet via a mobile device such as a smartphone.

Exclusion criteria

1. Plan to change or quit the job in the next 7 months.
2. Assistant nurses and helpers.
3. Non-regular or part-time employed.
4. Sick leave for 15 or more days for a physical or mental condition in the past 3 months.
5. Current treatment for a mental health problem from a mental health professional.

Procedure

Figure 1 shows the participant flow chart of this trial. Our preliminary research reported that about 60% of the nurses in the hospital have their own smartphone. In addition, a previous RCT reported that about 10% of participants had to be excluded according to two exclusion criteria, which were having sick leave for 15 or more days for own health problems in the past 3 months and receiving medical treatment for a mental health problem during the past month [33].

For this study, the clinical research coordinator (CRC) will send invitations to 2,000 nurses, of whom 1,200 are expected to have their own smartphone and give informed consent, and 1,080 are expected

to be eligible. These 1,080 will be randomized to either one intervention group (n = 360), the other intervention group (n = 360), or the control group (n = 360). Participants in the two intervention groups will be required to complete the intervention programs within 10 weeks after the baseline survey.

An invitation letter to all nurses will include a full explanation of the study and information on the eligibility criteria. After reading the explanation of the study, potential participants will be invited to give their written consent to participate in the study, and to complete and return the baseline survey to CRC within a week.

< Insert Figure 1 about here>

Intervention programs

In this study, two smartphone-based six-module stress management programs will be used. One (program A) is a free-choice, multi-module stress management program in which respondents are allowed to select one module per week in any order they prefer. The other (program B) is a fixed-sequence, multi-module stress management program in which respondents are required to study modules in a fixed order, one module per week. For both programs, it will take about 15 minutes to complete each module.

Program A includes 6 modules that provide six evidence-based stress management skills. This program is based on a previous web-based stress management program aimed to improve psychological distress of office workers [34], and modified on the basis of intensive consultation with nurses in Vietnam, e.g., replacing one module (on physical activity for stress management) with another (self-compassion). Participants may choose one module per week in any order they prefer. The program includes behavioral activation (Module 1), cognitive restructuring (Module 2), problem-solving (Module 3), assertiveness (Module 4), self-compassion (Module 5), and job crafting (Module 6).

Program B also includes 6 modules that provide CBT-based stress management skills, developed based on a previous iCBT program that successfully improved depression in office workers [33]. The 6 modules are presented in fixed order, with one module accessible per week, from Module 1 to Module 6. The program has two already established CBT packages as its basis. One is the cognitive therapy program developed by Beck [35]. The other is the 'Coping with Depression' program developed by Lewinsohn [36]. The program includes transactional model of stress and coping (Module 1), self-case formulation based on cognitive behavioral model (Module 2), behavioral activation skills (Module 3), cognitive restructuring skills (Modules 4 and 5), problem-solving skills (Module 6) and relaxation skills (Module 5). The program is modified so that the content relevant to and appropriate for the working situation and work culture of nurses in Vietnam. For instance, case stories are modified

reflecting major stressors (i.e., job overload) of these nurses.

Table 1 shows the stress management techniques included in Program A and Program B. Behavioral activation, cognitive restructuring, and problem solving techniques are included in both Program A and Program B. Assertiveness, self-compassion, and job crafting techniques are only included in Program A. The transactional model of stress and coping, self-case formulation based on cognitive behavioral model, and relaxation techniques are only included in Program B. Details of each of the components are as follows.

Table 1 Contents of the free-choice (Program A) and fixed-order (Program B) stress management programs

Techniques for stress management	Program A (Module No.)	Program B (Module No.)
Transactional model of stress and coping	Not included	Module 1
Self-case formulation based on cognitive behavioral model	Not included	Module 2
Behavioral activation	Module 1	Module 3
Cognitive restructuring	Module 2	Modules 4 and 5
Relaxation	Not included	Module 5
Problem solving	Module 3	Module 6
Assertiveness	Module 4	Not included
Self-compassion	Module 5	Not included
Job crafting	Module 6	Not included

Transactional model of stress and coping (Module 1 in Program B)

Transactional stress model is defined as perceptions that demands exceed coping strategies [37]. According to this model, an individual's reaction to stressors is determined, in part, by their own appraisal of the stressor. In keeping with this model, stress will be defined as the psychological response to a situation or stimuli whereby an individual appraises the situation or stressor as exceeding their capabilities or resources. In this module, participants learn about the relationship between stressors and stress reactions.

Self-case formulation based on cognitive behavioral model (Module 2 in Program B)

In this module, participants learn about a cognitive behavioral (CB) model, especially the five-part model (situation, thoughts, emotions, behavior, and physical feelings) [38] and a self-case formulation based on this model. Case formulation is a method used to understand the problem of a client [39]. Case formulation is necessary for clients to choose an appropriate approach to change the vicious circles of these five areas.

Behavioral activation (Module 1 in Program A and Module 3 in Program B)

Behavioral activation, one of the most readily applied techniques in CBT, is a process to increase pleasurable and rewarding activities using behavioral strategies such as activity scheduling [40]. This

module/program provides a behavioral activation technique on enhancing participants' liveliness. Participants learn about a theory of behavioral activation and how to plan an activity schedule for increasing pleasant activities.

Cognitive restructuring (Module 2 in Program A and Modules 4 and 5 in Program B)

The cognitive restructuring technique is one of the standard cognitive approaches of CBT utilized to change an automatic negative thought into an actual, realistic and flexible thought [35]. This module gives a lecture on a cognitive ABC model (Activating/Actual event, Belief, and Consequence) [35 41 42] and on identifying the automatic thoughts that cause a negative mood. Participants learn cognitive restructuring skills to change an automatic negative thought into an actual thought.

Relaxation (Module 5 in Program B)

Relaxation techniques are often added to the CBT intervention for workers, and they have shown significant effects on improving depression [22]. In the latter half of the Module 5, participants learn a relaxation technique using a breathing method.

Problem solving (Module 3 in Program A and Module 6 in Program B)

Problem solving technique is a CB intervention that focuses on training adaptive problem-solving attitudes and skills [43]. 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 [44]. In this module, participants learn problem-solving skills to sort out the problem and make a list of solutions.

Assertiveness (Module 4 in Program A)

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 [45 46]. In order to communicate assertively, the DESC (Describe, Express, Specify, and Choose or Consequence) script is used [47]. In this module, participants learn assertiveness skills to appropriately communicate their concerns to supervisors, coworkers or subordinates, based on the DESC script.

Self-compassion (Module 5 in Program A)

Self-compassion describes a positive and caring attitude of a person toward her- or himself in the face of failures and individual shortcomings [48]. As a result of this caring attitude, individuals high in self-compassion are assumed to experience higher individual well-being. There are three interrelated elements that determine the self-compassionate reactions to negative events and experiences: self-

kindness, sense of common humanity, and mindfulness [48 49]. In this module, participants learn a concept of self-compassion and how to express compassion toward themselves.

Job crafting (Module 6 in Program A)

Job crafting is defined as "the physical and cognitive change individuals make in the task or relational boundaries of their work" [50] and consists of the following three components: changing the job's boundaries (task crafting), changing the relational boundaries (relational crafting), and changing the cognitive task boundaries (cognitive crafting) [50]. In this module, participants learn about the concept of job crafting and how to craft their own job.

Intervention groups

Participants in the intervention groups will be required to complete Program A or B within 10 weeks after the baseline survey. Participants will be provided with their own ID and password to sign in to the program and asked not to tell anyone else this information. The participants will be reminded by email to complete the program if they have not already done so. Reminders will be sent from the research office. Before the start of the intervention program, participants in the intervention groups download the apps and view an introduction module that provides general explanations of the programs. The introduction module is common for the two intervention programs with brief explanations about the psychological stress model, self-assessment of their own mood using Kessler's Psychological Distress Scale (K6) [51], and an introduction of the two intervention programs. Participants can contact CRC if they have trouble downloading or using the apps. After 3 months from baseline survey, the intervention programs will be closed by CRC.

Control group

Participants in the control group do not receive any intervention programs during the intervention and follow-up period (7 months). Participants both in the intervention group and the control group will be able to use an internal employee assistance program service as a treatment as usual. Participants in the control group will be provided the opportunity to use the intervention programs after the 7-month follow-up.

Outcomes

Table 2 shows an overview of the outcome measures. All outcome measures will be assessed at baseline, the 3-month (the end of the intervention period) and 7-month follow-ups. Non-respondents will receive reminder email from the research center for each of the follow-up surveys. All participants will receive a paper-based survey questionnaire from CRC at baseline and each follow-up. Completed questionnaires will be returned to CRC in a sealed envelope.

Table 2 Overview of outcome measurements

Measurement	Aim	Baseline (T1)	3-M F/U (T2)	7-M F/U (T3)
Primary outcomes				
DASS	Severity of depressive symptoms	x	x	x
DASS	Severity of anxiety symptoms	x	x	x
Secondary outcomes				
UWES	Work engagement	x	x	x
HPQ	Sickness absence (absenteeism) and reduced job performance (presenteeism)	x	x	x
DASS	Severity of stress symptoms	x	x	x
JCQ	Psychosocial work environment	x	x	x
EQ-5D	Health-related quality of life	x	x	x

Note: DASS = Depression Anxiety and Stress Scales, UWES = Utrecht Work Engagement Scale, HPQ = Health and Work Performance Questionnaire, JCQ = Job Content Questionnaire.

Primary outcomes

Depression and anxiety

The Depression Anxiety and Stress Scales (DASS) is a widely used screening tool to assess symptoms of depression, anxiety, and stress in community settings [52]. The DASS comprises three subscales (i.e., depression, anxiety, and stress) The depression subscale measures dysphoria, hopelessness, devaluation of life, among others. The anxiety subscale measures autonomic arousal, skeletal musculature symptoms, situational anxiety, among others. The stress scale measures difficulty relaxation, nervous arousal, easily upset/agitated, among others. The short 21-item version (DASS 21, seven items in each of the three subscales) [53] will be used in this study. Items are scored on a 4-point scale ranging from 0 (*did not apply to me at all*) to 3 (*applied to me very much, or most of the time*). In order to yield equivalent scores to the full version of DASS (42-item), the total score of each scale is multiplied by 2 and ranges from 0 to 42 [53]. A Vietnamese version of DASS 21 has been developed and tested, and its reliability and validity have been confirmed [54]. The depression scale and the anxiety scale will be used to assess the depression and anxiety symptoms as primary outcomes in this study.

Secondary outcomes

Work engagement

Work engagement will be assessed using the short form of the Utrecht Work Engagement Scale (UWES) [55]. 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*). A total score is calculated from all nine items. The Vietnamese version will be developed and validated before the study.

Sick leave days and self-reported work performance

The WHO 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) [56]. 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. The Vietnamese version will be developed and validated before the study.

Stress symptoms

Stress symptoms will be assessed with the stress scales of DASS 21 [52-54], above.

Psychosocial work environment

The Job Content Questionnaire (JCQ) will be used to assess psychological job demands, control, and support by coworkers and supervisors [57]. The JCQ consists of a five-item psychological demand scale, a nine-item decision latitude scale, a four-item supervisor support scale, and a 4-item coworker support scale. Items are scored on a 4-point Likert scale, ranging from 1 (*strongly disagree*) to 4 (*strongly agree*). The Vietnamese version will be developed and validated before the study.

Health-related quality of life

Health-related quality of life will be assessed with the EQ-5D-5L [58]. The EQ-5D-5L 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. It is a widely applied quality of life instrument, and its reliability and validity are well established [58]. The Vietnamese version has been developed and tested for its reliability and validity [59].

Improvement of knowledge and self-efficacy.

Respondents will be asked to rate their improvement of knowledge and self-efficacy regarding the two intervention programs. Knowledge improvement will be assessed by asking participants, ''How much knowledge do you have about…,'' and self-efficacy improvement will be assessed by asking respondents ''How confident are you that you can do….'' Both items are scored on 5-point scale ranging from 0 (*none*) to 4 (*enough*). This scale is originally developed and has not yet been validated.

Process evaluation

Program satisfaction and usage

Participants in the intervention groups will be asked to rate their satisfaction with the intervention program at the end of the intervention period. To evaluate any difference in adherence to the two intervention programs, the usage of the intervention programs will be collected from the records of the apps system. It is technically difficult to make the content of the two intervention programs identical; the adaptation and modification process following the consultation with nurses in Vietnam make it more difficult. However, we still use the same CBT components (i.e., behavioral activation, cognitive restructuring, and problem solving) in both of the programs, keeping 50% of the content overlapping (see Table 1).

Contamination of information

To evaluate contamination of information among participants, participants will be asked at follow-up survey; "During the past 3 months, have you got to know information on stress management from your colleagues who used any smartphone-based stress management programs?", with a response option, yes/no. This scale will be originally developed.

Demographic characteristics

Demographic data, such as age, gender, marital status, occupation, education, chronic disease, and overtime hours during the past month also will be collected.

Sample size calculation

A required sample size was calculated for one of the outcome variables, i.e., depressive symptoms assessed by DASS. Previous meta-analyses of web-based psychological intervention on improving workers mental health in the workplace yielded effect sizes of 0.23 to 0.37 [25 26]. To detect a small effect size (i.e., 0.25) or more at an alpha error rate of 0.05 and a beta error rate of 0.15, the estimated sample size was 289 participants in each group. With an anticipated dropout rate of 25 %, the necessary sample size was 361 participants per arm. The statistical power was calculated using the G*Power 3 program [60 61].

Randomization

Participants who fulfil the inclusion criteria will be randomly allocated to one of the three trial arms (two intervention groups or control groups). Stratified permuted-block randomization will be conducted as well. The block sizes of this study will be fixed to three. Participants will be stratified into two strata according to the depression subscale score of DASS (10 or greater or less than 10) in the baseline survey [54]. 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

For the main pooled analysis, a mixed model for repeated measures conditional growth model analysis with an unstructured covariance matrix will be conducted using a group (intervention and control) × time (baseline, 3-month, and 7-month follow-ups) interaction as an indicator of intervention effect. For sensitivity analysis, a similar mixed model for repeated measures, but using the analysis of variance model. with an unstructured covariance matrix will be conducted. Missing values will be imputed applying the maximum likelihood estimation using the MIXED procedure. An intention-to-treat principle will be applied as well. The effect size indicators are two-fold. We will estimate a regression coefficient for a group (each of the two intervention groups vs. the control group) x time (baseline and two follow-ups) interaction using the MIXED procedure, that will be converted an effect size by dividing by a pooled SD at baseline and at follow-ups. Second, we will calculate Cohen's *d* among completers at baseline for each follow-up. The level of statistical significance for all analyses in this study will be set at 0.05 (two-tailed), and 95% CIs will be calculated. For Cohen's d, the values of 0.2, 0.5 and 0.8 are generally interpreted as being suggestive of small, medium and large effects, respectively [62]. For process measures, the chi-square test will be performed to examine the difference between the two intervention groups. All statistical analyses will be conducted using the SPSS Statistics V.22.0 (IBM Corp., USA).

Subgroup analysis

The effectiveness of the program may differ according to the initial severity of depressive symptoms. We will therefore use the stratification factor (i.e., participants who scored 10 or more in DASS depression subscale at the baseline survey) and analyze the results according to a priori-defined subgroups (selective intervention effect).

Data monitoring

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 3 months after the first participant 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).

Patient and Public Involvement

In the present study, the research question, the study design, and the outcome measures were determined based on a discussion with representatives of hospital nurses in the target hospital (chief nurses). Senior nurses of the target hospital (who were not participants of the study) were invited to a meeting with researchers to review and comment on the intervention programs based on their priorities, experience, and preferences. The representatives of hospital nurses in the target hospital will help recruiting and conducting the study. The results of the study will be disseminated to all nurses in the hospital via a newsletter or with other media, after the study is done, with an opportunity for them to enjoy the intervention programs. In this RCT, the burden of the intervention will be assessed by participants themselves.

ETHICS AND DISSEMINATION

Ethical and safety considerations

Written informed consent will be obtained from all participants included in this study after full disclosure and explanation of the purpose and procedures of the study. Candidates will be informed that their participation is totally voluntary, that even after voluntarily participating they can withdraw from the study at any time without stating the reason, and that neither participation nor withdrawal will cause any advantage or disadvantage to them.

We expect no adverse health effect from this intervention, except possibly for deterioration in depressive/anxiety symptoms. We will provide the emergency phone call number and e-mail address at the central office. The CRC (TTran), who is a registered nurse, will then deal with the emergency call or e-mail first by herself, and then consult with the clinical supervisors (NK) to provide appropriate care.

Data confidentiality

Participants will complete a baseline/follow-up questionnaire with a sealed envelope and submit it to the research center. After the survey, the collected data will be entered into a password-locked stand-alone PC by the CRC. 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. If the intervention programs are found to produce a significant positive effect in this RCT, these programs can be made available for all nurses in Vietnam in the future.

Strengths and limitations

The greatest strength of this study is its focus on the effect of the fully automated web-based smartphone application intervention programs on improving depressive and anxiety symptoms among Vietnamese nurses using RCT design. This study is also intended to add evidence for the effect of e-stress management programs on positive work outcomes (e.g., work engagement and work performance) among nurses. To our knowledge, the present study will be the first to determine whether a fully automated smartphone-based stress management programs is effective in improving depressive and anxiety symptoms and relevant work outcomes among nurses in Vietnam, a middle income country in Southeast Asia, using a well designed study protocol. This study will contribute to future development of strategies in the primary prevention of depression and anxiety and promotion of

positive mental health among nurses in the low- and middle-income countries.

Another strength of this study is to contribute to the creation of a new option for mental health services if this RCT will demonstrates the effectiveness of e-stress management programs developed in this project in a low- and middle-income country context. Such programs would provide hospital nurses in Vietnam with an opportunity to have access to a low-cost mental health service.

One of the major weaknesses of this study is that all outcomes will be measured by self-report, which may be affected by the perceptions of the participants or by situational factors at work. Next, participants will be recruited from full-time nurses of one big general hospital in Vietnam. Therefore, generalization of the findings to nurses working under different contract and work environments may be limited. Third, a slight difference in the content between the two intervention programs may be also a limitation in comparing the adherence between the free-choice program and the fixed-order program.

ACKNOWLEDGEMENT

Authors' contribution

KI, TTran, HN, KK, AS, TB, AN, QN, KN, GN, XT, TTruong, MZ, HM, YS, NS, AT, and NK conceived and designed the experiments. KI, TTran, HN, KK, AS, YS, NS, and NK contributed reagents/materials/analysis tools. KI, TTran, HN, HM, and NK wrote the paper. All authors read and approved the final paper.

Funding statement

This research was supported by AMED under Grant Number JP17jk0110014. The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interest

NK reports grants from Infocom Corp, Fujitsu Ltd, Fujitsu Software Technologies, and TAK Ltd, personal fees from Occupational Health Foundation, Japan Dental Association, Sekisui Chemicals, Junpukai Health Care Center, Osaka Chamber of Commerce and Industry, outside the submitted work. The other authors declare that they have no competing interests.

Figure 1 Participant flowchart.

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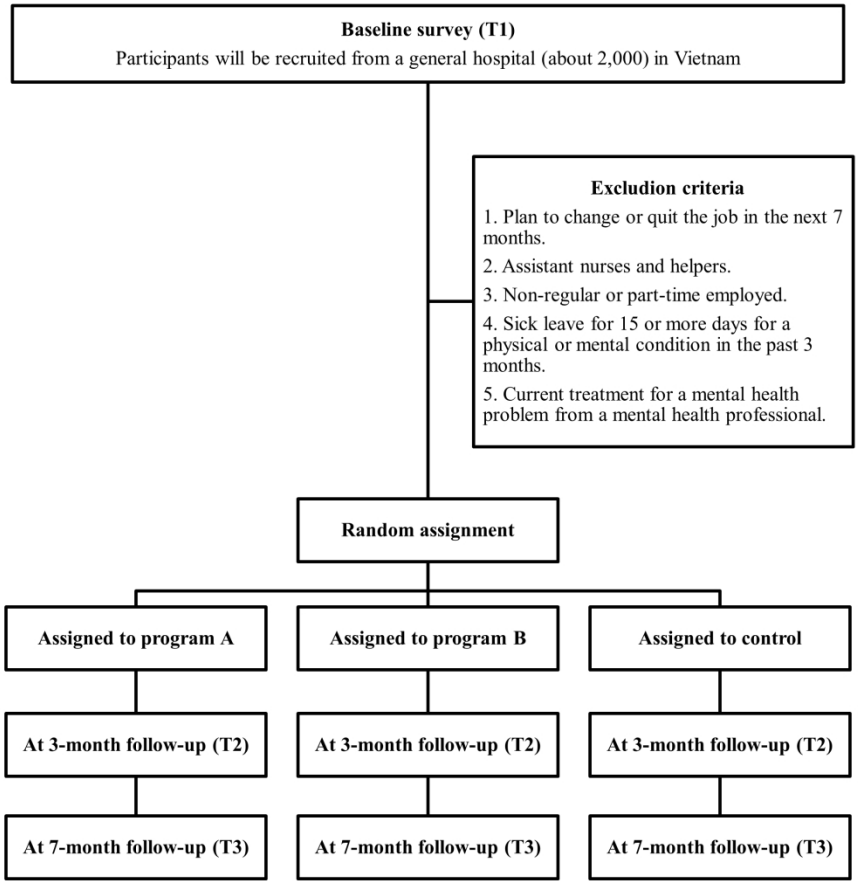

Figure 1 Participant flowchart.

190x254mm (300 x 300 DPI)

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-2, 18
	5b	Name and contact information for the trial sponsor	2
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	16

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	N/A
Objectives	7	Specific objectives or hypotheses	5-6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
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	7-8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12
	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	13-15
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)	7-8

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	_____15_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____7-8_____
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	_____15-16___
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____15-16___
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____15-16___
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____N/A_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____N/A_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_____12_____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_____12_____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	17
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	16
	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	N/A
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	17
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17
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)	N/A

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	17
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
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	17
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	N/A
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	17
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

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