BMJ Open

Effects of brief family psychoeducation for caregivers of people with schizophrenia in Japan provided by visiting nurses: protocol for a cluster randomized controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-034425
Article Type:	Protocol
Date Submitted by the Author:	21-Sep-2019
Complete List of Authors:	Yasuma, Naonori; The University of Tokyo, ; Sato, Sayaka; National Institute of Mental Health, Community mental health and law; NCNP Matsunaga, Asami; National Center of Neurology and Psychiatry, Department of Community Mental Health & Law, National Institute of Mental Health Yamaguchi, Sosei; National Center of Neurology and Psychiatry, Department of Community Mental Health & Law, National Institute of Mental Health Shiozawa, Takuma; National Center of Neurology and Psychiatry, Watanabe, Kazuhiro; The University of Tokyo, Department of Mental Health, Graduate School of Medicine Imamura, Kotaro Tachimori, Hisateru; National Center of Neurology and Psychiatry Translational Medical Center Nishi, Daisuke Fujii, Chiyo; National Center of Neurology and Psychiatry, Department of Community Mental Health & Law, National Institute of Mental Health Kawakami, Norito; The University of Tokyo, Department of Mental Health
Keywords:	Brief family psychoeducation, schizophrenia, caregivers, visiting nurses

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Effects of brief family psychoeducation for caregivers of people with schizophrenia in Japan provided by visiting nurses: protocol for a cluster randomized controlled trial

Naonori Yasuma[1,2]: nnyy712@gmail.com
Sayaka Sato[2]: sayakas@ncnp.go.jp
Asami Matsunaga[2]: asamim@ncnp.go.jp
Sosei Yamaguchi[2]: sosei.yama@ncnp.go.jp
Takuma Shiozawa[2]: takuma-shozw@umin.ac.jp
Hisateru Tachimori[3]: tachi@ncnp.go.jp
Kazuhiro Watanabe[1]: kzwatanabe-tky@umin.ac.jp
Kotaro Imamura[1]: kouima-tky@umin.ac.jp
Daisuke Nishi[1]: d-nishi@m.u-tokyo.ac.jp
Chiyo Fujii[2]: chyfujii@ncnp.go.jp
Norito Kawakami[1]: nkawakami@m.u-tokyo.ac.jp

1 Department of Graduate School of Medicine, The University of Tokyo

2 Department of Community Mental Health and Law, National Institute of Mental Health, National Center of Neurology and Psychiatry, Kodaira, Tokyo, Japan

3 Department of Translational Medical Center, National Institute of Mental Health, National Center of Neurology and Psychiatry, Kodaira, Tokyo, Japan

Corresponding author:
Naonori Yasuma, MD
Department of Mental Health, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 1130033 Japan
E-mail: nnyy712@gmail.com
Phone: +81-3-5841-3521
Fax: +81-3-5841-3521

Word count: 4,190 words

ABSTRACT

Introduction

Development of a support system for families caring for people with schizophrenia in routine psychiatric care settings is an important issue worldwide. Regional mental health systems are inadequate for delivering effective services to such family members. Despite evidence that family psychoeducation (FPE) alleviates the burden of schizophrenia on families, its dissemination in routine clinical practice remains insufficient, suggesting the need for developing an effective and implementable intervention for family caregivers in the existing mental health system setting. In Japan, the visiting nurse service system would be a practical way of providing family services. Visiting nurses in local communities are involved in the everyday lives of people with schizophrenia and their families. Accordingly, they understand their needs and are able to provide family support as a service covered by national health insurance. The purpose of this study is to discover whether a brief FPE program provided by visiting nurses caring for people with schizophrenia will alleviate family burden through a cluster randomised controlled trial (cRCT).

Methods and analysis

The study will be a two-arm, parallel-group (a visiting nurse agency) cRCT. Forty-seven visiting nurse agencies will be randomly allocated to the brief FPE group (intervention group) or treatment as usual group (control group). Caregivers of people with schizophrenia will be randomly recruited by visiting nurses. The primary outcome will be caregiver burden, measured using the Zarit Burden Interview–Japanese version (ZBI-J-22). Outcome assessments will be conducted at baseline, at 1-month follow-up, and at 6-month follow-up. Multiple levels of three-way interaction of mixed models will be conducted to examine whether the brief FPE program will alleviate the burden on caregivers relative to treatment as usual.

Ethics and dissemination

The Research Ethics Committee of the Graduate School of Medicine and Faculty of Medicine, the University of Tokyo, Japan (No. 2019065NI) approved this study. The results will be published in a scientific peer-reviewed journal.

Registration number

UMIN000038044; Pre-results.

INTRODUCTION

Families caring for people with schizophrenia receiving mental health care in the community have a great need for support. Schizophrenia, a chronic psychiatric illness that requires long-term care, imposes a significant burden on families providing such care.[1] For example, the financial burden on the family is severe because considerable amounts of time are devoted to caregiving, resulting in the loss of work opportunities and reduced income.[2] Moreover, insufficient downtime to recover from the stress of caregiving results in both physical and mental illnesses.[3] Families also become worn out and stressed by the demands of coping with this illness, which is characterized by repeated hallucinations and delusions if symptoms do not stabilize.[4] Furthermore, a parent of a schizophrenic son or daughter might worry about what will become of their child after his or her death. They might also feel they are not getting adequate information about what social services are available to them.[5] Stigma against the illness is also deeply rooted and can lead to families becoming socially isolated.[3] Therefore, families of people with schizophrenia have various physical, psychological, economic, and social burdens.

Several studies have addressed the development and evaluation of effective family interventions. According to a systematic review, family psychoeducation (FPE) is a scientifically effective psychological intervention that has been used to reduce caregiver burden.[6,7] The components of FPE mainly include information sharing about the disorder, early warning signs, and relapse prevention as well as and skills training in coping, communication, and problem solving.[8] FPE was considered to directly improve caregivers' knowledge about schizophrenia and related caregiving problems.[9] Improved knowledge of coping strategies and resources can lead to a more positive appraisal of families' caregiving experiences as well as the caregivers' own self-efficacy in coping with the demands of caring for people with schizophrenia, thereby lessening the burden.[6]

Despite the accumulation of evidence, there are several barriers to FPE implementation. The initial report on the Schizophrenia Patient Outcomes Research Team (PORT) Treatment Recommendations found that FPE was provided to 31.6% of inpatients and 9.6% of outpatients who could have benefited from it.[10] A nationwide survey in Japan revealed that implementation rates for FPE programs in psychiatric facilities are similarly low: 35.9% in hospitals and 14.5% in clinics.[11] One challenge in implementing these programs is the length of the intervention. Most research has found that such interventions range from 9 months to 2 years, which is impractical for medical staff and families in a clinical setting.[12] Other reasons include funding and staff

shortages, as well as providing necessary training.[13] For example, in Japan, FPE does not incur a medical treatment fee, even if it is performed for a family. In addition, while the Meriden Family Program appears to be effective, training takes "a large amount of hours and money."[14] The medical treatment fee system in most countries including Japan does not cover such a comprehensive family intervention. The development of a brief and implementable FPE program within the existing mental health system that is covered by national health insurance is greatly needed.[15]

Brief FPE programs have been examined in previous studies. In terms of the program framework, studies have found that brief FPE programs, delivered in five sessions or fewer or lasting no more than 3 months, were easy to conduct for both practitioners and caregivers.[16] Brief FPE programs have been shown to significantly increase caregivers' knowledge of the disorder, leading to reductions in relapse and rehospitalisation rates in diverse settings.[17,18] In addition, recent research has shown that a brief FPE program may be beneficial in reducing caregiver burden. In a pre-post test in India, a brief FPE program comprised of three 1-hour sessions aimed at educating the primary caregiver and patient about schizophrenia, communication skills, and problem-solving skills. A significant decrease in caregiver burden, measured using the Burden Assessment Scale (BAS), was found between baseline and the final follow-up at 3 months.[19] In a randomised controlled trial in Iran, brief FPE consisted of ten 90-minute sessions held over 5 weeks (two sessions each week) conducted by a psychiatric nurse or psychiatrist. Caregiver burden measured using the Family Burden Scale (FBS) was significantly reduced both immediately after the intervention and 1 month later.[20] However, the effects of brief FPE programs were still inconclusive due to relatively low methodological quality in prior studies.[7,16] In other words, evidence from a trial with a better design is needed.

Practical implementation strategies for a brief FPE program need to be considered in addition to a scientific evaluation of the effects. Brief FPE programs provided by visiting nurses appear to be a potentially feasible and sustainable way of implementing FPE in a Japanese clinical setting. Visiting nurses routinely visit clients with schizophrenia and their family members. They have already built rapport with clients and family members and would be able to respond according to their needs, which means they could seamlessly provide highly individualized brief FPE.[21] In addition, the system of visiting nurses could easily be applied because the number of visiting nurses has been increasing recently in Japan. From a cost perspective, it would be possible to make family support a reimbursable service under national health insurance to cover psychiatric visiting nurse consultancy fees.[22] Taken together, brief

FPE provided by visiting nurses could overcome the poor implementation rate and become effective family interventions in the community setting in Japan. The purpose of this study is to clarify, through a cluster randomised controlled trial (cRCT), whether visiting nurses providing brief FPE to families caring for people with schizophrenia will alleviate family burden.

METHODS AND ANALYSIS

Trial design

This study is a two-arm, parallel-group cRCT. The randomisation procedure is conducted at the cluster level (visiting nurse agencies). Visiting nurse agencies will be randomly assigned to the intervention or control (treatment as usual (TAU)) group in a 1:1 ratio. Data will be collected at the individual level. Analyses to evaluate the efficacy of the intervention program will be conducted at the individual level, taking into consideration cluster-level effects. The study protocol was registered in the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN-CTR ID, UMIN000038044). This protocol was reported according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.[23]

Setting and site selection at the cluster level

Figure 1 shows the participant flow chart for this study. We recruited 47 visiting nurse agencies in four prefectures in Japan, namely Tokyo, Saitama, Kanagawa, and Chiba prefectures. All the participating visiting nurse agencies are managed by one organisation. The corresponding author (NY) explained the purpose of this study to the organisation and asked the organisation to recruit 47 visiting nurse agencies.

To be included, a visiting nurse agency must have been mainly providing services for psychiatric patients or clients, not elderly people or those with other physical diseases, for at least 1 year. In each agency, visiting nurses care for at least two people with schizophrenia who live with their family. There are no exclusion criteria at the cluster level.

Participant eligibility criteria and recruitment procedure at the individual level

At the individual level, we set the following inclusion criteria for a caregiver of a person with schizophrenia: 1) is the primary caregiver; 2) aged over 20 years; 3) is a family member of the person with schizophrenia such as a parent, sibling, spouse, or child; and 4) lives with the person with schizophrenia. There are no exclusion criteria for caregivers. In addition, the inclusion criteria for people with schizophrenia are as

follows: 1) diagnosis of schizophrenia based on the International Statistical Classification of Diseases and Related Health Problems, 10th revision and 2) use of visiting nurse services.

In each agency, potential participants (caregivers of people with schizophrenia and people with schizophrenia) will be randomly extracted using a recruitment sequence table. The recruitment sequence table will be created using a random number generation method with the Stata statistical software program, version 15. Based on the recruitment sequence table, consent acquisition will be performed by visiting nurses who have attended a lecture on study design and ethical considerations. The study will include only caregivers who voluntarily agree to participate in the study. The average cluster size will be approximately five caregivers. Visiting nurse agencies will be allocated randomly to the intervention or control group. The intervention program will last one month. The study has three planned assessment points including baseline assessment prior to the intervention (T1), immediately after the completion of the intervention (1-month follow-up assessment, T2), and 6 months after the baseline assessment (6-month follow-up assessment, T3) in both the intervention and control groups.

Intervention program

The intervention program is a single-family intervention conducted by psychiatric visiting nurses. It is based on the Family Intervention and Support in Schizophrenia: A Manual on Family Intervention for the Mental Health Professional.[24] This program was developed through discussions and collaborations among members of the Family Association of Schizophrenia, psychiatric visiting nurses, FPE experts, psychiatrists, psychiatric nurses, clinical psychologists, and mental health social workers based on the concept of coproduction and Patient and Public Involvement (PPI).[25] During the development process, we tried to avoid long sentences, enlarged the characters, and used visually appealing drawings. The program consists of four sessions that last 60 minutes each using the above tool. It will be completed over a period of a month. Psychiatric visiting nurses will provide appropriate information using this intervention tool and advice to the family about living problems based on their own nursing clinical experience.

Before the intervention, we will provide the intervention team of psychiatric visiting nurses with a 1-day lecture. The lecture will consist of three parts. First, a caregiver of a person with schizophrenia will talk about their life problems and what they want visiting nurses to do; this is expected to increase the motivation of visiting nurses. Second, basic communication training will be conducted through role-playing.

Visiting nurses, who will be brief FPE providers, will be in groups of three. They will each play the role of a visiting nurse, caregiver, and evaluator. They will practice listening to caregivers. Third, the primary investigator (NY) will equip them with basic knowledge about FPE and explain the contents of this intervention tool and the points the primary investigator wants to emphasise. Through these trainings, we expect to improve the motivation, knowledge, and skills of the visiting nurses in providing the brief FPE program.

Table 1 shows the contents of the intervention tool. Session I covers general knowledge about schizophrenia: definition, causes, symptoms, prognosis, pharmacological treatment, and psychosocial rehabilitation. Regarding definition and causes, visiting nurses will stress that schizophrenia is a brain disease that can manifest in anyone using the diathesis-stress model and the dopamine hypothesis. It is important to provide the family with a biological explanation about the aetiology of schizophrenia because there might be family members who think people become schizophrenic because of family relationships.[26] In addition to an explanation of the symptoms themselves, visiting nurses will describe how people with schizophrenia have difficulties living their own lives due to their symptoms. Visiting nurses will explain the disease course such as the prodromal phase, acute phase, and recovery phase. Next, visiting nurses will explain the characteristics of each phase and what to do during each phase. In terms of prognosis, visiting nurses will address that over 70% of people can recover if they receive appropriate pharmacological therapy.[27] Concerning medication, visiting nurses will appreciate the idea that people with schizophrenia usually do not want to take medication. Visiting nurses will talk about the necessity, safety, and reasons for adherence to pharmacological therapy. In addition, the side effects of antipsychotic medications will be described clearly, using relevant pictures. Finally, visiting nurses will give an outline of psychosocial therapy. At the end, participants will answer questions with dichotomous answers—"yes" or "no"—to confirm what they have learned from the session.

Session II deals with how to cope with people with schizophrenia and problem-solving skills. The contents of this session include how to cope with hallucinations and delusions; signs of recurrence; how to prevent recurrences; how to cope when the disease gets worse; what to do with people with schizophrenia when they stay at home all day; how to respond to people with schizophrenia who do not want to take their medication; how to respond when domestic violence is imminent, is occurring, or has occurred; and how to get involved when self-injury or suicide is suspected. Finally, visiting nurses will explain problem-solving skills. In the routine clinical setting, the

family will work on matters that are causing trouble in daily life using problem-solving skills.

Session III includes communication and emotions: understanding the feelings of people with schizophrenia, expressed emotion (EE) theory, basic knowledge and skills about communication, and a lecture on desirable and undesirable communication with people with schizophrenia. In the first section, visiting nurses will describe the importance of understanding that people with schizophrenia are likely to have a pessimistic view about their future. In the second section on EE theory, visiting nurses will appreciate that it is natural for a family to have high EE with poor knowledge and lack of support about mental illness.[28] Of note, visiting nurses are not forcing family members to play the role of supporter. When family members hear the explanation of high EE, many might feel that they are responsible for their burden. Visiting nurses will emphasise that both families and people with schizophrenia should think about positive and constructive communication to ensure mutual independence. In the third section on basic knowledge about communication and the lecture of desirable and undesirable communication with patients, caregivers will practice conversations using real cases and will be given time to consider better communication strategies.

Session IV focuses on the family's recovery. Topics include thinking about the family's recovery, the importance of living one's own life, taking care of the family's physical and mental health needs, proper stress management, experiences and messages from members of the Family Association, and identifying available social resources in the community. During this session, visiting nurses will stress that people with schizophrenia and family members each have their own lifestyle and individual goals. Visiting nurses will also encourage family members to live their own lives using a variety of social resources instead of working hard to take care of a person with schizophrenia. In addition, visiting nurses expect that the family will improve their physical and mental health by acquiring knowledge on self-care and stress management skills. Furthermore, visiting nurses will introduce the experiences of three members of the Family Association who have taken care of a person with schizophrenia. It is expected that others' similar experiences will help family members understand that they are not the only people experiencing such a hard time and relieve their feelings of sadness or hopelessness. Finally, visiting nurses will explain the social resources available in the community for family members and confirm the importance of connecting with many supporters around them.

Control group

Visiting nurse agencies in the control group will offer TAU. Caregivers enrolled in the control group will be put on a waiting list to receive the same intervention program after completing the 6-month follow-up assessment.

Outcomes

Table 2 shows an overview of the outcome measures. Outcome measures will be assessed baseline assessment prior to the intervention (T1), immediately after the completion of the intervention (1-month follow-up assessment, T2), and 6 months after the baseline assessment (6-month follow-up assessment, T3).

Primary outcome for caregivers

Zarit burden interview (ZBI-22)

ZBI-22 is used to measure caregiver burden. It consists of 22 items scored on a five-point Likert scale from 0 (never) to 4 (nearly always), except for the final item on global burden, which is rated from 0 (not at all) to 4 (extremely). The total score ranges from 0 to 88, with higher scores indicating higher burden. The Japanese version of ZBI-22 had a high test-retest reproducibility and internal consistency. Construct validity has also been confirmed.[29]

Secondary outcome for caregivers

K6

K6 is used to measure non-clinical depression and anxiety disorders as part of a self-administered questionnaire. It consists of six items answered on a five-point Likert scale. Scores thus range from 0 to 24, with higher scores representing higher degrees of non-clinical depression and anxiety disorder. The Japanese versions of the K6 have essentially equivalent screening performance as the original English versions.[30]

General Self Efficacy Scale (GSES)

GSES is a measurement of self-efficacy in daily living. It includes 16 items with dichotomous questions. The higher the score, the better the self-efficacy, in general. GSES had high test-retest reproducibility and internal consistency. Construct validity has been confirmed.[31]

WHO-5

WHO-5 is used to measure subjective quality of life based on positive mood (good spirits and relaxation), vitality (being active and waking up fresh and rested), and

general interest (being interested in things). It consists of five items rated on a six-point Likert scale. Higher scores mean higher well-being. The Japanese version of WHO-5 has adequate internal consistency. It was also confirmed to have external concurrent validity and external discriminatory validity.[32]

Knowledge of Illness and Drug Inventory (KIDI)
KIDI is used to assess knowledge regarding mental illness and the effects of medications on mental illness. There are two sub-scales: 10 items assessing knowledge of mental illness and 10 items assessing knowledge of the effects of antipsychotic drugs. This inventory consists of a self-reported inventory where respondents are asked to select the correct answer from three choices, with higher scores representing greater knowledge. KIDI is frequently used to assess knowledge about mental disorders and treatments in Japan.[33]

Primary outcome for people with schizophrenia
Behavior and Symptoms Identification Scale (BASIS-32)
BASIS-32 is a commonly used measure in mental health. It includes 32 items on a five-point Likert scale, where 0 indicates no difficulties and 4 indicates severe difficulties. The scale measures five factors: (1) relation to self and others (seven items); (2) depression/anxiety (six items); (3) everyday life and role functioning (nine items); (4) impulsive and addictive behaviour (six items); and (5) psychosis (four items). Factors 1, 2, 4, and 5 are assessed as the total score divided by the number of items answered (mean score), while factor 3 is assessed based non the highest rating. Internal consistency and construct validity of the Japanese version of BASIS-32 have been demonstrated.[34]

Secondary outcome for people with schizophrenia
WHO-5
WHO-5 is used to measure subjective quality of life based on positive mood (good spirits and relaxation), vitality (being active and waking up fresh and rested), and general interest (being interested in things). WHO-5 comprises five items rated on a six-point Likert scale. Higher scores mean higher well-being. The Japanese version of WHO-5 has adequate internal consistency. It was also confirmed to have external concurrent validity and external discriminatory validity.[32]

Hospitalisation by 6-month follow-up

This is a question with a dichotomous answer (yes or no) about whether the patient has been hospitalised during the past 6 months. The answer will be provided by the caregiver at baseline and the 6-month follow-up.

Sample size calculation

The sample size required was calculated according to guidelines in the Consolidated Standards of Reporting Trials (CONSORT) for cRCTs,[35] taking into account intra-class correlations (ICCs). The effect size of a brief FPE program for individual caregiver burden was estimated based on a previous pre-post test.[19] The pre-post test concluded that the standardised mean difference (d) of brief FPE on family burden was 0.46. Sample size was estimated as 76 in each arm based on an alpha error probability of 0.05 and power (1-β) of 0.80, using G*Power version 3.1.9.2.[36 37] cRCT should be multiplied by design effect (1+[m-1]ρ), where m is the average cluster size and ρ is the ICC.[38] The estimated ICC for the primary outcome in this study was set to 0.05 and the average number of caregivers per cluster was set at five people. Assuming an attrition rate of 20%, the required sample size was 110 caregivers in each arm; thus, at least 44 visiting nurse stations will be recruited.

Randomisation

Visiting nurse agencies that meet the inclusion criteria will be randomised to the intervention group (brief FPE program) or the control (TAU) group. Randomisation will be stratified by the median of the average caseload of visiting nurses in each agency since the effect of the intervention might differ based on this factor. If a visiting nurse has a large number of patients, it is expected that family support will be neglected. A random sequence table will be created by a researcher (HT) in an independent department of our institution who was not involved in the study protocol development process. In addition, another independent researcher (SY) who is not involved in intervention and analysis will conduct the randomisation. SY will inform each visiting nurse agency of the randomisation results. The primary investigator (NY) will be blinded through the entire randomisation process.

Statistical analysis

The statistician will be blinded to the treatment group. We will analyse clinical outcomes on the basis of intention to treat and model the effect of the intervention on primary and secondary continuous outcomes using generalised linear latent and mixed models (GLLAMMs). This will allow for missing data to be taken into account within

the statistical model. In this study, a three-level model will be used, with repeated measures nested in participants and participants nested in clusters. Time (baseline, 1-month follow-up, 6-month follow-up) will be considered level 1, individual caregivers will be considered level 2, and clusters (visiting nurse stations) will be considered level 3. Regarding fixed effects, condition (intervention versus control), time, and a two-way interaction effect, condition by time, will be included. Models will adjust for baseline differences in caregiver socio-demographics such as age, gender, education, household income, family relationship with the person with schizophrenia, length of caregiving, and length of visiting nurse system use. Multiple levels of Cox proportional hazards regression models will also be used for the dichotomous question of hospitalisation at the 6-month follow-up. A *p*-value of less than 0.05 will be considered statistically significant.

Data monitoring

A data monitoring committee (DMC) will be set up. It will consist of at least two independent members. The DMC will meet monthly after the first participant is randomised. The purpose of the meeting will be to review participation rates and reasons for study dropout. The DMC will be independent from any sponsor and competing interest.

Patient and public involvement

The research question, study design, and outcome measures were determined based on a discussion with representatives of the Family Association of Schizophrenia. This intervention program was also developed through the discussion and collaboration among members of the Family Association of Schizophrenia, psychiatric visiting nurses, FPE experts, psychiatrists, psychiatric nurses, clinical psychologists, and mental health social workers. After the completion of the study, this intervention tool will be available for anyone who wants to use it via the internet.

Ethics and dissemination

Ethical considerations

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The study protocol was approved by the Research Ethics Committee of the Graduate School of Medicine and the Faculty of Medicine at the University of Tokyo, Japan (No. 2019065NI). We will obtain

informed consent from all caregivers and patients. The consent form will inform caregivers and patients that we guarantee protection of personal information and that the data will be anonymous and used only for academic purposes. There are no competing interests. This study is supported by fundamental study on effective community services for people with severe mental disorders and their families.

Dissemination of the research findings

The findings will be published in a scientific peer-reviewed journal according to the CONSORT guidelines for cRCTs.[35] The participants will be informed of conference presentations and publications.

Strengths and limitations

The study has both strengths and limitations. First, the study will evaluate an implementable brief FPE program that potentially reduces time, cost, and staffing problems by incorporating the program into an existing mental health service system, namely visiting nurse services. Second, this is the first cRCT of a brief FPE program, a trial with a better study design. It will provide better evidence than past studies. Third, based on the concept of coproduction and PPI,[25] the study was developed with incorporation of a variety of views from caregivers, visiting nurses, and FPE experts.

We recognise three limitations of this study. First, since the sampling method for participating agencies was not random, there is a possibility of selection bias. Second, since subjects provide data through a self-reported questionnaire, information bias or random error is possible. Third, each visiting nurse may not be able to complete all four sessions using the tool in the actual clinical setting, leading to the possibility of a high attrition rate during implementation.

Acknowledgments

The authors would like to thank the members of the *Mokuseikai* Family Association of Schizophrenia for their invaluable advice on many aspects of the project.

Contributors

NY is the principal investigator responsible for the initial draft of this manuscript and organising and implementing the study. NY and KW calculated the sample size. NY, KW, SY, and MA decided on the analytic strategy. All authors contributed to the development of the intervention and study design. All authors have read and approved the final manuscript.

Funding: This work is supported by Fundamental study on effective community services for people with severe mental disorders and their families.

Competing interests: None declared.

Patient Consent: Obtained.

Ethics approval: Research Committee of the Graduate School of Medicine and the Faculty of Medicine at the University of Tokyo, Japan.

REFERENCES

1. Awad AG, Voruganti LN. The burden of schizophrenia on caregivers: a review. *Pharmacoecon Open* 2008;26:149–62. doi:10.2165/00019053-200826020-00005

2. Saunders JC. Families living with severe mental illness: a literature review. *Issues Ment Health Nurs* 2003;24:175–98. doi:10.1080/01612840305301

3. Shah AJ, Wadoo O, Latoo J. Psychological distress in carers of people with mental disorders. *British Journal of Medical Practitioners* 2010;3:a327.

4. Gopinath PA, Chaturvedi S. Distress behaviour of schizophrenics at home. *Acta Psychiatr Scand* 1992;86:185–8. doi:10.1111/j.1600-0447.1992.tb03249.x

5. McAuliffe R, O'Connor L, Meagher D. Parents' experience of living with and caring for an adult son or daughter with schizophrenia at home in Ireland: a qualitative study. *J Psychiatr Ment Health Nurs* 2014;21:145–53. doi:10.1111/jpm.12065

6. Sin J, Gillard S, Spain D, *et al.* Effectiveness of psychoeducational interventions for family carers of people with psychosis: a systematic review and meta-analysis. *Clin Psychol Rev* 2017;56:13–24. doi:10.1016/j.cpr.2017.05.002

7. Sin J, Jordan CD, Barley EA, *et al.* Psychoeducation for siblings of people with severe mental illness. *Cochrane Database Syst Rev* 2015;5:Cd010540. doi:10.1002/14651858.CD010540.pub2

8. Dixon L, McFarlane WR, Lefley H, *et al.* Evidence-based practices for services to families of people with psychiatric disabilities. *Psychiatr Serv* 2001;52:903–10. doi:10.1176/appi.ps.52.7.903

9. Birchwood M, Smith J, Cochrane R. Specific and non-specific effects of educational intervention for families living with schizophrenia. A comparison of three methods. *Br J Psychiatry* 1992;160:806–14. doi:10.1192/bjp.160.6.806

10. Lehman AF, Steinwachs DM. Patterns of usual care for schizophrenia: initial results from the Schizophrenia Patient Outcomes Research Team (PORT) Client Survey.

Schizophr Bull 1998;24:11–20; discussion 20–32. doi:10.1093/oxfordjournals.schbul.a033303

11. Oshima I, Mino Y, Nakamura Y, *et al.* Implementation and dissemination of family psychoeducation in Japan: nationwide survey on psychiatric hospitals in 1995 and 2001. *Journal of Social Policy & Social Work* 2007;11:5–16.

12. Rummel-Kluge C, Kissling W. Psychoeducation in schizophrenia: new developments and approaches in the field. *Curr Opin Psychiatry* 2008;21:168–72. doi:10.1097/YCO.0b013e3282f4e574

13. Harvey C. Family psychoeducation for people living with schizophrenia and their families. *BJPsych Adv* 2018;24:9–19. doi:10.1192/bja.2017.4

14. Fadden G, Heelis R. 2011. The Meriden Family Programme: lessons learned over 10 years. *J Ment Health* 2011;20:79–88. doi:10.3109/09638237.2010.492413 [published online first: 2 September 2010].

15. McFarlane WR, Dixon L, Lukens E, *et al.* Family psychoeducation and schizophrenia: a review of the literature. *J Marital Fam Ther* 2003;29:223–45.

16. Okpokoro U, Adams CE, Sampson S. Family intervention (brief) for schizophrenia. *Cochrane Database Syst Rev* 2014;3:Cd009802. doi:10.1002/14651858.CD009802.pub2

17. Pitschel-Walz G, Leucht S, Bauml J, *et al.* The effect of family interventions on relapse and rehospitalization in schizophrenia—a meta-analysis. *Schizophr Bull* 2001;27:73–92. doi:10.1093/oxfordjournals.schbul.a006861.

18. Smith JV, Birchwood MJ. Specific and non-specific effects of educational intervention with families living with a schizophrenic relative. *Br J Psychiatry* 1987;150:645–52. doi:10.1192/bjp.150.5.645.

19. Devaramane V, Pai NB, Vella SL. The effect of a brief family intervention on primary carer's functioning and their schizophrenic relatives levels of

psychopathology in India. *Asian J Psychiatr* 2011;4:183–7. doi:10.1016/j.ajp.2011.06.004

20. Sharif F, Shaygan M, Mani A. Effect of a psycho-educational intervention for family members on caregiver burdens and psychiatric symptoms in patients with schizophrenia in Shiraz, Iran. *BMC Psychiatry* 2012;12:48. doi:10.1186/1471-244x-12-48

21. Huang XY, Ma WF, Shih HH, *et al.* Roles and functions of community mental health nurses caring for people with schizophrenia in Taiwan. *J Clin Nurs* 2008;17:3030–40. doi:10.1111/j.1365-2702.2008.02426.x

22. Setoya N, Kayama M, Tsunoda A, *et al.* A survey of the family care provided in psychiatric home-visit nursing and related characteristics of clients. *Japanese Bulletin of Social Psychiatry* 2011;20:17–25.

23. Chan AW, Tetzlaff JM, Altman DG, *et al.* SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158:200–7. doi:10.7326/0003-4819-158-3-201302050-00583

24. Varghese M, Shah A, Kumar GSU, *et al.* Family intervention and support in schizophrenia: a manual on family intervention for the mental health professional, version 2. Bangalore, India: National Institute of Mental Health and Neurosciences.

25. Batalden M, Batalden P, Margolis P, *et al.* Coproduction of healthcare service. *BMJ Qual Safe* 2016;25:509–17. doi:10.1136/bmjqs-2015-004315

26. Ferriter M, Huband N. Experiences of parents with a son or daughter suffering from schizophrenia. *J Psychiatr Ment Health Nurs* 2003;10:552–60. doi:10.1046/j.1365-2850.2003.00624.x

27. Menezes NM, Arenovich T, Zipursky RB. A systematic review of longitudinal outcome studies of first-episode psychosis. *Psychol Med* 2006;36:1349–62. doi:10.1017/s0033291706007951

28. Amaresha AC, Venkatasubramanian G. Expressed emotion in schizophrenia: an overview. *Indian J Psychol Med* 2012;34:12–20. doi:10.4103/0253-7176.96149

29. Arai Y, Kudo K, Hosokawa T, *et al.* Reliability and validity of the Japanese version of the Zarit Caregiver Burden interview. *Psychiatry Clin Neurosci* 1997;51:281–7. doi:10.1111/j.1440-1819.1997.tb03199.x

30. Sakurai K, Nishi A, Kondo K, *et al.* Screening performance of K6/K10 and other screening instruments for mood and anxiety disorders in Japan. *Psychiatry Clin Neurosci* 2011;65:434–41. doi:10.1111/j.1440-1819.2011.02236.x

31. Sakano Y, Tohjoh M. The General Self-Efficacy Scale (GSES): scale development and validation. *Japanese Journal of Behavior Therapy* 1986;12:73–82.

32. Awata S, Bech P, Yoshida S, *et al.* Reliability and validity of the Japanese version of the World Health Organization-Five Well-Being Index in the context of detecting depression in diabetic patients. *Psychiatry Clin Neurosci* 2007;61:112–9. doi:10.1111/j.1440-1819.2007.01619.x

33. Maeda M, OM, Renri T, *et al.* It is as a result of disease drug knowledge degree investigation (Knowledge of Illness and Drugs Inventory, KIDI) for a person with IIB-29 schizophrenia and the family. *Japanese Bulletin of Social Psychiatry* 1994;2:173–4.

34. Setoya Y, N. Y., Kurita H. Utility of the Japanese version of the BASIS-32 in inpatients in psychiatric hospital. *Japanese Journal of Clinical Psychiatry* 2002;31:571–5.

35. Campbell MK, Piaggio G, Elbourne DR, *et al.* Consort 2010 statement: extension to cluster randomised trials. *BMJ* 2012;345:e5661. doi:10.1136/bmj.e5661

36. Faul F, Erdfelder E, Buchner A, *et al.* Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. *Behav Res Methods* 2009;41:1149–60. doi:10.3758/brm.41.4.1149

37. Faul F, Erdfelder E, Lang AG, *et al.* G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods* 2007;39:175–91.

38. Campbell MK, Elbourne DR, Altman DG. CONSORT statement: extension to cluster randomised trials. *BMJ* 2004;328:702–8. doi:10.1136/bmj.328.7441.702

Table 1. Outline of the brief family psychoeducation program

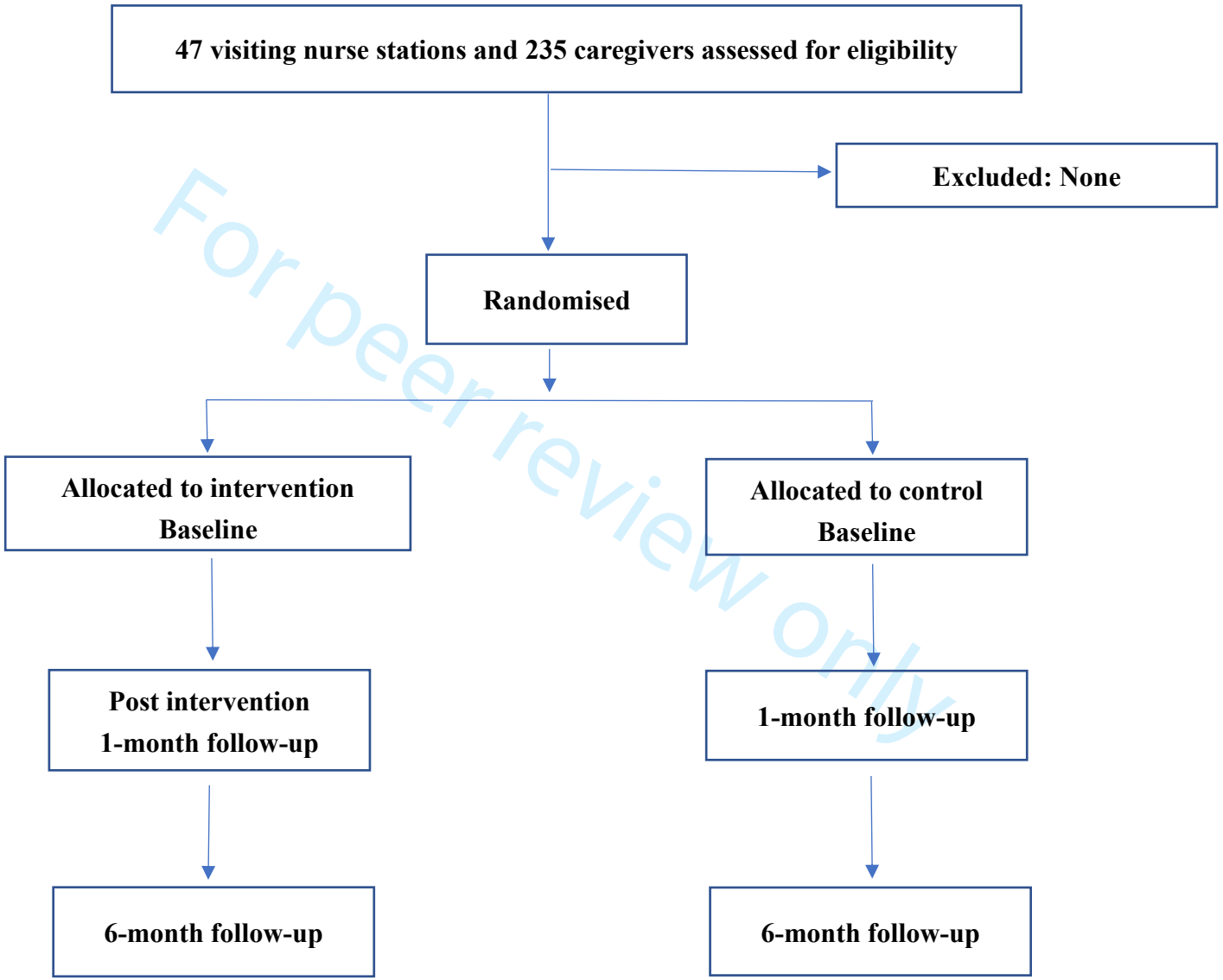
Session number	Session aim	Contents
I	General knowledge about schizophrenia	Definition, causes, symptoms, prognosis, pharmacological treatment, psychosocial rehabilitation. Work: Let's review the knowledge gained in this session.
II	How to cope with people with schizophrenia using problem-solving skills	How to cope with hallucinations and delusions; signs of recurrence and how to prevent recurrence; how to cope when the disease gets worse; what to do with people with schizophrenia when they stay at home all day; how to respond to people with schizophrenia who do not want to take their medication; what to do when domestic violence is imminent, is happening, or has happened; how to get involved when self-injury or suicide is suspected. Work: How to apply problem-solving skills.
III	Handling communication and emotions	Understanding the feelings of people with schizophrenia, expressed emotion (EE) theory, basic knowledge about communication, and a lecture about desirable and undesirable communication with people with schizophrenia. Work: Let's practice conversations using real cases.
IV	Family's recovery	Thinking about the family's recovery, importance of living one's own life, taking care of a family's physical and mental health needs, proper stress management, experiences and messages from members of the Family Association. Work: Let's identify social resources in the community and recognise the importance of connecting with many supporters around families.

This intervention program consists of four 60-minute modules completed over the period of 1 month.

Table 2. Outcome measures

	Outcome measure	Baseline	1-month follow-up	6-month follow-up
Caregivers	Zarit Burden Interview (ZBI)	✓	✓	✓
	K6	✓	✓	✓
	General Self-Efficacy Scale (GSES)	✓	✓	✓
	WHO-5	✓	✓	✓
	Knowledge of Illness and Drug Inventory (KIDI)	✓	✓	✓
People with schizophrenia	Behavior and Symptoms Identification Scale (BASIS-32)	✓	✓	✓
	WHO-5	✓	✓	✓
	Hospitalisation during the past 6 months	✓	–	✓

Figure 1. Participant flow chart



SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	ItemNo	Description	
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	P2
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	NA
Funding	4	Sources and types of financial, material, and other support	P13
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	P1
	5b	Name and contact information for the trial sponsor	NA
	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	NA
	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)	NA
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	P3-5
	6b	Explanation for choice of comparators	P3-5

Objectives	7	Specific objectives or hypotheses	P5
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)	P5
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	P5-6
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)	P5-6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	P6-8
	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)	P6-8
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	P6-8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	P6-8
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	P9-10
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)	P5-6

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	P10-11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	P5-6
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	P11
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	P11
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	P11
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	P11
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	P11
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	P11-12
	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	P11-12

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	P12
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	P11-12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	P11-12
	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)	P11-12
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	P12
	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	NA
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	NA
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	P12

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)	NA
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	P5-6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	P12
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	P13
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	P12
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	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	P13
	31b	Authorship eligibility guidelines and any intended use of professional writers	P13
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	P13
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*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 brief family psychoeducation for caregivers of people with schizophrenia in Japan provided by visiting nurses: protocol for a cluster randomized controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-034425.R1
Article Type:	Protocol
Date Submitted by the Author:	12-Dec-2019
Complete List of Authors:	Yasuma, Naonori; The University of Tokyo, ; Sato, Sayaka; National Institute of Mental Health, Community mental health and law; NCNP Yamaguchi, Sosei; National Center of Neurology and Psychiatry, Department of Community Mental Health & Law, National Institute of Mental Health Matsunaga, Asami; National Center of Neurology and Psychiatry, Department of Community Mental Health & Law, National Institute of Mental Health Shiozawa, Takuma; National Center of Neurology and Psychiatry, Watanabe, Kazuhiro; The University of Tokyo, Department of Mental Health, Graduate School of Medicine Imamura, Kotaro Tachimori, Hisateru; National Center of Neurology and Psychiatry Translational Medical Center Nishi, Daisuke Fujii, Chiyo; National Center of Neurology and Psychiatry, Department of Community Mental Health & Law, National Institute of Mental Health Kawakami, Norito; The University of Tokyo, Department of Mental Health
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Mental health
Keywords:	Brief family psychoeducation, schizophrenia, caregivers, visiting nurses

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Effects of brief family psychoeducation for caregivers of people with schizophrenia in Japan provided by visiting nurses: protocol for a cluster randomized controlled trial

Naonori Yasuma[1,2]: nnyy712@gmail.com
Sayaka Sato[2]: sayakas@ncnp.go.jp
Sosei Yamaguchi[2]: sosei.yama@ncnp.go.jp
Asami Matsunaga[2]: asamim@ncnp.go.jp
Takuma Shiozawa[2]: takuma-shozw@umin.ac.jp
Hisateru Tachimori[3]: tachi@ncnp.go.jp
Kazuhiro Watanabe[1]: kzwatanabe-tky@umin.ac.jp
Kotaro Imamura[1]: kouima-tky@umin.ac.jp
Daisuke Nishi[1]: d-nishi@m.u-tokyo.ac.jp
Chiyo Fujii[2]: chyfujii@ncnp.go.jp
Norito Kawakami[1]: nkawakami@m.u-tokyo.ac.jp

1 Department of Graduate School of Medicine, The University of Tokyo

2 Department of Community Mental Health and Law, National Institute of Mental Health, National Center of Neurology and Psychiatry, Kodaira, Tokyo, Japan

3 Department of Translational Medical Center, National Institute of Mental Health, National Center of Neurology and Psychiatry, Kodaira, Tokyo, Japan

Corresponding author:
Naonori Yasuma, MD
Department of Mental Health, Graduate School of Medicine, The University of Tokyo,
7-3-1 Hongo, Bunkyo-ku, Tokyo 1130033 Japan
E-mail: nnyy712@gmail.com
Phone: +81-3-5841-3521
Fax: +81-3-5841-3521

Word count: 4,315 words

ABSTRACT

Introduction

Development of a support system for families caring for people with schizophrenia in routine psychiatric care settings is an important issue worldwide. Regional mental health systems are inadequate for delivering effective services to such family members. Despite evidence that family psychoeducation (FPE) alleviates the burden of schizophrenia on families, its dissemination in routine clinical practice remains insufficient, suggesting the need for developing an effective and implementable intervention for family caregivers in the existing mental health system setting. In Japan, the visiting nurse service system would be a practical way of providing family services. Visiting nurses in local communities are involved in the everyday lives of people with schizophrenia and their families. Accordingly, they understand their needs and are able to provide family support as a service covered by national health insurance. The purpose of this study is to discover whether a brief FPE program provided by visiting nurses caring for people with schizophrenia will alleviate family burden through a cluster randomised controlled trial (cRCT).

Methods and analysis

The study will be a two-arm, parallel-group (a visiting nurse agency) cRCT. Forty-seven visiting nurse agencies will be randomly allocated to the brief FPE group (intervention group) or treatment as usual group (control group). Caregivers of people with schizophrenia will be randomly recruited by visiting nurses. The primary outcome will be caregiver burden, measured using the Zarit Burden Interview–Japanese version (ZBI-22). Outcome assessments will be conducted at baseline, at 1-month follow-up, and at 6-month follow-up. Multiple levels of three-way interaction of mixed models will be conducted to examine whether the brief FPE program will alleviate the burden on caregivers relative to treatment as usual.

Ethics and dissemination

The Research Ethics Committee of the Graduate School of Medicine and Faculty of Medicine, the University of Tokyo, Japan (No. 2019065NI) approved this study. The results will be published in a scientific peer-reviewed journal.

Registration number

UMIN000038044; Pre-results.

Strengths and Limitations

- This study will evaluate an implementable brief FPE program that potentially reduces time, cost, and staffing problems by incorporating the program into an existing mental health service system, namely visiting nurse services.

- This is the first cRCT of a brief FPE program, a trial with a better study design, which will provide better evidence than past studies.

- A limitation of this study is that all outcomes will be measured by self-report, which may cause information bias or random error.

INTRODUCTION

Families caring for people with schizophrenia receiving community-based mental health care have a great need for support. People with schizophrenia who have severe symptoms require long-term care, which imposes a significant burden on families providing such care.[1] For example, the financial burden on the family is severe because considerable amounts of time are devoted to caregiving, resulting in the loss of work opportunities and reduced income.[2] Moreover, insufficient downtime to recover from the stress of caregiving results in both physical and mental illnesses.[3] Families also become worn out and stressed by the demands of coping with this illness, which is characterized by repeated hallucinations and delusions if symptoms do not stabilize.[4] Furthermore, a parent of a schizophrenic son or daughter might worry about what will become of their child after his or her death. They might also feel they are not getting adequate information about what social services are available to them.[5] Stigma against the illness is also deeply rooted and can lead to families becoming socially isolated.[3] Therefore, families of people with schizophrenia have various physical, psychological, economic, and social burdens.

Several studies have addressed the development and evaluation of effective family interventions. According to a systematic review, family psychoeducation (FPE) is a scientifically effective psychological intervention that has been used to reduce caregiver burden.[6,7] The components of FPE mainly include information sharing about the disorder, early warning signs, and relapse prevention as well as and skills training in coping, communication, and problem solving.[8] FPE can directly improve caregivers' knowledge about schizophrenia and related caregiving problems.[9] Improved knowledge of coping strategies and resources can lead to a more positive appraisal of caregiving experiences by families as well as caregivers' own self-efficacy in coping with the demands of caring for people with schizophrenia, thereby lessening the burden.[6]

Despite the accumulation of evidence, there are several barriers to FPE implementation. The initial report on the Schizophrenia Patient Outcomes Research Team (PORT) Treatment Recommendations found that FPE was provided to 31.6% of inpatients and 9.6% of outpatients who could have benefited from it.[10] A nationwide survey in Japan revealed that the implementation rate for FPE programs at psychiatric facilities are similarly low: 35.9% in hospitals and 14.5% in outpatient settings.[11] One challenge in implementing these programs is the length of the intervention. Most studies have found that such interventions range from 9 months to 2 years, which is impractical for medical staff and families in a clinical setting.[12] Other reasons include funding and

staff shortages, as well as providing necessary training.[13] In Japan, even if healthcare professionals perform FPE for a family, they cannot obtain medical expenses. In addition, while the Meriden Family Program appears to be effective, training is "time-consuming and expensive."[14] The medical treatment fee system in most countries including Japan does not cover such a comprehensive family intervention. The development of a brief and implementable FPE program within the existing mental health system that is covered by national health insurance is greatly needed.[15]

Brief FPE programs have been examined in previous studies. In terms of the program framework, studies have found that brief FPE programs, delivered in five sessions or fewer or lasting no more than 3 months, were easy to conduct for both practitioners and caregivers.[16] Brief FPE programs have been shown to significantly increase caregivers' knowledge of the disorder, leading to reductions in relapse and rehospitalisation rates in diverse settings.[17,18] In addition, recent research has shown that a brief FPE program may be beneficial in reducing caregiver burden. In a pre-post test in India, a brief FPE program comprised of three 1-hour sessions aimed at educating the primary caregiver and patient about schizophrenia and imparting communication and problem-solving skills. A significant decrease in caregiver burden, measured using the Burden Assessment Scale (BAS), was found between baseline and the final follow-up at 3 months.[19] In a randomised controlled trial in Iran, brief FPE consisted of ten 90-minute sessions held over 5 weeks (two sessions each week) conducted by a psychiatric nurse or psychiatrist. Caregiver burden measured using the Family Burden Scale (FBS) was significantly reduced both immediately after the intervention and 1 month later.[20] However, the effects of brief FPE programs are still inconclusive due to relatively low methodological quality in prior studies.[7,16] In other words, evidence from a trial with a better design is needed.

Practical implementation strategies for a brief FPE program need to be considered in addition to a scientific evaluation of the effects. Brief FPE programs provided by visiting nurses appear to be a potentially feasible and sustainable way of implementing FPE in a Japanese clinical setting. Visiting nurses routinely visit clients with schizophrenia and their family members. They have already built rapport with clients and family members and would be able to respond according to their needs, which means they could seamlessly provide highly individualized brief FPE.[21] In addition, the system of visiting nurses could easily be applied because the number of visiting nurses has been increasing recently in Japan. From a cost perspective, it would be possible to make family support a reimbursable service under national health

insurance to cover psychiatric visiting nurse consultancy fees.[22] Taken together, brief FPE provided by visiting nurses could overcome the poor implementation rate and become effective family interventions in the community setting in Japan.

Hypothesis and aims

We hypothesise that brief FPE provided by visiting nurses could alleviate the burden on families and caregivers of people with schizophrenia. The aim of this study is to clarify whether visiting nurses providing brief FPE to families caring for people with schizophrenia alleviates family burden through a cluster randomised controlled trial (cRCT).

METHODS AND ANALYSIS

Trial design

This study is a two-arm, parallel-group cRCT. The randomisation procedure will be conducted at the cluster level (visiting nurse agencies). Visiting nurse agencies will be randomly assigned to the intervention or control (treatment as usual (TAU)) group in a 1:1 ratio. Data will be collected at the individual level. Analyses to evaluate the efficacy of the intervention program will be conducted at the individual level, taking into consideration cluster-level effects. The study protocol was registered in the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN-CTR ID, UMIN000038044). This protocol has been reported according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.[23] The anticipated trial start date will be 1 October 2019 and the date of last follow-up date will be 31 May 2020.

Setting and site selection at the cluster level

Figure 1 shows the participant flow chart for this study. The corresponding author (NY) explained the purpose of this study to 68 visiting nurse agencies in four prefectures in Japan (Tokyo, Saitama, Kanagawa, and Chiba) through the organisation. Forty-seven visiting nurse agencies agreed to participate in the study. All the participating visiting nurse agencies are managed by one organisation.

To be included, a visiting nurse agency must provide services mostly to psychiatric patients or clients, not elderly people or those with physical diseases. In each agency, visiting nurses care for at least two people with schizophrenia who live with their family. There are no exclusion criteria at the cluster level.

Participant eligibility criteria and recruitment procedure at the individual level

At the individual level, we set the following inclusion criteria for a caregiver of a person with schizophrenia: 1) is the primary caregiver; 2) aged over 20 years; 3) is a family member of the person with schizophrenia such as a parent, sibling, spouse, or child; and 4) lives with the person with schizophrenia. There are no exclusion criteria for caregivers. In addition, the inclusion criteria for people with schizophrenia are as follows: 1) diagnosis of schizophrenia based on the International Statistical Classification of Diseases and Related Health Problems, 10th revision and 2) use of visiting nurse services.

At each agency, potential participants (caregivers of people with schizophrenia and people with schizophrenia) will be randomly ordered using a recruitment sequence table. To avoid selection bias, the recruitment sequence table will be created using a random number generation method in the Stata statistical software program, version 15. After attending a lecture on study design and ethical considerations, visiting nurses will recruit participants in order starting from the top of the recruitment sequence table until five participants have been recruited. The study will include only participants who voluntarily agree to participate in the study.

Randomisation

Visiting nurse agencies that meet the inclusion criteria will be randomly allocated to the intervention group (brief FPE program) or the control group. Randomisation will be stratified by the median of the average caseload of visiting nurses in each agency since the effect of the intervention might differ based on this factor. If a visiting nurse has many patients, it is expected that family support will be neglected. A random sequence table will be created by a researcher (HT) in another department at our institution who is not involved in the study protocol development process. In addition, another independent researcher (SY) who is not involved in intervention and analysis will conduct the randomisation. SY will inform each visiting nurse agency of the randomisation results. The primary investigator (NY) will be blinded through the entire randomisation process.

Intervention program

The intervention program is a single-family intervention conducted by psychiatric visiting nurses. It is based on the Family Intervention and Support in Schizophrenia: A Manual on Family Intervention for the Mental Health Professional.[24] This program was developed through discussions and collaborations among members of the Family

Association of Schizophrenia, psychiatric visiting nurses, FPE experts, psychiatrists, psychiatric nurses, clinical psychologists, and mental health social workers based on the concept of coproduction and Patient and Public Involvement (PPI).[25] During the development process, we tried to avoid long sentences, enlarged the characters, and used visually appealing drawings. The program consists of four sessions that last 60 minutes each using the above tool. It will be completed over a period of a month. Psychiatric visiting nurses will provide appropriate information using this intervention tool and advice to the family about living problems based on their own nursing clinical experience. We will also create a checklist to confirm how many sessions visiting nurses are actually able to conduct with the participants.

Before the intervention, we will provide the intervention team of psychiatric visiting nurses with a 1-day lecture. The lecture will consist of three parts. First, a caregiver of a person with schizophrenia will talk about their life problems and what they want visiting nurses to do; this is expected to increase the motivation of visiting nurses. Second, basic communication training will be conducted through role-playing. Visiting nurses, who will be brief FPE providers, will be in groups of three. They will each play the role of a visiting nurse, caregiver, and evaluator. They will practice listening to caregivers. Third, the primary investigator (NY) will equip them with basic knowledge about FPE and explain the contents of this intervention tool and the points the primary investigator wants to emphasise. Through these trainings, we expect to improve the motivation, knowledge, and skills of the visiting nurses in providing the brief FPE program.

Table 1 shows the contents of the intervention tool. Session I will cover general knowledge about schizophrenia: definition, causes, symptoms, prognosis, pharmacological treatment, and psychosocial rehabilitation. Regarding definition and causes, visiting nurses will stress that schizophrenia is a brain disease that can manifest in anyone using the diathesis-stress model and the dopamine hypothesis. It is important to provide the family with a biological explanation about the aetiology of schizophrenia because there might be family members who think people become schizophrenic because of family relationships.[26] In addition to an explanation of the symptoms themselves, visiting nurses will describe how people with schizophrenia have difficulties living their own lives due to their symptoms. Visiting nurses will explain the disease course such as the prodromal phase, acute phase, and recovery phase. Next, visiting nurses will explain the characteristics of each phase and what to do during each phase. In terms of prognosis, visiting nurses will emphasise that schizophrenia is not necessarily a disease with a bad prognosis. In people with their first episode of

schizophrenia, about 70% will have a good intermediate to long-term outcome if they receive appropriate pharmacological therapy.[27] Concerning medication, visiting nurses will appreciate the idea that people with schizophrenia usually do not want to take medication. Visiting nurses will talk about the necessity, safety, and reasons for adherence to pharmacological therapy. In addition, the side effects of antipsychotic medications will be described clearly, using relevant pictures. Finally, visiting nurses will give an outline of psychosocial therapy. At the end, participants will answer questions with dichotomous answers—"yes" or "no"—to confirm what they have learned from the session.

Session II will deal with how to cope with people with schizophrenia and problem-solving skills. The contents of this session include how to cope with hallucinations and delusions; signs of recurrence; how to prevent recurrences; how to cope when the disease gets worse; what to do with people with schizophrenia when they stay at home all day; how to respond to people with schizophrenia who do not want to take their medication; how to respond when domestic violence is imminent, is occurring, or has occurred; and how to get involved when self-injury or suicide is suspected. Finally, visiting nurses will explain problem-solving skills. In the routine clinical setting, the family will work on matters that are causing trouble in daily life using problem-solving skills.

Session III will cover communication and emotions: understanding the feelings of people with schizophrenia, expressed emotion (EE) theory, basic knowledge and skills about communication, and a lecture on desirable and undesirable communication with people with schizophrenia. In the first section, visiting nurses will describe the importance of understanding that people with schizophrenia are likely to have a pessimistic view about their future. In the second section on EE theory, visiting nurses will appreciate that it is natural for a family to have high EE with poor knowledge and lack of support about mental illness.[28] Of note, visiting nurses will not force family members to play the role of supporter. When family members hear the explanation of high EE, many might feel that they are responsible for their burden. Visiting nurses will emphasise that both families and people with schizophrenia should think about positive and constructive communication to ensure mutual independence. In the third section on basic knowledge about communication and the lecture of desirable and undesirable communication with patients, caregivers will practice conversations using real cases and will be given time to consider better communication strategies.

Session IV will focus on the family's recovery. Topics will include thinking about the family's recovery, the importance of living one's own life, taking care of the

family's physical and mental health needs, proper stress management, experiences and messages from members of the Family Association, and identifying available social resources in the community. During this session, visiting nurses will stress that people with schizophrenia and family members each have their own lifestyle and individual goals. Visiting nurses will also encourage family members to live their own lives using a variety of social resources instead of only working hard to take care of a person with schizophrenia. In addition, visiting nurses expect that family members will improve their physical and mental health by acquiring knowledge on self-care and stress management skills. Furthermore, visiting nurses will introduce the experiences of three members of the Family Association who have taken care of a person with schizophrenia. It is expected that others' similar experiences will help family members understand that they are not the only people experiencing such a hard time and relieve their feelings of sadness or hopelessness. Finally, visiting nurses will explain the social resources available in the community for family members and confirm the importance of connecting with many supporters around them.

Control group

Caregivers enrolled in the control group will receive usual care from visiting nurses. They will be put on a waiting list to receive the same intervention program after completing the 6-month follow-up assessment. They will not receive any type of psychoeducation or supportive therapies.

Outcomes

Table 2 shows an overview of the outcome measures. Outcome measures will be assessed at baseline prior to the intervention (T1), immediately after the completion of the intervention (1-month follow-up, T2), and 6 months after the baseline assessment (6-month follow-up, T3).

Primary outcome for caregivers

Zarit Burden Interview (ZBI-22)

ZBI-22 will be used to measure caregiver burden. It consists of 22 items scored on a five-point Likert scale from 0 (never) to 4 (nearly always), except for the final item on global burden, which is rated from 0 (not at all) to 4 (extremely). The total score ranges from 0 to 88, with higher scores indicating higher burden. The Japanese version of ZBI-22 had a high test-retest reproducibility and internal consistency. Construct validity has also been confirmed.[29]

Secondary outcome for caregivers

K6

K6 will be used to measure sub-clinical depression and anxiety disorders as part of a self-administered questionnaire. It consists of six items answered on a five-point Likert scale. Scores range from 0 to 24, with higher scores representing higher degrees of sub-clinical depression and anxiety disorder. The Japanese versions of the K6 have essentially equivalent screening performance as the original English versions.[30]

General Self Efficacy Scale (GSES)

GSES is a measurement of self-efficacy in daily living. It includes 16 items with dichotomous questions. The higher the score, the better the self-efficacy, in general. GSES had high test-retest reproducibility and internal consistency. Construct validity has been confirmed.[31]

WHO-5

WHO-5 will be used to measure subjective quality of life based on positive mood (good spirits and relaxation), vitality (being active and waking up fresh and rested), and general interest (being interested in things). It consists of five items rated on a six-point Likert scale. Higher scores mean higher well-being. The Japanese version of WHO-5 has adequate internal consistency. It has been confirmed to have external concurrent validity and external discriminatory validity.[32]

Knowledge of Illness and Drug Inventory (KIDI)

KIDI will be used to assess knowledge regarding mental illness and the effects of medications on mental illness. There are two sub-scales: 10 items assessing knowledge of mental illness and 10 items assessing knowledge of the effects of antipsychotic drugs. This inventory consists of a self-reported inventory where respondents are asked to select the correct answer from three choices, with higher scores representing greater knowledge. KIDI is frequently used to assess knowledge about mental disorders and treatments in Japan.[33]

Secondary outcomes in people with schizophrenia

Behavior and Symptom Identification Scale (BASIS-32)

BASIS-32 is a commonly used measure in mental health. It includes 32 items on a five-point Likert scale, where 0 indicates no difficulties and 4 indicates severe difficulties.

The scale measures five factors: (1) relation to self and others (seven items); (2) depression/anxiety (six items); (3) everyday life and role functioning (nine items); (4) impulsive and addictive behaviour (six items); and (5) psychosis (four items). Factors 1, 2, 4, and 5 are assessed as the total score divided by the number of items answered (mean score), while factor 3 is assessed based non the highest rating. Internal consistency and construct validity of the Japanese version of BASIS-32 have been demonstrated.[34]

WHO-5

WHO-5 is used to measure subjective quality of life based on positive mood (good spirits and relaxation), vitality (being active and waking up fresh and rested), and general interest (being interested in things). WHO-5 comprises five items rated on a six-point Likert scale. Higher scores mean higher well-being. The Japanese version of WHO-5 has adequate internal consistency. It has been confirmed to have external concurrent validity and external discriminatory validity.[32]

Hospitalisation by 6-month follow-up

This is a question with a dichotomous answer (yes or no) about whether the patient has been hospitalised during the past 6 months. The answer will be provided by the caregiver at baseline and the 6-month follow-up.

Sample size calculation

The sample size required was calculated according to guidelines in the Consolidated Standards of Reporting Trials (CONSORT) for cRCTs,[35] taking into account intra-class correlations (ICCs). The effect size of a brief FPE program for individual caregiver burden was estimated based on a previous pre-post test.[19] The pre-post test concluded that the standardised mean difference (d) of brief FPE on family burden was 0.46. Sample size was estimated as 76 in each arm based on an alpha error probability of 0.05 and power (1-β) of 0.80, using G*Power version 3.1.9.2.[36 37] cRCTs should be multiplied by design effect (1+[m-1]ρ), where m is the average cluster size and ρ is the ICC.[38] The estimated ICC for the primary outcome in this study was set to 0.05 and the average number of caregivers per cluster was set at five people. Assuming an attrition rate of 20%, the required sample size is 110 caregivers in each arm; thus, at least 44 visiting nurse agencies will be recruited.

Quantitative analysis

The statistician will be blinded to the treatment group. We will analyse clinical outcomes on the basis of intention to treat and model the effect of the intervention on primary and secondary continuous outcomes using generalised linear latent and mixed models (GLLAMMs). This will allow for missing data to be taken into account within the statistical model. In this study, a three-level model will be used, with repeated measures nested in participants and participants nested in clusters. Time (baseline, 1-month follow-up, 6-month follow-up) will be considered level 1, individual caregivers will be considered level 2, and clusters (visiting nurse stations) will be considered level 3. Regarding fixed effects, condition (intervention versus control), time, and a two-way interaction effect, condition by time, will be included. Models will adjust for baseline differences in caregiver socio-demographics such as age, gender, education, household income, family relationship with the person with schizophrenia, length of caregiving, and length of visiting nurse system use. Multiple levels of Cox proportional hazards regression models will also be used for the dichotomous question of hospitalisation at the 6-month follow-up. A *p*-value of less than 0.05 will be considered statistically significant.

Data monitoring

A data monitoring committee (DMC) will be set up. It will consist of at least two independent members. The DMC will meet monthly after the first participant has been randomised. The purpose of the meeting will be to review participation rates and reasons for study dropout. The DMC will be independent from any sponsor and competing interest.

Patient and public involvement

The research question, study design, and outcome measures were determined based on a discussion with representatives of the Family Association of Schizophrenia. The intervention program was also developed through the discussion and collaboration among members of the Family Association of Schizophrenia, psychiatric visiting nurses, FPE experts, psychiatrists, psychiatric nurses, clinical psychologists, and mental health social workers. After the completion of the study, this intervention tool will be available for anyone who wants to use it via the internet.

Ethics and dissemination

Ethical considerations

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The study protocol was approved by the Research Ethics Committee of the Graduate School of Medicine and the Faculty of Medicine at the University of Tokyo, Japan (No. 2019065NI). We will obtain informed consent from all caregivers and patients. The consent form will inform caregivers and patients that we guarantee protection of personal information and that the data will be anonymous and used only for academic purposes. There are no competing interests. This study is supported by fundamental study on effective community services for people with severe mental disorders and their families.

Dissemination of the research findings

The findings will be published in a scientific peer-reviewed journal according to the CONSORT guidelines for cRCTs.[35] The participants will be informed of conference presentations and publications.

Strengths and limitations

The study has both strengths and limitations. First, the study will evaluate an implementable brief FPE program that potentially reduces time, cost, and staffing problems by incorporating the program into an existing mental health service system, namely visiting nurse services. Second, this is the first cRCT of a brief FPE program, a trial with a better study design. It will provide better evidence than past studies. Third, based on the concept of coproduction and PPI,[25] the study incorporated a variety of viewpoints from caregivers, visiting nurses, and FPE experts.

We recognise three limitations of this study. First, since the sampling method for participating agencies was not random, there is a possibility of selection bias. Second, since subjects will provide data through a self-reported questionnaire, information bias or random error is possible. For example, the severity of symptoms in people with schizophrenia that impact a caregiver's burden may not be accurately measured. Third, we designed the study and intervention based on coproduction, but there are still concerns about its feasibility in actual clinical settings. For example, participants might not complete all four sessions due to the condition of people with schizophrenia, family work, and family hospitalisation. These may lead to a high attrition rate during implementation.

Acknowledgments

The authors would like to thank the members of the *Mokuseikai* Family Association of Schizophrenia for their invaluable advice on many aspects of the project.

Contributors

NY is the principal investigator responsible for the initial draft of this manuscript and organising and implementing the study. NY and KW calculated the sample size. NY, KW, SY, and MA decided on the analytic strategy. SS, TS, HT, KI, DN, CF and NK helped throughout the development of the interventions and gave valuable feedback to the present study protocol. All authors have read and approved the final manuscript.

Funding: This work is supported by Fundamental study on effective community services for people with severe mental disorders and their families.

Competing interests: None declared.

Patient Consent: Obtained.

Ethics approval: Research Committee of the Graduate School of Medicine and the Faculty of Medicine at the University of Tokyo, Japan.

REFERENCES

1. Awad AG, Voruganti LN. The burden of schizophrenia on caregivers: a review. *Pharmacoecon Open* 2008;26:149–62. doi:10.2165/00019053-200826020-00005

2. Saunders JC. Families living with severe mental illness: a literature review. *Issues Ment Health Nurs* 2003;24:175–98. doi:10.1080/01612840305301

3. Shah AJ, Wadoo O, Latoo J. Psychological distress in carers of people with mental disorders. *British Journal of Medical Practitioners* 2010;3:a327.

4. Gopinath PA, Chaturvedi S. Distress behaviour of schizophrenics at home. *Acta Psychiatr Scand* 1992;86:185–8. doi:10.1111/j.1600-0447.1992.tb03249.x

5. McAuliffe R, O'Connor L, Meagher D. Parents' experience of living with and caring for an adult son or daughter with schizophrenia at home in Ireland: a qualitative study. *J Psychiatr Ment Health Nurs* 2014;21:145–53. doi:10.1111/jpm.12065

6. Sin J, Gillard S, Spain D, *et al.* Effectiveness of psychoeducational interventions for family carers of people with psychosis: a systematic review and meta-analysis. *Clin Psychol Rev* 2017;56:13–24. doi:10.1016/j.cpr.2017.05.002

7. Sin J, Jordan CD, Barley EA, *et al.* Psychoeducation for siblings of people with severe mental illness. *Cochrane Database Syst Rev* 2015;5:Cd010540. doi:10.1002/14651858.CD010540.pub2

8. Dixon L, McFarlane WR, Lefley H, *et al.* Evidence-based practices for services to families of people with psychiatric disabilities. *Psychiatr Serv* 2001;52:903–10. doi:10.1176/appi.ps.52.7.903

9. Birchwood M, Smith J, Cochrane R. Specific and non-specific effects of educational intervention for families living with schizophrenia. A comparison of three methods. *Br J Psychiatry* 1992;160:806–14. doi:10.1192/bjp.160.6.806

10. Lehman AF, Steinwachs DM. Patterns of usual care for schizophrenia: initial results from the Schizophrenia Patient Outcomes Research Team (PORT) Client Survey. *Schizophr Bull* 1998;24:11–20; discussion 20–32. doi:10.1093/oxfordjournals.schbul.a033303

11. Oshima I, Mino Y, Nakamura Y, *et al.* Implementation and dissemination of family psychoeducation in Japan: nationwide survey on psychiatric hospitals in 1995 and 2001. *Journal of Social Policy & Social Work* 2007;11:5–16.

12. Rummel-Kluge C, Kissling W. Psychoeducation in schizophrenia: new developments and approaches in the field. *Curr Opin Psychiatry* 2008;21:168–72. doi:10.1097/YCO.0b013e3282f4e574

13. Harvey C. Family psychoeducation for people living with schizophrenia and their families. *BJPsych Adv* 2018;24:9–19. doi:10.1192/bja.2017.4

14. Fadden G, Heelis R. 2011. The Meriden Family Programme: lessons learned over 10 years. *J Ment Health* 2011;20:79–88. doi:10.3109/09638237.2010.492413 [published online first: 2 September 2010].

15. McFarlane WR, Dixon L, Lukens E, *et al.* Family psychoeducation and schizophrenia: a review of the literature. *J Marital Fam Ther* 2003;29:223–45.

16. Okpokoro U, Adams CE, Sampson S. Family intervention (brief) for schizophrenia. *Cochrane Database Syst Rev* 2014;3:Cd009802. doi:10.1002/14651858.CD009802.pub2

17. Pitschel-Walz G, Leucht S, Bauml J, *et al.* The effect of family interventions on relapse and rehospitalization in schizophrenia—a meta-analysis. *Schizophr Bull* 2001;27:73–92. doi:10.1093/oxfordjournals.schbul.a006861.

18. Smith JV, Birchwood MJ. Specific and non-specific effects of educational intervention with families living with a schizophrenic relative. *Br J Psychiatry* 1987;150:645–52. doi:10.1192/bjp.150.5.645.

19. Devaramane V, Pai NB, Vella SL. The effect of a brief family intervention on primary carer's functioning and their schizophrenic relatives levels of psychopathology in India. *Asian J Psychiatr* 2011;4:183–7. doi:10.1016/j.ajp.2011.06.004

20. Sharif F, Shaygan M, Mani A. Effect of a psycho-educational intervention for family members on caregiver burdens and psychiatric symptoms in patients with schizophrenia in Shiraz, Iran. *BMC Psychiatry* 2012;12:48. doi:10.1186/1471-244x-12-48

21. Huang XY, Ma WF, Shih HH, *et al.* Roles and functions of community mental health nurses caring for people with schizophrenia in Taiwan. *J Clin Nurs* 2008;17:3030–40. doi:10.1111/j.1365-2702.2008.02426.x

22. Setoya N, Kayama M, Tsunoda A, *et al.* A survey of the family care provided in psychiatric home-visit nursing and related characteristics of clients. *Japanese Bulletin of Social Psychiatry* 2011;20:17–25.

23. Chan AW, Tetzlaff JM, Altman DG, *et al.* SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158:200–7. doi:10.7326/0003-4819-158-3-201302050-00583

24. Varghese M, Shah A, Kumar GSU, *et al.* Family intervention and support in schizophrenia: a manual on family intervention for the mental health professional, version 2. Bangalore, India: National Institute of Mental Health and Neurosciences.

25. Batalden M, Batalden P, Margolis P, *et al.* Coproduction of healthcare service. *BMJ Qual Safe* 2016;25:509–17. doi:10.1136/bmjqs-2015-004315

26. Ferriter M, Huband N. Experiences of parents with a son or daughter suffering from schizophrenia. *J Psychiatr Ment Health Nurs* 2003;10:552–60. doi:10.1046/j.1365-2850.2003.00624.x

27. Menezes NM, Arenovich T, Zipursky RB. A systematic review of longitudinal outcome studies of first-episode psychosis. *Psychol Med* 2006;36:1349–62. doi:10.1017/s0033291706007951

28. Amaresha AC, Venkatasubramanian G. Expressed emotion in schizophrenia: an overview. *Indian J Psychol Med* 2012;34:12–20. doi:10.4103/0253-7176.96149

29. Arai Y, Kudo K, Hosokawa T, *et al.* Reliability and validity of the Japanese version of the Zarit Caregiver Burden interview. *Psychiatry Clin Neurosci* 1997;51:281–7. doi:10.1111/j.1440-1819.1997.tb03199.x

30. Sakurai K, Nishi A, Kondo K, *et al.* Screening performance of K6/K10 and other screening instruments for mood and anxiety disorders in Japan. *Psychiatry Clin Neurosci* 2011;65:434–41. doi:10.1111/j.1440-1819.2011.02236.x

31. Sakano Y, Tohjoh M. The General Self-Efficacy Scale (GSES): scale development and validation. *Japanese Journal of Behavior Therapy* 1986;12:73–82.

32. Awata S, Bech P, Yoshida S, *et al.* Reliability and validity of the Japanese version of the World Health Organization-Five Well-Being Index in the context of detecting depression in diabetic patients. *Psychiatry Clin Neurosci* 2007;61:112–9. doi:10.1111/j.1440-1819.2007.01619.x

33. Maeda M, OM, Renri T, *et al.* It is as a result of disease drug knowledge degree investigation (Knowledge of Illness and Drugs Inventory, KIDI) for a person with IIB-29 schizophrenia and the family. *Japanese Bulletin of Social Psychiatry* 1994;2:173–4.

34. Setoya Y, N. Y., Kurita H. Utility of the Japanese version of the BASIS-32 in inpatients in psychiatric hospital. *Japanese Journal of Clinical Psychiatry* 2002;31:571–5.

35. Campbell MK, Piaggio G, Elbourne DR, *et al.* Consort 2010 statement: extension to cluster randomised trials. *BMJ* 2012;345:e5661. doi:10.1136/bmj.e5661

36. Faul F, Erdfelder E, Buchner A, *et al.* Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. *Behav Res Methods* 2009;41:1149–60. doi:10.3758/brm.41.4.1149

37. Faul F, Erdfelder E, Lang AG, *et al.* G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods* 2007;39:175–91.

38. Campbell MK, Elbourne DR, Altman DG. CONSORT statement: extension to cluster randomised trials. *BMJ* 2004;328:702–8. doi:10.1136/bmj.328.7441.702

Table 1. Outline of the brief family psychoeducation program

Session number	Session aim	Content
I	General knowledge about schizophrenia	Definition, causes, symptoms, prognosis, pharmacological treatment, psychosocial rehabilitation. Activity: Let's review the knowledge gained in this session.
II	How to cope with people with schizophrenia using problem-solving skills	How to cope with hallucinations and delusions; signs of recurrence and how to prevent recurrence; how to cope when the disease gets worse; what to do with people with schizophrenia when they stay at home all day; how to respond to people with schizophrenia who do not want to take their medication; what to do when domestic violence is imminent, is happening, or has happened; how to get involved when self-injury or suicide is suspected. Activity: Let's learn how to apply problem-solving skills.
III	Handling communication and emotions	Understanding the feelings of people with schizophrenia, expressed emotion theory, basic knowledge about communication, and lecture about desirable and undesirable communication with people with schizophrenia. Activity: Let's practice conversations using real cases.
IV	Family recovery	Thinking about the family's recovery, importance of living one's own life, taking care of the family's physical and mental health needs, proper stress management, and experiences and messages from members of the Family Association. Activity: Let's identify social resources in the community and recognise the importance of connecting with many supporters around families.

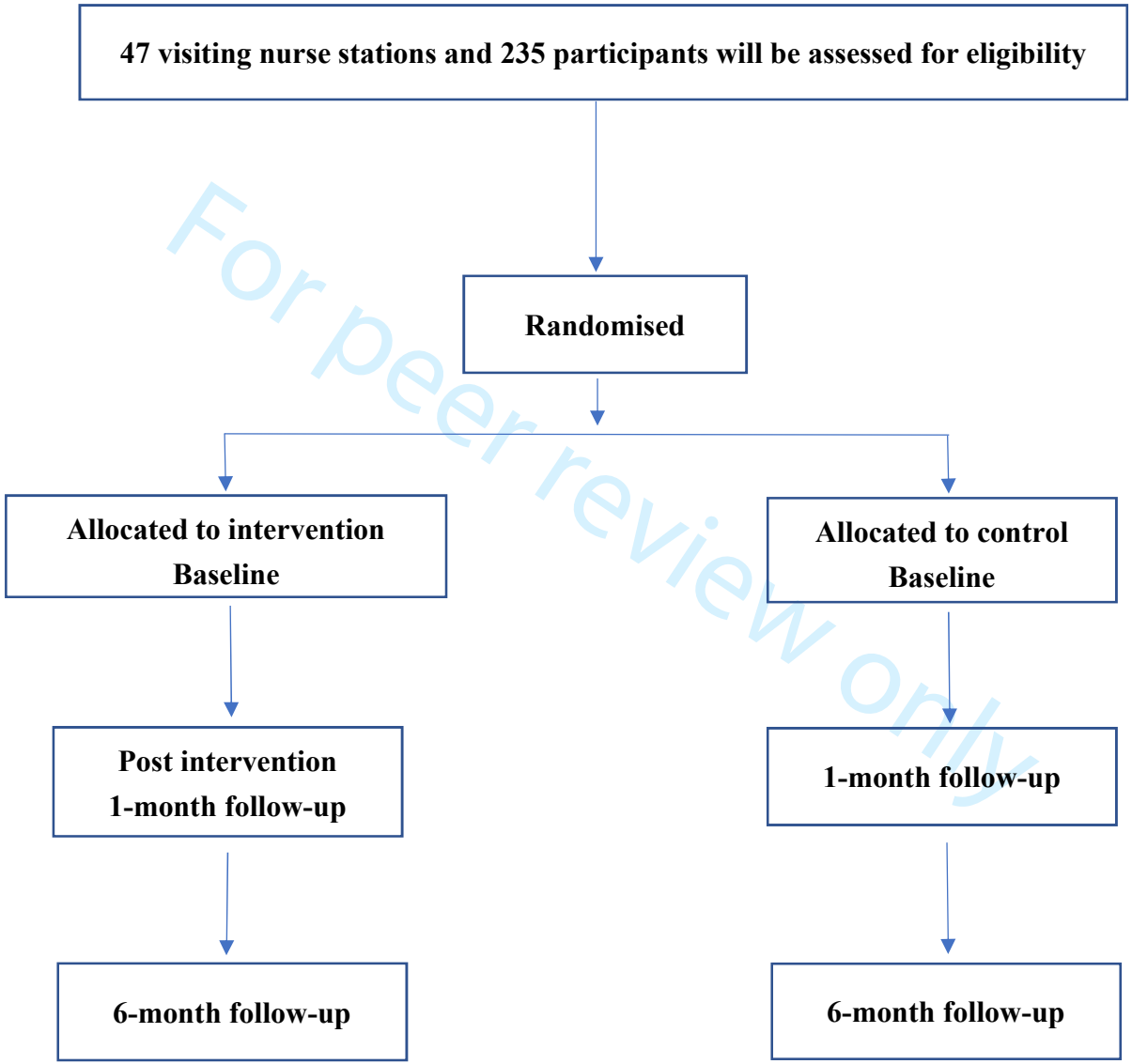
This intervention program consists of four 60-minute modules completed over 1 month.

Table 2. Outcome measures

	Outcome measure	Baseline	1-month follow-up	6-month follow-up
Caregivers	Zarit Burden Interview (ZBI-22)	✓	✓	✓
	K6	✓	✓	✓
	General Self-Efficacy Scale (GSES)	✓	✓	✓
	WHO-5	✓	✓	✓
	Knowledge of Illness and Drug Inventory (KIDI)	✓	✓	✓
People with schizophrenia	Behavior and Symptom Identification Scale (BASIS-32)	✓	✓	✓
	WHO-5	✓	✓	✓
	Hospitalisation during the past 6 months	✓	–	✓

Figure 1: Participant flow chart

Figure 1. Participant flow chart



SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	ItemNo	Description	
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	P2
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	NA
Funding	4	Sources and types of financial, material, and other support	P15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	P1
	5b	Name and contact information for the trial sponsor	NA
	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	NA
	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)	NA
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	P4-6

	6b	Explanation for choice of comparators	P4-6
Objectives	7	Specific objectives or hypotheses	P6
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)	P6
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	P6-7
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)	P6-7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	P7-9
	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)	P7-9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	P7-9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	P7-9
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	P10-12
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)	P6-7

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	P12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	P6-7
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	P7
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	P7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	P7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	P7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	P7
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	P13

	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	P13
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	P13
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	P12-13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	P12-13
	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)	P12-13
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	P13
	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	NA
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	NA
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	P13-P14
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)	NA
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	P6-7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	P13
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	P15
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	P16
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	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	P14
	31b	Authorship eligibility guidelines and any intended use of professional writers	P14
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	P14

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	See supplementary file
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*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 brief family psychoeducation for caregivers of people with schizophrenia in Japan provided by visiting nurses: protocol for a cluster randomised controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-034425.R2
Article Type:	Protocol
Date Submitted by the Author:	02-Mar-2020
Complete List of Authors:	Yasuma, Naonori; The University of Tokyo, ; Sato, Sayaka; National Institute of Mental Health, Community mental health and law; NCNP Yamaguchi, Sosei; National Center of Neurology and Psychiatry, Department of Community Mental Health & Law, National Institute of Mental Health Matsunaga, Asami; National Center of Neurology and Psychiatry, Department of Community Mental Health & Law, National Institute of Mental Health Shiozawa, Takuma; National Center of Neurology and Psychiatry, Tachimori, Hisateru; National Center of Neurology and Psychiatry Translational Medical Center Watanabe, Kazuhiro; The University of Tokyo, Department of Mental Health, Graduate School of Medicine Imamura, Kotaro Nishi, Daisuke Fujii, Chiyo; National Center of Neurology and Psychiatry, Department of Community Mental Health & Law, National Institute of Mental Health Kawakami, Norito; The University of Tokyo, Department of Mental Health
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Mental health
Keywords:	Brief family psychoeducation, schizophrenia, caregivers, visiting nurses

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Effects of brief family psychoeducation for caregivers of people with schizophrenia in Japan provided by visiting nurses: protocol for a cluster randomised controlled trial

Naonori Yasuma[1,2]: nnyy712@gmail.com
Sayaka Sato[2]: sayakas@ncnp.go.jp
Sosei Yamaguchi[2]: sosei.yama@ncnp.go.jp
Asami Matsunaga[2]: asamim@ncnp.go.jp
Takuma Shiozawa[2]: takuma-shozw@umin.ac.jp
Hisateru Tachimori[3]: tachi@ncnp.go.jp
Kazuhiro Watanabe[1]: kzwatanabe-tky@umin.ac.jp
Kotaro Imamura[1]: kouima-tky@umin.ac.jp
Daisuke Nishi[1]: d-nishi@m.u-tokyo.ac.jp
Chiyo Fujii[2]: chyfujii@ncnp.go.jp
Norito Kawakami[1]: nkawakami@m.u-tokyo.ac.jp

1 Department of Graduate School of Medicine, The University of Tokyo

2 Department of Community Mental Health and Law, National Institute of Mental Health, National Center of Neurology and Psychiatry, Kodaira, Tokyo, Japan

3 Department of Translational Medical Center, National Institute of Mental Health, National Center of Neurology and Psychiatry, Kodaira, Tokyo, Japan

Corresponding author:
Naonori Yasuma, MD
Department of Mental Health, Graduate School of Medicine, The University of Tokyo,
7-3-1 Hongo, Bunkyo-ku, Tokyo 1130033 Japan
E-mail: nnyy712@gmail.com
Phone: +81-3-5841-3521
Fax: +81-3-5841-3521

Word count: 6,266 words

ABSTRACT

Introduction

Development of a support system for families caring for people with schizophrenia in routine psychiatric care settings is an important issue worldwide. Regional mental health systems are inadequate for delivering effective services to such family members. Despite evidence that family psychoeducation (FPE) alleviates the burden of schizophrenia on families, its dissemination in routine clinical practice remains insufficient, suggesting the need for developing an effective and implementable intervention for family caregivers in the existing mental health system setting. In Japan, the visiting nurse service system would be a practical way of providing family services. Visiting nurses in local communities are involved in the everyday lives of people with schizophrenia and their families. Accordingly, they understand their needs and are able to provide family support as a service covered by national health insurance. The purpose of this study is to discover whether a brief FPE program provided by visiting nurses caring for people with schizophrenia will alleviate family burden through a cluster randomised controlled trial (cRCT).

Methods and analysis

The study will be a two-arm, parallel-group (a visiting nurse agency) cRCT. Forty-seven visiting nurse agencies will be randomly allocated to the brief FPE group (intervention group) or treatment as usual group (control group). Caregivers of people with schizophrenia will be recruited by visiting nurses using a randomly ordered list. The primary outcome will be caregiver burden, measured using the Zarit Burden Interview–Japanese version (ZBI-22). Outcome assessments will be conducted at baseline, at 1-month follow-up, and at 6-month follow-up. Multiple levels of three-way interaction of mixed models will be conducted to examine whether the brief FPE program will alleviate the burden on caregivers relative to treatment as usual.

Ethics and dissemination

The Research Ethics Committee of the Graduate School of Medicine and Faculty of Medicine, the University of Tokyo, Japan (No. 2019065NI) approved this study. The results will be published in a scientific peer-reviewed journal.

Registration number

UMIN000038044; Pre-results.

Strengths and Limitations

- This study will evaluate an implementable brief family psychoeducation (FPE) program that potentially reduces time, cost, and staffing problems by incorporating the program into an existing mental health service system, namely visiting nurse services.

- The study incorporated a variety of viewpoints from caregivers, visiting nurses, and FPE experts based on the concept of coproduction and Patient and Public Involvement (PPI).

- One study limitation is that all outcomes will be based on self-reports, which may cause information bias or random error.

INTRODUCTION

Families caring for people with schizophrenia receiving community-based mental health care have a great need for support. People with schizophrenia who have severe symptoms require long-term care, which imposes a significant burden on families providing such care.[1] For example, the financial burden on the family is severe because considerable amounts of time are devoted to caregiving, resulting in the loss of work opportunities and reduced income.[2] Moreover, insufficient downtime to recover from the stress of caregiving results in both physical and mental illnesses.[3] Families also become worn out and stressed by the demands of coping with this illness, which is characterized by repeated hallucinations and delusions if symptoms do not stabilize.[4] Furthermore, a parent of a schizophrenic son or daughter might worry about what will become of their child after his or her death. They might also feel they are not getting adequate information about what social services are available to them.[5] Stigma against the illness is also deeply rooted and can lead to families becoming socially isolated.[3] Therefore, families of people with schizophrenia have various physical, psychological, economic, and social burdens.

Several studies have addressed the development and evaluation of effective family interventions. According to a systematic review, family psychoeducation (FPE) is a scientifically effective psychological intervention that has been used to reduce caregiver burden.[6,7] The components of FPE mainly include information sharing about the disorder, early warning signs, and relapse prevention as well as and skills training in coping, communication, and problem solving.[8] FPE can directly improve caregivers' knowledge about schizophrenia and related caregiving problems.[9] Improved knowledge of coping strategies and resources can lead to a more positive appraisal of caregiving experiences by families as well as caregivers' own self-efficacy in coping with the demands of caring for people with schizophrenia, thereby lessening the burden.[6]

Despite the accumulation of evidence, there are several barriers to FPE implementation. The initial report on the Schizophrenia Patient Outcomes Research Team (PORT) Treatment Recommendations found that FPE was provided to 31.6% of inpatients and 9.6% of outpatients who could have benefited from it.[10] A nationwide survey in Japan revealed that the implementation rate for FPE programs at psychiatric facilities are similarly low: 35.9% in hospitals and 14.5% in outpatient settings.[11] One challenge in implementing these programs is the length of the intervention. Most studies have found that such interventions range from 9 months to 2 years, which is impractical for medical staff and families in a clinical setting.[12] Other reasons include funding and staff shortages, as well as providing necessary training.[13] In Japan, even if healthcare

professionals perform FPE for a family, they cannot obtain medical expenses. In addition, while the Meriden Family Program appears to be effective, training is time-consuming and expensive.[14] The medical treatment fee system in most countries including Japan does not cover such a comprehensive family intervention. The development of a brief and implementable FPE program within the existing mental health system that is covered by national health insurance is greatly needed.[15]

Brief FPE programs have been examined in previous studies. In terms of the program framework, studies have found that brief FPE programs, delivered in five sessions or fewer or lasting no more than 3 months, were easy to conduct for both practitioners and caregivers.[16] Brief FPE programs have been shown to significantly increase caregivers' knowledge of the disorder, leading to reductions in relapse and rehospitalisation rates in diverse settings.[17,18] In addition, recent research has shown that a brief FPE program may be beneficial in reducing caregiver burden. In a pre-post test in India, a brief FPE program comprised of three 1-hour sessions aimed at educating the primary caregiver and patient about schizophrenia and imparting communication and problem-solving skills. A significant decrease in caregiver burden, measured using the Burden Assessment Scale (BAS), was found between baseline and the final follow-up at 3 months.[19] In a randomised controlled trial in Iran, brief FPE consisted of ten 90-minute sessions held over 5 weeks (two sessions each week) conducted by a psychiatric nurse or psychiatrist. Caregiver burden measured using the Family Burden Scale (FBS) was significantly reduced both immediately after the intervention and 1 month later.[20] However, the effects of brief FPE programs are still inconclusive due to relatively low methodological quality in prior studies.[7,16] In other words, evidence from a trial with a better design is needed.

Practical implementation strategies for a brief FPE program need to be considered in addition to a scientific evaluation of the effects. Brief FPE programs provided by visiting nurses appear to be a potentially feasible and sustainable way of implementing FPE in a Japanese clinical setting. Visiting nurses routinely visit clients with schizophrenia and their family members. They have already built rapport with clients and family members and would be able to respond according to their needs, which means they could seamlessly provide highly individualized brief FPE.[21] In addition, the system of visiting nurses could easily be applied because the number of visiting nurses has been increasing recently in Japan. From a cost perspective, it would be possible to make family support a reimbursable service under national health insurance to cover psychiatric visiting nurse consultancy fees.[22] Taken together, brief

FPE provided by visiting nurses could overcome the poor implementation rate and become effective family interventions in the community setting in Japan.

Hypothesis and aims

We hypothesise that brief FPE provided by visiting nurses could alleviate the burden on families and caregivers of people with schizophrenia. The aim of this study is to clarify whether visiting nurses providing brief FPE to families caring for people with schizophrenia alleviates family burden through a cluster randomised controlled trial (cRCT).

METHODS AND ANALYSIS

Trial design

This study is a two-arm, parallel-group cRCT. The randomisation procedure will be conducted at the cluster level (visiting nurse agencies). Visiting nurse agencies will be randomly assigned to the intervention or control (treatment as usual (TAU)) group in a 1:1 ratio. Data will be collected at the individual level. Analyses to evaluate the efficacy of the intervention program will be conducted at the individual level, taking into consideration cluster-level effects. The study protocol was registered in the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN-CTR ID, UMIN000038044). This protocol has been reported according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.[23] The anticipated trial start date will be 18 September 2019 and the date of last follow-up will be 31 May 2020.

Setting and site selection at the cluster level

Figure 1 shows the participant flow chart for this study. The corresponding author (NY) explained the purpose of this study to 68 visiting nurse agencies in four prefectures in Japan (Tokyo, Saitama, Kanagawa, and Chiba) through the organisation. Forty-seven visiting nurse agencies agreed to participate in the study. All the participating visiting nurse agencies are managed by one organisation.

To be included, a visiting nurse agency must provide services mostly to psychiatric patients or clients, not elderly people or those with physical diseases. In each agency, visiting nurses care for at least two people with schizophrenia who live with their family. There are no exclusion criteria at the cluster level.

Randomisation at the cluster level

Visiting nurse agencies that meet the inclusion criteria will be randomly allocated to the intervention group (brief FPE program) or the control group. Randomisation will be stratified by the median of the average caseload of visiting nurses in each agency. We used stratified randomisation based on this factor because the number of patients for whom a visiting nurse can maintain service quality is generally fixed.[24] If a visiting nurse has too many patients, family support will probably be neglected. A random sequence table will be created by a researcher (HT) in another department at our institution who is not involved in the study protocol development process. In addition, another independent researcher (SY) who is not involved in intervention and analysis will conduct the randomisation. SY will inform each visiting nurse agency of the randomisation results. The primary investigator (NY) will be blinded through the entire randomisation process.

Participant eligibility criteria and recruitment procedure at the individual level

At the individual level, we set the following inclusion criteria for a caregiver of a person with schizophrenia: 1) is the primary caregiver; 2) aged over 20 years; 3) is a family member of the person with schizophrenia such as a parent, sibling, spouse, or child; and 4) lives with the person with schizophrenia. There are no exclusion criteria for caregivers. In addition, the inclusion criteria for people with schizophrenia are as follows: 1) diagnosis of schizophrenia based on the International Statistical Classification of Diseases and Related Health Problems, 10th revision and 2) receiving services from visiting nurses.

As part of the recruitment procedure at the individual level, all potential participants (caregivers of people with schizophrenia and people with schizophrenia) at each agency will be listed. Second, a randomly ordered list will be created using a random number generator in the Stata statistical software program, version 15, in order to avoid selection bias at the individual level. Third, visiting nurses who have attended a lecture on study design and ethical considerations will recruit participants in accordance with the randomly ordered list until five participants have been recruited. The study will include only participants who voluntarily agree to participate in the study.

Intervention program

The intervention program is a single-family intervention conducted by psychiatric visiting nurses. It is based on the Family Intervention and Support in Schizophrenia: A Manual on Family Intervention for the Mental Health Professional.[25] This program was developed through discussions and collaborations among members of the Family

Association of Schizophrenia, psychiatric visiting nurses, FPE experts, psychiatrists, psychiatric nurses, clinical psychologists, and mental health social workers based on the concept of coproduction and Patient and Public Involvement (PPI).[26] During the development process, we tried to avoid long sentences, enlarged the characters, and used visually appealing drawings. The program consists of four sessions that last 60 minutes each using the above tool. It will be completed over a period of a month. Attendance of at least one session is required. Psychiatric visiting nurses will provide appropriate information using this intervention tool and advice to the family about living problems based on their own nursing clinical experience. We will also create a checklist to confirm how many sessions visiting nurses are actually able to conduct with participants.

Before the intervention, we will provide the intervention team of psychiatric visiting nurses with a 1-day lecture. The lecture will consist of three parts. First, a caregiver of a person with schizophrenia will talk about their life problems and what they want visiting nurses to do; this is expected to increase the motivation of visiting nurses. Second, basic communication training will be conducted through role-playing. Visiting nurses, who will be brief FPE providers, will be in groups of three. They will each play the role of a visiting nurse, caregiver, and evaluator. They will practice listening to caregivers. Third, the primary investigator (NY) will equip them with basic knowledge about FPE and explain the contents of this intervention tool and the points the primary investigator wants to emphasise. Through these trainings, we expect to improve the motivation, knowledge, and skills of the visiting nurses in providing the brief FPE program.

Table 1 shows the contents of the intervention tool. Session I will cover general knowledge about schizophrenia: definition, causes, symptoms, prognosis, pharmacological treatment, and psychosocial rehabilitation. Regarding definition and causes, visiting nurses will stress that schizophrenia is a brain disease that can manifest in anyone using the diathesis-stress model and the dopamine hypothesis. It is important to provide the family with a biological explanation about the aetiology of schizophrenia because there might be family members who think people become schizophrenic because of family relationships.[27] In addition to an explanation of the symptoms themselves, visiting nurses will describe how people with schizophrenia have difficulties living their own lives due to their symptoms. Visiting nurses will explain the disease course such as the prodromal phase, acute phase, and recovery phase. Next, visiting nurses will explain the characteristics of each phase and what to do during each phase. In terms of prognosis, visiting nurses will emphasise that schizophrenia is not

necessarily a disease with a bad prognosis. In people with their first episode of schizophrenia, about 70% will have a good intermediate to long-term outcome if they receive appropriate pharmacological therapy.[28] Concerning medication, visiting nurses will appreciate the idea that people with schizophrenia usually do not want to take medication. Visiting nurses will talk about the necessity, safety, and reasons for adherence to pharmacological therapy. In addition, the side effects of antipsychotic medications will be described clearly, using relevant pictures. Finally, visiting nurses will give an outline of psychosocial therapy. At the end, participants will answer questions with dichotomous answers—"yes" or "no"—to confirm what they have learned from the session.

Session II will deal with how to cope with people with schizophrenia and problem-solving skills. The contents of this session include how to cope with hallucinations and delusions; signs of recurrence; how to prevent recurrences; how to cope when the disease gets worse; what to do with people with schizophrenia when they stay at home all day; how to respond to people with schizophrenia who do not want to take their medication; how to respond when domestic violence is imminent, is occurring, or has occurred; and how to get involved when self-injury or suicide is suspected. Finally, visiting nurses will explain problem-solving skills. In the routine clinical setting, the family will work on matters that are causing trouble in daily life using problem-solving skills.

Session III will cover communication and emotions: understanding the feelings of people with schizophrenia, expressed emotion (EE) theory, basic knowledge and skills about communication, and a lecture on desirable and undesirable communication with people with schizophrenia. In the first section, visiting nurses will describe the importance of understanding that people with schizophrenia are likely to have a pessimistic view about their future. In the second section on EE theory, visiting nurses will appreciate that it is natural for a family to have high EE with poor knowledge and lack of support about mental illness.[29] Of note, visiting nurses will not force family members to play the role of supporter. When family members hear the explanation of high EE, many might feel that they are responsible for their burden. Visiting nurses will emphasise that both families and people with schizophrenia should think about positive and constructive communication to ensure mutual independence. In the third section on basic knowledge about communication and the lecture of desirable and undesirable communication with patients, caregivers will practice conversations using real cases and will be given time to consider better communication strategies.

Session IV will focus on the family's recovery. Topics will include thinking about the family's recovery, the importance of living one's own life, taking care of the family's physical and mental health needs, proper stress management, experiences and messages from members of the Family Association, and identifying available social resources in the community. During this session, visiting nurses will stress that people with schizophrenia and family members each have their own lifestyle and individual goals. Visiting nurses will also encourage family members to live their own lives using a variety of social resources instead of only working hard to take care of a person with schizophrenia. In addition, visiting nurses expect that family members will improve their physical and mental health by acquiring knowledge on self-care and stress management skills. Furthermore, visiting nurses will introduce the experiences of three members of the Family Association who have taken care of a person with schizophrenia. It is expected that others' similar experiences will help family members understand that they are not the only people experiencing such a hard time and relieve their feelings of sadness or hopelessness. Finally, visiting nurses will explain the social resources available in the community for family members and confirm the importance of connecting with many supporters around them.

Control group

Caregivers enrolled in the control group will receive usual care from visiting nurses. They will be put on a waiting list to receive the same intervention program after completing the 6-month follow-up assessment. They will not receive any type of psychoeducation or supportive therapies.

Outcomes

Table 2 shows an overview of the outcome measures. Outcome measures will be assessed at baseline prior to the intervention (T1), immediately after the completion of the intervention (1-month follow-up, T2), and 6 months after the baseline assessment (6-month follow-up, T3).

Primary outcome for caregivers

Zarit Burden Interview (ZBI-22)

ZBI-22 will be used to measure caregiver burden. It consists of 22 items scored on a five-point Likert scale from 0 (never) to 4 (nearly always), except for the final item on global burden, which is rated from 0 (not at all) to 4 (extremely). The total score ranges from 0 to 88, with higher scores indicating higher burden. The Japanese version of ZBI-

22 had a high test-retest reproducibility and internal consistency. Construct validity has also been confirmed.[30]

Secondary outcome for caregivers

K6

K6 will be used to measure sub-clinical depression and anxiety disorders as part of a self-administered questionnaire. It consists of six items answered on a five-point Likert scale. Scores range from 0 to 24, with higher scores representing higher degrees of sub-clinical depression and anxiety disorder. The Japanese versions of the K6 have essentially equivalent screening performance as the original English versions.[31]

General Self Efficacy Scale (GSES)

GSES is a measurement of self-efficacy in daily living. It includes 16 items with dichotomous questions. The higher the score, the better the self-efficacy, in general. GSES had high test-retest reproducibility and internal consistency. Construct validity has been confirmed.[32]

WHO-5

WHO-5 will be used to measure subjective quality of life based on positive mood (good spirits and relaxation), vitality (being active and waking up fresh and rested), and general interest (being interested in things). It consists of five items rated on a six-point Likert scale. Higher scores mean higher well-being. The Japanese version of WHO-5 has adequate internal consistency. It has been confirmed to have external concurrent validity and external discriminatory validity.[33]

Knowledge of Illness and Drug Inventory (KIDI)

KIDI will be used to assess knowledge regarding mental illness and the effects of medications on mental illness. There are two sub-scales: 10 items assessing knowledge of mental illness and 10 items assessing knowledge of the effects of antipsychotic drugs. This inventory consists of a self-reported inventory where respondents are asked to select the correct answer from three choices, with higher scores representing greater knowledge. KIDI is frequently used to assess knowledge about mental disorders and treatments in Japan.[34]

Secondary outcomes in people with schizophrenia

Behavior and Symptom Identification Scale (BASIS-32)

BASIS-32 is a commonly used measure in mental health. It includes 32 items on a five-point Likert scale, where 0 indicates no difficulties and 4 indicates severe difficulties. The scale measures five factors: (1) relation to self and others (seven items); (2) depression/anxiety (six items); (3) everyday life and role functioning (nine items); (4) impulsive and addictive behaviour (six items); and (5) psychosis (four items). Factors 1, 2, 4, and 5 are assessed as the total score divided by the number of items answered (mean score), while factor 3 is assessed based non the highest rating. Internal consistency and construct validity of the Japanese version of BASIS-32 have been demonstrated.[35]

WHO-5

WHO-5 is used to measure subjective quality of life based on positive mood (good spirits and relaxation), vitality (being active and waking up fresh and rested), and general interest (being interested in things). WHO-5 comprises five items rated on a six-point Likert scale. Higher scores mean higher well-being. The Japanese version of WHO-5 has adequate internal consistency. It has been confirmed to have external concurrent validity and external discriminatory validity.[33]

Hospitalisation by 6-month follow-up

This is a question with a dichotomous answer (yes or no) about whether the patient has been hospitalised during the past 6 months. The answer will be provided by the caregiver at baseline and the 6-month follow-up.

Sample size calculation

The sample size required was calculated according to guidelines in the Consolidated Standards of Reporting Trials (CONSORT) for cRCTs,[36] taking into account intra-class correlations (ICCs). The effect size of a brief FPE program for individual caregiver burden was estimated based on a previous pre-post test.[19] The pre-post test concluded that the standardised mean difference (d) of brief FPE on family burden was 0.46. Sample size was estimated as 76 in each arm based on an alpha error probability of 0.05 and power (1-β) of 0.80, using G*Power version 3.1.9.2.[37 38] cRCTs should be multiplied by design effect (1+[m-1]ρ), where m is the average cluster size and ρ is the ICC.[39] The estimated ICC for the primary outcome in this study was set to 0.05 and the average number of caregivers per cluster was set at five people. Assuming an attrition rate of 20%, the required sample size is 110 caregivers in each arm. Thus, at least 44 visiting nurse agencies will be recruited.

Quantitative analysis

The statistician will be blinded to the treatment group. We will analyse clinical outcomes on the basis of intention to treat and model the effect of the intervention on primary and secondary continuous outcomes using generalised linear latent and mixed models (GLLAMMs). This will allow for missing data to be taken into account within the statistical model. In this study, a three-level model will be used, with repeated measures nested in participants and participants nested in clusters. Time (baseline, 1-month follow-up, 6-month follow-up) will be considered level 1, individual caregivers will be considered level 2, and clusters (visiting nurse agencies) will be considered level 3. Regarding fixed effects, condition (intervention versus control), time, and a two-way interaction effect, condition by time, will be included. Models will adjust for baseline differences in caregiver socio-demographics such as age, gender, education, household income, family relationship with the person with schizophrenia, length of caregiving, and length of visiting nurse system use. Multiple levels of Cox proportional hazards regression models will also be used for the dichotomous question of hospitalisation at the 6-month follow-up. A *p*-value of less than 0.05 will be considered statistically significant.

Data monitoring

A data monitoring committee (DMC) will be set up. It will consist of at least two independent members. The DMC will meet monthly after the first participant has been randomised. The purpose of the meeting will be to review participation rates and reasons for study dropout. The DMC will be independent from any sponsor and competing interest.

Patient and public involvement

The research question, study design, and outcome measures were determined based on a discussion with representatives of the Family Association of Schizophrenia. The intervention program was also developed through the discussion and collaboration among members of the Family Association of Schizophrenia, psychiatric visiting nurses, FPE experts, psychiatrists, psychiatric nurses, clinical psychologists, and mental health social workers. After the completion of the study, this intervention tool will be available for anyone who wants to use it via the internet.

Ethics and dissemination

Ethical considerations

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The study protocol was approved by the Research Ethics Committee of the Graduate School of Medicine and the Faculty of Medicine at the University of Tokyo, Japan (No. 2019065NI). We will obtain informed consent from all caregivers and patients. The consent form will inform caregivers and patients that we guarantee protection of personal information and that the data will be anonymous and used only for academic purposes. There are no competing interests. This study is supported by fundamental study on effective community services for people with severe mental disorders and their families.

Dissemination of the research findings

The findings will be published in a scientific peer-reviewed journal according to the CONSORT guidelines for cRCTs.[36] The participants will be informed of conference presentations and publications.

Strengths and limitations

The study has both strengths and limitations. First, the study will evaluate an implementable brief FPE program that potentially reduces time, cost, and staffing problems by incorporating the program into an existing mental health service system, namely visiting nurse services. Second, this is the first cRCT of a brief FPE program, which could prevent contamination between the intervention and control groups. Third, based on the concept of coproduction and PPI,[26] the study incorporated a variety of viewpoints from caregivers, visiting nurses, and FPE experts.

We recognise three limitations of this study. First, since the sampling method for participating agencies was not random, there is a possibility of selection bias. Second, since subjects will provide data through a self-reported questionnaire, information bias or random error is possible. For example, the severity of symptoms in people with schizophrenia that impact a caregiver's burden may not be accurately measured. Third, we designed the study and intervention based on coproduction, but there are still concerns about its feasibility in actual clinical settings. For example, participants might not complete all four sessions due to the condition of people with schizophrenia, family work, and family hospitalisation. Fourth, due to the short study period, the number of

participants may not be able to meet the target sample size. These may lead to a high attrition rate during implementation.

Acknowledgments

The authors would like to thank the members of the *Mokusei* Family Association of Schizophrenia and N・FIELD Co., Ltd. for their invaluable advice on many aspects of the project.

Contributors

NY is the principal investigator responsible for the initial draft of this manuscript and organising and implementing the study. NY and KW calculated the sample size. NY, KW, SY, and MA decided on the analytic strategy. SS, TS, HT, KI, DN, CF, and NK helped throughout the development of the interventions and gave valuable feedback on the study protocol. All authors have read and approved the final manuscript.

Funding: This work is supported by Fundamental study on effective community services for people with severe mental disorders and their families.

Competing interests: None declared.

Patient Consent: Obtained.

Ethics approval: Research Committee of the Graduate School of Medicine and the Faculty of Medicine at the University of Tokyo, Japan.

REFERENCES

1. Awad AG, Voruganti LN. The burden of schizophrenia on caregivers: a review. *Pharmacoecon Open* 2008;26:149–62. doi:10.2165/00019053-200826020-00005

2. Saunders JC. Families living with severe mental illness: a literature review. *Issues Ment Health Nurs* 2003;24:175–98. doi:10.1080/01612840305301

3. Shah AJ, Wadoo O, Latoo J. Psychological distress in carers of people with mental disorders. *British Journal of Medical Practitioners* 2010;3:a327.

4. Gopinath PA, Chaturvedi S. Distress behaviour of schizophrenics at home. *Acta Psychiatr Scand* 1992;86:185–8. doi:10.1111/j.1600-0447.1992.tb03249.x

5. McAuliffe R, O'Connor L, Meagher D. Parents' experience of living with and caring for an adult son or daughter with schizophrenia at home in Ireland: a qualitative study. *J Psychiatr Ment Health Nurs* 2014;21:145–53. doi:10.1111/jpm.12065

6. Sin J, Gillard S, Spain D, *et al.* Effectiveness of psychoeducational interventions for family carers of people with psychosis: a systematic review and meta-analysis. *Clin Psychol Rev* 2017;56:13–24. doi:10.1016/j.cpr.2017.05.002

7. Sin J, Jordan CD, Barley EA, *et al.* Psychoeducation for siblings of people with severe mental illness. *Cochrane Database Syst Rev* 2015;5:Cd010540. doi:10.1002/14651858.CD010540.pub2

8. Dixon L, McFarlane WR, Lefley H, *et al.* Evidence-based practices for services to families of people with psychiatric disabilities. *Psychiatr Serv* 2001;52:903–10. doi:10.1176/appi.ps.52.7.903

9. Birchwood M, Smith J, Cochrane R. Specific and non-specific effects of educational intervention for families living with schizophrenia. A comparison of three methods. *Br J Psychiatry* 1992;160:806–14. doi:10.1192/bjp.160.6.806

10. Lehman AF, Steinwachs DM. Patterns of usual care for schizophrenia: initial results from the Schizophrenia Patient Outcomes Research Team (PORT) Client Survey. *Schizophr Bull* 1998;24:11–20; discussion 20–32. doi:10.1093/oxfordjournals.schbul.a033303

11. Oshima I, Mino Y, Nakamura Y, *et al.* Implementation and dissemination of family psychoeducation in Japan: nationwide survey on psychiatric hospitals in 1995 and 2001. *Journal of Social Policy & Social Work* 2007;11:5–16.

12. Rummel-Kluge C, Kissling W. Psychoeducation in schizophrenia: new developments and approaches in the field. *Curr Opin Psychiatry* 2008;21:168–72. doi:10.1097/YCO.0b013e3282f4e574

13. Harvey C. Family psychoeducation for people living with schizophrenia and their families. *BJPsych Adv* 2018;24:9–19. doi:10.1192/bja.2017.4

14. Fadden G, Heelis R. 2011. The Meriden Family Programme: lessons learned over 10 years. *J Ment Health* 2011;20:79–88. doi:10.3109/09638237.2010.492413 [published online first: 2 September 2010].

15. McFarlane WR, Dixon L, Lukens E, *et al.* Family psychoeducation and schizophrenia: a review of the literature. *J Marital Fam Ther* 2003;29:223–45.

16. Okpokoro U, Adams CE, Sampson S. Family intervention (brief) for schizophrenia. *Cochrane Database Syst Rev* 2014;3:Cd009802. doi:10.1002/14651858.CD009802.pub2

17. Pitschel-Walz G, Leucht S, Bauml J, *et al.* The effect of family interventions on relapse and rehospitalization in schizophrenia—a meta-analysis. *Schizophr Bull* 2001;27:73–92. doi:10.1093/oxfordjournals.schbul.a006861.

18. Smith JV, Birchwood MJ. Specific and non-specific effects of educational intervention with families living with a schizophrenic relative. *Br J Psychiatry* 1987;150:645–52. doi:10.1192/bjp.150.5.645.

19. Devaramane V, Pai NB, Vella SL. The effect of a brief family intervention on primary carer's functioning and their schizophrenic relatives levels of psychopathology in India. *Asian J Psychiatr* 2011;4:183–7. doi:10.1016/j.ajp.2011.06.004

20. Sharif F, Shaygan M, Mani A. Effect of a psycho-educational intervention for family members on caregiver burdens and psychiatric symptoms in patients with schizophrenia in Shiraz, Iran. *BMC Psychiatry* 2012;12:48. doi:10.1186/1471-244x-12-48

21. Huang XY, Ma WF, Shih HH, *et al.* Roles and functions of community mental health nurses caring for people with schizophrenia in Taiwan. *J Clin Nurs* 2008;17:3030–40. doi:10.1111/j.1365-2702.2008.02426.x

22. Setoya N, Kayama M, Tsunoda A, *et al.* A survey of the family care provided in psychiatric home-visit nursing and related characteristics of clients. *Japanese Bulletin of Social Psychiatry* 2011;20:17–25.

23. Chan AW, Tetzlaff JM, Altman DG, *et al.* SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158:200–7. doi:10.7326/0003-4819-158-3-201302050-00583

24. Mueser, K. T., Bond, G. R., Drake, R. E., & Resnick, S. G. (1998). Models of community care for severe mental illness: a review of research on case management. Schizophr Bull, 24(1), 37-74. doi:10.1093/oxfordjournals.schbul.a033314

25. Varghese M, Shah A, Kumar GSU, *et al.* Family intervention and support in schizophrenia: a manual on family intervention for the mental health professional, version 2. Bangalore, India: National Institute of Mental Health and Neurosciences.

26. Batalden M, Batalden P, Margolis P, *et al.* Coproduction of healthcare service. *BMJ Qual Safe* 2016;25:509–17. doi:10.1136/bmjqs-2015-004315

27. Ferriter M, Huband N. Experiences of parents with a son or daughter suffering from schizophrenia. *J Psychiatr Ment Health Nurs* 2003;10:552–60. doi:10.1046/j.1365-2850.2003.00624.x

28. Menezes NM, Arenovich T, Zipursky RB. A systematic review of longitudinal outcome studies of first-episode psychosis. *Psychol Med* 2006;36:1349–62. doi:10.1017/s0033291706007951

29. Amaresha AC, Venkatasubramanian G. Expressed emotion in schizophrenia: an overview. *Indian J Psychol Med* 2012;34:12–20. doi:10.4103/0253-7176.96149

30. Arai Y, Kudo K, Hosokawa T, *et al.* Reliability and validity of the Japanese version of the Zarit Caregiver Burden interview. *Psychiatry Clin Neurosci* 1997;51:281–7. doi:10.1111/j.1440-1819.1997.tb03199.x

31. Sakurai K, Nishi A, Kondo K, *et al.* Screening performance of K6/K10 and other screening instruments for mood and anxiety disorders in Japan. *Psychiatry Clin Neurosci* 2011;65:434–41. doi:10.1111/j.1440-1819.2011.02236.x

32. Sakano Y, Tohjoh M. The General Self-Efficacy Scale (GSES): scale development and validation. *Japanese Journal of Behavior Therapy* 1986;12:73–82.

33. Awata S, Bech P, Yoshida S, *et al.* Reliability and validity of the Japanese version of the World Health Organization-Five Well-Being Index in the context of detecting depression in diabetic patients. *Psychiatry Clin Neurosci* 2007;61:112–9. doi:10.1111/j.1440-1819.2007.01619.x

34. Maeda M, OM, Renri T, *et al.* It is as a result of disease drug knowledge degree investigation (Knowledge of Illness and Drugs Inventory, KIDI) for a person with IIB-29 schizophrenia and the family. *Japanese Bulletin of Social Psychiatry* 1994;2:173–4.

35. Setoya Y, N. Y., Kurita H. Utility of the Japanese version of the BASIS-32 in inpatients in psychiatric hospital. *Japanese Journal of Clinical Psychiatry* 2002;31:571–5.

36. Campbell MK, Piaggio G, Elbourne DR, *et al.* Consort 2010 statement: extension to cluster randomised trials. *BMJ* 2012;345:e5661. doi:10.1136/bmj.e5661

37. Faul F, Erdfelder E, Buchner A, *et al.* Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. *Behav Res Methods* 2009;41:1149–60. doi:10.3758/brm.41.4.1149

38. Faul F, Erdfelder E, Lang AG, *et al.* G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods* 2007;39:175–91.

39. Campbell MK, Elbourne DR, Altman DG. CONSORT statement: extension to cluster randomised trials. *BMJ* 2004;328:702–8. doi:10.1136/bmj.328.7441.702

Table 1. Outline of the brief family psychoeducation program

Session number	Session aim	Content
I	General knowledge about schizophrenia	Definition, causes, symptoms, prognosis, pharmacological treatment, psychosocial rehabilitation. Activity: Let's review the knowledge gained in this session.
II	How to cope with people with schizophrenia using problem-solving skills	How to cope with hallucinations and delusions; signs of recurrence and how to prevent recurrence; how to cope when the disease gets worse; what to do with people with schizophrenia when they stay at home all day; how to respond to people with schizophrenia who do not want to take their medication; what to do when domestic violence is imminent, is happening, or has happened; how to get involved when self-injury or suicide is suspected. Activity: Let's learn how to apply problem-solving skills.
III	Handling communication and emotions	Understanding the feelings of people with schizophrenia, expressed emotion theory, basic knowledge about communication, and lecture about desirable and undesirable communication with people with schizophrenia. Activity: Let's practice conversations using real cases.
IV	Family recovery	Thinking about the family's recovery, importance of living one's own life, taking care of the family's physical and mental health needs, proper stress management, and experiences and messages from members of the Family Association. Activity: Let's identify social resources in the community and recognise the importance of connecting with many supporters around families.

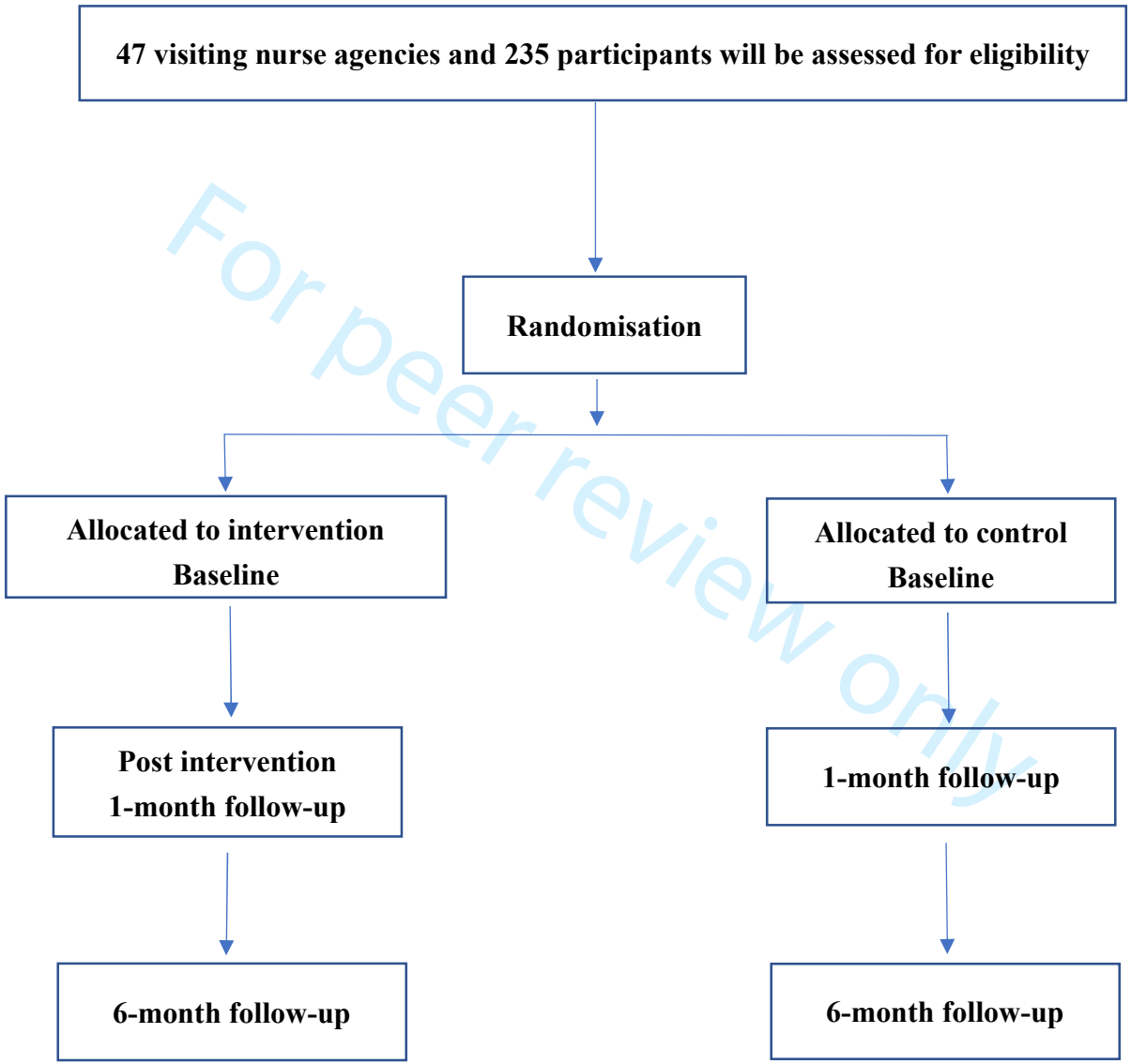
This intervention program consists of four 60-minute modules completed over 1 month.

Table 2. Outcome measures

	Outcome measure	Baseline	1-month follow-up	6-month follow-up
Caregivers	Zarit Burden Interview (ZBI-22)	✓	✓	✓
	K6	✓	✓	✓
	General Self-Efficacy Scale (GSES)	✓	✓	✓
	WHO-5	✓	✓	✓
	Knowledge of Illness and Drug Inventory (KIDI)	✓	✓	✓
People with schizophrenia	Behavior and Symptom Identification Scale (BASIS-32)	✓	✓	✓
	WHO-5	✓	✓	✓
	Hospitalisation during the past 6 months	✓	–	✓

Figure 1

Figure 1. Study flow chart



BMJ Open

Effects of brief family psychoeducation for caregivers of people with schizophrenia in Japan provided by visiting nurses: protocol for a cluster randomised controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-034425.R3
Article Type:	Protocol
Date Submitted by the Author:	23-Mar-2020
Complete List of Authors:	Yasuma, Naonori; The University of Tokyo, ; Sato, Sayaka; National Institute of Mental Health, Community mental health and law; NCNP Yamaguchi, Sosei; National Center of Neurology and Psychiatry, Department of Community Mental Health & Law, National Institute of Mental Health Matsunaga, Asami; National Center of Neurology and Psychiatry, Department of Community Mental Health & Law, National Institute of Mental Health Shiozawa, Takuma; National Center of Neurology and Psychiatry, Tachimori, Hisateru; National Center of Neurology and Psychiatry Translational Medical Center Watanabe, Kazuhiro; The University of Tokyo, Department of Mental Health, Graduate School of Medicine Imamura, Kotaro; The University of Tokyo, Department of Graduate School of Medicine Nishi, Daisuke; The University of Tokyo, Department of Graduate School of Medicine Fujii, Chiyo; National Center of Neurology and Psychiatry, Department of Community Mental Health & Law, National Institute of Mental Health Kawakami, Norito; The University of Tokyo, Department of Mental Health
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Mental health
Keywords:	Brief family psychoeducation, schizophrenia, caregivers, visiting nurses

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Effects of brief family psychoeducation for caregivers of people with schizophrenia in Japan provided by visiting nurses: protocol for a cluster randomised controlled trial

Naonori Yasuma[1,2]: nnyy712@gmail.com
Sayaka Sato[2]: sayakas@ncnp.go.jp
Sosei Yamaguchi[2]: sosei.yama@ncnp.go.jp
Asami Matsunaga[2]: asamim@ncnp.go.jp
Takuma Shiozawa[2]: takuma-shozw@umin.ac.jp
Hisateru Tachimori[3]: tachi@ncnp.go.jp
Kazuhiro Watanabe[1]: kzwatanabe-tky@umin.ac.jp
Kotaro Imamura[1]: kouima-tky@umin.ac.jp
Daisuke Nishi[1]: d-nishi@m.u-tokyo.ac.jp
Chiyo Fujii[2]: chyfujii@ncnp.go.jp
Norito Kawakami[1]: nkawakami@m.u-tokyo.ac.jp

1 Department of Graduate School of Medicine, The University of Tokyo

2 Department of Community Mental Health and Law, National Institute of Mental Health, National Center of Neurology and Psychiatry, Kodaira, Tokyo, Japan

3 Department of Translational Medical Center, National Institute of Mental Health, National Center of Neurology and Psychiatry, Kodaira, Tokyo, Japan

Corresponding author:
Naonori Yasuma, MD
Department of Mental Health, Graduate School of Medicine, The University of Tokyo,
7-3-1 Hongo, Bunkyo-ku, Tokyo 1130033 Japan
E-mail: nnyy712@gmail.com
Phone: +81-3-5841-3521
Fax: +81-3-5841-3521

Word count: 6,261 words

ABSTRACT

Introduction

Development of a support system for families caring for people with schizophrenia in routine psychiatric care settings is an important issue worldwide. Regional mental health systems are inadequate for delivering effective services to such family members. Despite evidence that family psychoeducation (FPE) alleviates the burden of schizophrenia on families, its dissemination in routine clinical practice remains insufficient, suggesting the need for developing an effective and implementable intervention for family caregivers in the existing mental health system setting. In Japan, the visiting nurse service system would be a practical way of providing family services. Visiting nurses in local communities are involved in the everyday lives of people with schizophrenia and their families. Accordingly, visiting nurses understand their needs and are able to provide family support as a service covered by national health insurance. The purpose of this study is to discover whether a brief FPE program provided by visiting nurses caring for people with schizophrenia will alleviate family burden through a cluster randomised controlled trial (cRCT).

Methods and analysis

The study will be a two-arm, parallel-group (visiting nurse agency) cRCT. Forty-seven visiting nurse agencies will be randomly allocated to the brief FPE group (intervention group) or treatment as usual group (control group). Caregivers of people with schizophrenia will be recruited by visiting nurses using a randomly ordered list. The primary outcome will be caregiver burden, measured using the Zarit Burden Interview–Japanese version (ZBI-22). Outcome assessments will be conducted at baseline, 1-month follow-up, and 6-month follow-up. Multiple levels of three-way interactions in mixed models will be used to examine whether the brief FPE program will alleviate the burden on caregivers relative to treatment as usual.

Ethics and dissemination

The Research Ethics Committee of the Graduate School of Medicine and Faculty of Medicine, The University of Tokyo, Japan (No. 2019065NI) approved this study. The results will be published in a scientific peer-reviewed journal.

Registration number

UMIN000038044; Pre-results.

Strengths and Limitations

- This study will evaluate an implementable brief family psychoeducation (FPE) program that potentially reduces time, cost, and staffing problems by incorporating the program into an existing mental health service system, namely visiting nurse services.

- The study incorporated a variety of viewpoints from caregivers, visiting nurses, and FPE experts based on the concept of coproduction and Patient and Public Involvement (PPI).

- One study limitation is that all outcomes will be based on self-reports, which may cause information bias or random error.

INTRODUCTION

Families caring for people with schizophrenia receiving community-based mental health care have a great need for support. People with schizophrenia who have severe symptoms require long-term care, which imposes a significant burden on families providing such care.[1] For example, the financial burden on the family is severe because considerable amounts of time are devoted to caregiving, resulting in the loss of work opportunities and reduced income.[2] Moreover, insufficient downtime to recover from the stress of caregiving results in both physical and mental illness.[3] Families also become worn out and stressed by the demands of coping with this illness, which is characterized by repeated hallucinations and delusions if symptoms do not stabilize.[4] Furthermore, a parent of a son or daughter with schizophrenia might worry about what will become of their child after his or her death. They might also feel they are not getting adequate information about what social services are available to them.[5] Stigma against the illness is also deeply rooted and can lead to families becoming socially isolated.[3] Therefore, families of people with schizophrenia have various physical, psychological, economic, and social burdens.

Several studies have addressed the development and evaluation of effective family interventions. According to a systematic review, family psychoeducation (FPE) is a scientifically effective psychological intervention that has been used to reduce caregiver burden.[6,7] The components of FPE mainly include sharing information about the disorder, early warning signs, relapse prevention, as well as skills training in coping, communication, and problem solving.[8] FPE can directly improve caregivers' knowledge about schizophrenia and related caregiving problems.[9] Improved knowledge of coping strategies and resources can lead to a more positive appraisal of caregiving experiences by families as well as caregivers' own self-efficacy in coping with the demands of caring for people with schizophrenia, thereby lessening the burden.[6]

Despite the accumulation of evidence, there are several barriers to FPE implementation. The initial report on the Schizophrenia Patient Outcomes Research Team (PORT) Treatment Recommendations found that FPE was provided to 31.6% of inpatients and 9.6% of outpatients who could have benefited from it.[10] A nationwide survey in Japan revealed that the implementation rate for FPE programs at psychiatric facilities is similarly low: 35.9% in hospitals and 14.5% in outpatient settings.[11] One challenge in implementing these programs is the length of the intervention. Most studies have found that such interventions range from 9 months to 2 years, which is impractical for medical staff and families in a clinical setting.[12] Other reasons include funding and staff shortages, as well as providing necessary training.[13] In Japan, even if healthcare

professionals perform FPE for a family, they cannot obtain reimbursement for medical expenses. In addition, while the Meriden Family Program appears to be effective, training is time-consuming and expensive.[14] The medical treatment fee system in most countries including Japan does not cover such a comprehensive family intervention. The development of a brief and implementable FPE program within the existing mental health system that is covered by national health insurance is greatly needed.[15]

Brief FPE programs have been examined in previous studies. In terms of the program framework, studies have found that brief FPE programs, delivered in five sessions or fewer or lasting no more than 3 months, were easy to conduct for both practitioners and caregivers.[16] Brief FPE programs have been shown to significantly increase caregivers' knowledge of the disorder, leading to reductions in relapse and rehospitalisation rates in diverse settings.[17,18] In addition, recent research has shown that a brief FPE program may be beneficial in reducing caregiver burden. In a pre-post test in India, a brief FPE program comprised of three 1-hour sessions aimed at educating the primary caregiver and patient about schizophrenia and imparting communication and problem-solving skills. A significant decrease in caregiver burden, measured using the Burden Assessment Scale (BAS), was found between baseline and the final follow-up at 3 months.[19] In a randomised controlled trial in Iran, brief FPE consisted of ten 90-minute sessions held over 5 weeks (two sessions each week) conducted by a psychiatric nurse or psychiatrist. Caregiver burden measured using the Family Burden Scale (FBS) was significantly reduced both immediately after the intervention and 1 month later.[20] However, the effects of brief FPE programs are still inconclusive due to relatively low methodological quality in prior studies.[7,16] In other words, evidence from a trial with a better design is needed.

Practical implementation strategies for a brief FPE program need to be considered in addition to a scientific evaluation of the effects. Brief FPE programs provided by visiting nurses appear to be a potentially feasible and sustainable way of implementing FPE in a Japanese clinical setting. Visiting nurses routinely visit clients with schizophrenia and their family members. They have already built rapport with clients and family members and would be able to respond according to their needs, which means they could seamlessly provide highly individualized brief FPE.[21] In addition, the system of visiting nurses could easily be applied because the number of visiting nurses has been increasing recently in Japan. From a cost perspective, it would be possible to make family support a reimbursable service under national health insurance to cover psychiatric visiting nurse consultancy fees.[22] Taken together, brief

FPE provided by visiting nurses could overcome the poor implementation rate and become effective family interventions in the community setting in Japan.

Hypothesis and aims

We hypothesise that brief FPE provided by visiting nurses could alleviate the burden on families and caregivers of people with schizophrenia. The aim of this study is to clarify whether visiting nurses providing brief FPE to families caring for people with schizophrenia alleviates family burden through a cluster randomised controlled trial (cRCT).

METHODS AND ANALYSIS

Trial design

This study is a two-arm, parallel-group cRCT. The randomisation procedure will be conducted at the cluster level (visiting nurse agencies). Visiting nurse agencies will be randomly assigned to the intervention or control (treatment as usual (TAU)) group in a 1:1 ratio. Data will be collected at the individual level. Analyses to evaluate the efficacy of the intervention program will be conducted at the individual level, taking into consideration cluster-level effects. The study protocol was registered in the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN-CTR ID, UMIN000038044). This protocol has been reported according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.[23] The anticipated trial start date will be 18 September 2019 and the date of last follow-up will be 31 May 2020.

Setting and site selection at the cluster level

Figure 1 shows the participant flow chart for this study. The corresponding author (NY) explained the purpose of this study to 68 visiting nurse agencies in four prefectures in Japan (Tokyo, Saitama, Kanagawa, and Chiba) through the organisation. Forty-seven visiting nurse agencies agreed to participate in the study. All the participating visiting nurse agencies are managed by one organisation.

To be included, a visiting nurse agency must provide services mostly to psychiatric patients or clients, not elderly people or those with physical diseases. In each agency, visiting nurses must care for at least two people with schizophrenia who live with their family. There are no exclusion criteria at the cluster level.

Randomisation at the cluster level

Visiting nurse agencies that meet the inclusion criteria will be randomly allocated to the intervention group (brief FPE program) or the control group. Randomisation will be stratified by the median of the average caseload of visiting nurses in each agency. We used stratified randomisation based on this factor because the number of patients for whom a visiting nurse can maintain service quality is generally fixed.[24] If a visiting nurse has too many patients, family support will probably be neglected. A random sequence table will be created by a researcher (HT) in another department at our institution who is not involved in the study protocol development process. In addition, another independent researcher (SY) who is not involved in intervention and analysis will conduct the randomisation and will inform each visiting nurse agency of the randomisation results. The primary investigator (NY) will be blinded through the entire randomisation process.

Participant eligibility criteria and recruitment procedure at the individual level

At the individual level, we set the following inclusion criteria for a caregiver of a person with schizophrenia: 1) is the primary caregiver; 2) aged over 20 years; 3) is a family member of the person with schizophrenia such as a parent, sibling, spouse, or child; and 4) lives with the person with schizophrenia. There are no exclusion criteria for caregivers. In addition, the inclusion criteria for people with schizophrenia are as follows: 1) diagnosis of schizophrenia based on the International Statistical Classification of Diseases and Related Health Problems, 10th revision and 2) receiving services from visiting nurses.

As part of the recruitment procedure at the individual level, all potential participants (caregivers of people with schizophrenia and people with schizophrenia) at each agency will be listed. Second, a randomly ordered list will be created using a random number generator in the Stata statistical software program, version 15, in order to avoid selection bias at the individual level. Third, each visiting nurse, after attending a lecture on study design and ethical considerations, will recruit participants in accordance with the randomly ordered list until five participants have been recruited. The study will include only participants who voluntarily agree to participate in the study.

Intervention program

The intervention program consists of a single-family intervention conducted by psychiatric visiting nurses. It is based on the Family Intervention and Support in Schizophrenia: A Manual on Family Intervention for the Mental Health Professional.[25]

This program was developed through discussions and collaborations among members of the Family Association of Schizophrenia, psychiatric visiting nurses, FPE experts, psychiatrists, psychiatric nurses, clinical psychologists, and mental health social workers based on the concept of coproduction and Patient and Public Involvement (PPI).[26] During the development process, we tried to avoid long sentences, enlarged the characters, and used visually appealing drawings. The program consists of four sessions that last 60 minutes each using the above tool. It will be completed over a period of a month. Attendance of at least one session is required. Using this intervention tool, psychiatric visiting nurses will provide appropriate information and advice to the family about living problems based on their own nursing clinical experience. We will also create a checklist to confirm how many sessions visiting nurses are actually able to conduct with participants.

Before the intervention, we will provide the intervention team of psychiatric visiting nurses with a 1-day lecture. The lecture will consist of three parts. First, caregivers will talk about their life problems and what they want visiting nurses to do; this is expected to increase the motivation of visiting nurses. Second, basic communication training will be conducted through role-playing. Visiting nurses, who will be brief FPE providers, will be in groups of three. They will each play the role of a visiting nurse, caregiver, and evaluator. They will practice listening to caregivers. Third, the primary investigator (NY) will equip them with basic knowledge about FPE and explain the contents of this intervention tool and the points that the primary investigator wants to emphasise. Through these trainings, we expect to improve the motivation, knowledge, and skills of the visiting nurses in providing the brief FPE program.

Table 1 shows the contents of the intervention tool. Session I will cover general knowledge about schizophrenia: definition, causes, symptoms, prognosis, pharmacological treatment, and psychosocial rehabilitation. Regarding definition and causes, visiting nurses will stress that schizophrenia is a brain disease that can manifest in anyone using the diathesis-stress model and the dopamine hypothesis. It is important to provide the family with a biological explanation about the aetiology of schizophrenia because there might be family members who think people become schizophrenic because of family relationships.[27] In addition to an explanation of the symptoms themselves, visiting nurses will describe how people with schizophrenia have difficulties living their own lives due to their symptoms. Visiting nurses will explain the disease course such as the prodromal phase, acute phase, and recovery phase. Next, visiting nurses will explain the characteristics of each phase and what to do during each phase. In terms of prognosis, visiting nurses will emphasise that schizophrenia is not

necessarily a disease with a bad prognosis. In people with their first episode of schizophrenia, about 70% will have a good intermediate to long-term outcome if they receive appropriate pharmacological therapy.[28] Concerning medication, visiting nurses will appreciate the idea that people with schizophrenia usually do not want to take medication. Visiting nurses will talk about the necessity, safety, and reasons for adherence to pharmacological therapy. In addition, the side effects of antipsychotic medications will be described clearly, using relevant pictures. Finally, visiting nurses will give an outline of psychosocial therapy. At the end, participants will answer questions with dichotomous answers—"yes" or "no"—to confirm what they have learned from the session.

Session II will deal with how to cope with people with schizophrenia and provide problem-solving skills. The contents of this session include how to cope with hallucinations and delusions; signs of recurrence; how to prevent recurrences; how to cope when the disease gets worse; what to do with people with schizophrenia when they stay at home all day; how to respond to people with schizophrenia who do not want to take their medication; how to respond when domestic violence is imminent, is occurring, or has occurred; and how to get involved when self-injury or suicide is suspected. Finally, visiting nurses will explain problem-solving skills. In a routine clinical setting, the family will work on matters that are causing trouble in daily life using problem-solving skills.

Session III will cover communication and emotions: understanding the feelings of people with schizophrenia, expressed emotion (EE) theory, basic knowledge and skills about communication, and a lecture on desirable and undesirable communication with people with schizophrenia. In the first section, visiting nurses will describe the importance of understanding that people with schizophrenia are likely to have a pessimistic view about their future. In the second section on EE theory, visiting nurses will appreciate that it is natural for a family to have high EE, poor knowledge, and lack of support for mental illness.[29] Of note, visiting nurses will not force family members to play the role of supporter. When family members hear the explanation of high EE, many might feel that they are responsible for their burden. Visiting nurses will emphasise that both families and people with schizophrenia should think about positive and constructive communication to ensure mutual independence. In the third section on basic knowledge about communication and the lecture of desirable and undesirable communication with patients, caregivers will practice conversations using real cases and will be given time to consider better communication strategies.

Session IV will focus on the family's recovery. Topics will include thinking about the family's recovery, the importance of living one's own life, taking care of the family's physical and mental health needs, proper stress management, experiences and messages from members of the Family Association, and identifying available social resources in the community. During this session, visiting nurses will stress that people with schizophrenia and family members each have their own lifestyle and individual goals. Visiting nurses will also encourage family members to live their own lives using a variety of social resources instead of only working hard to take care of a person with schizophrenia. In addition, visiting nurses expect that family members will improve their physical and mental health by acquiring knowledge on self-care and stress management skills. Furthermore, visiting nurses will introduce the experiences of three members of the Family Association who have taken care of a person with schizophrenia. It is expected that others' similar experiences will help family members understand that they are not the only people experiencing such a hard time and relieve their feelings of sadness or hopelessness. Finally, visiting nurses will explain the social resources available in the community for family members and confirm the importance of connecting with many supporters around them.

Control group

Caregivers enrolled in the control group will receive usual care from visiting nurses. They will be put on a waiting list to receive the same intervention program after completing the 6-month follow-up assessment. They will not receive any type of psychoeducation or supportive therapies.

Outcomes

Table 2 shows an overview of the outcome measures. Outcome measures will be assessed at baseline prior to the intervention (T1), immediately after the completion of the intervention (1-month follow-up, T2), and 6 months after the baseline assessment (6-month follow-up, T3).

Primary outcome for caregivers

Zarit Burden Interview (ZBI-22)

ZBI-22 will be used to measure caregiver burden. It consists of 22 items scored on a five-point Likert scale from 0 (never) to 4 (nearly always), except for the final item on global burden, which is rated from 0 (not at all) to 4 (extremely). The total score ranges from 0 to 88, with higher scores indicating higher burden. The Japanese version of ZBI-

22 has high test-retest reproducibility and internal consistency. Construct validity has also been confirmed.[30]

Secondary outcome for caregivers

K6

K6 will be used to measure sub-clinical depression and anxiety disorders as part of a self-administered questionnaire. It consists of six items answered on a five-point Likert scale. Scores range from 0 to 24, with higher scores representing higher degrees of sub-clinical depression and anxiety disorder. The Japanese versions have essentially equivalent screening performance as the original English versions.[31]

General Self Efficacy Scale (GSES)

GSES is a measurement of self-efficacy in daily living. It includes 16 items with dichotomous questions. The higher the score, the better the self-efficacy, in general. GSES has high test-retest reproducibility and internal consistency. Construct validity has been confirmed.[32]

WHO-5

WHO-5 will be used to measure subjective quality of life based on positive mood (good spirits and relaxation), vitality (being active and waking up fresh and rested), and general interest (being interested in things). It consists of five items rated on a six-point Likert scale. Higher scores mean higher well-being. The Japanese version of WHO-5 has adequate internal consistency. It has been confirmed to have external concurrent validity and external discriminatory validity.[33]

Knowledge of Illness and Drug Inventory (KIDI)

KIDI will be used to assess knowledge regarding mental illness and the effects of medications on mental illness. There are two sub-scales: 10 items assessing knowledge of mental illness and 10 items assessing knowledge of the effects of antipsychotic drugs. This inventory consists of a self-reported inventory where respondents are asked to select the correct answer from three choices, with higher scores representing greater knowledge. KIDI is frequently used to assess knowledge about mental disorders and treatments in Japan.[34]

Secondary outcomes in people with schizophrenia

Behavior and Symptom Identification Scale (BASIS-32)

BASIS-32 is a commonly used measure in mental health. It includes 32 items on a five-point Likert scale, where 0 indicates no difficulties and 4 indicates severe difficulties. The scale measures five factors: (1) relation to self and others (seven items); (2) depression/anxiety (six items); (3) everyday life and role functioning (nine items); (4) impulsive and addictive behaviour (six items); and (5) psychosis (four items). Factors 1, 2, 4, and 5 are assessed as the total score divided by the number of items answered (mean score). Factor 3 is assessed based on the highest rating. Internal consistency and construct validity of the Japanese version of BASIS-32 have been demonstrated.[35]

WHO-5

WHO-5 is used to measure subjective quality of life based on positive mood (good spirits and relaxation), vitality (being active and waking up fresh and rested), and general interest (being interested in things). WHO-5 comprises five items rated on a six-point Likert scale. Higher scores mean higher well-being. The Japanese version of WHO-5 has adequate internal consistency. It has been confirmed to have external concurrent validity and external discriminatory validity.[33]

Hospitalisation by 6-month follow-up

This is a question with a dichotomous answer (yes or no) about whether the patient has been hospitalised during the past 6 months. The answer will be provided by the caregiver at baseline and the 6-month follow-up.

Sample size calculation

The sample size required was calculated according to guidelines in the Consolidated Standards of Reporting Trials (CONSORT) for cRCTs,[36] taking into account intra-class correlations (ICCs). The effect size of a brief FPE program for individual caregiver burden was estimated based on a previous pre-post test.[19] The pre-post test concluded that the standardised mean difference (d) of brief FPE on family burden was 0.46. Sample size was estimated as 76 in each arm based on an alpha error probability of 0.05 and power (1-β) of 0.80, using G*Power version 3.1.9.2.[37 38] For cRCTs, this value should be multiplied by design effect (1+[m-1]ρ), where m is the average cluster size and ρ is the ICC.[39] The estimated ICC for the primary outcome in this study was set to 0.05 and the average number of caregivers per cluster was set at 5. Assuming an attrition rate of 20%, the required sample size is 110 caregivers in each arm. Thus, at least 44 visiting nurse agencies will be recruited.

Quantitative analysis

The statistician will be blinded to the treatment group. We will analyse clinical outcomes on the basis of intention to treat and model the effect of the intervention on primary and secondary continuous outcomes using generalised linear latent and mixed models (GLLAMMs). This will allow for missing data to be taken into account within the statistical model. In this study, a three-level model will be used, with repeated measures nested in participants and participants nested in clusters. Time (baseline, 1-month follow-up, 6-month follow-up) will be considered level 1, individual caregivers will be considered level 2, and clusters (visiting nurse agencies) will be considered level 3. Regarding fixed effects, condition (intervention versus control), time, and a two-way interaction effect, condition by time, will be included. Models will adjust for baseline differences in caregiver socio-demographics such as age, gender, education, household income, family relationship with the person with schizophrenia, length of caregiving, and length of visiting nurse system use. Multiple levels of Cox proportional hazards regression models will also be used for the dichotomous question of hospitalisation at the 6-month follow-up. A *p*-value of less than 0.05 will be considered statistically significant.

Data monitoring

A data monitoring committee (DMC) will be set up. It will consist of at least two independent members. The DMC will meet monthly after the first participant has been randomised. The purpose of the meeting will be to review participation rates and reasons for study dropout. The DMC will be independent from any sponsor and competing interest.

Patient and public involvement

The research question, study design, and outcome measures were determined based on a discussion with representatives of the Family Association of Schizophrenia. The intervention program was developed through discussion and collaboration among members of the Family Association of Schizophrenia, psychiatric visiting nurses, FPE experts, psychiatrists, psychiatric nurses, clinical psychologists, and mental health social workers. After the completion of the study, this intervention tool will be available for anyone who wants to use it via the internet.

Ethics and dissemination

Ethical considerations

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The study protocol was approved by the Research Ethics Committee of the Graduate School of Medicine and the Faculty of Medicine at the University of Tokyo, Japan (No. 2019065NI). We will obtain informed consent from all caregivers and patients. The consent form will inform caregivers and patients that we guarantee protection of personal information and that the data will be anonymous and used only for academic purposes. There are no competing interests. This study is supported by the fundamental study on effective community services for people with severe mental disorders and their families.

Dissemination of the research findings

The findings will be published in a scientific peer-reviewed journal according to the CONSORT guidelines for cRCTs.[36] The participants will be informed of conference presentations and publications.

Strengths and limitations

The study has both strengths and limitations. First, the study will evaluate an implementable brief FPE program that potentially reduces time, cost, and staffing problems by incorporating the program into an existing mental health service system, namely visiting nurse services. Second, this is the first cRCT of a brief FPE program, which could prevent contamination between the intervention and control groups. Third, based on the concept of coproduction and PPI,[26] the study incorporated a variety of viewpoints from caregivers, visiting nurses, and FPE experts.

We recognise three limitations of this study. First, since the sampling method for participating agencies was not random, there is a possibility of selection bias. Second, since subjects will provide data through a self-reported questionnaire, information bias or random error is possible. For example, the severity of symptoms in people with schizophrenia that impact a caregiver's burden may not be accurately measured. Third, we designed the study and intervention based on coproduction, but there are still concerns about its feasibility in actual clinical settings. For example, participants might not complete all four sessions due to the condition of people with schizophrenia, family work, and family hospitalisation. Fourth, due to the short study period, the number of participants may not be able to meet the target sample size. These may lead to a high attrition rate during implementation.

Acknowledgments

The authors would like to thank the members of the *Mokusei* Family Association of Schizophrenia and N・FIELD Co., Ltd. for their invaluable advice on many aspects of the project.

Contributors

NY is the principal investigator responsible for the initial draft of this manuscript and organising and implementing the study. NY and KW calculated the sample size. NY, KW, SY, and MA decided on the analytic strategy. SS, TS, HT, KI, DN, CF, and NK helped throughout the development of the interventions and gave valuable feedback on the study protocol. All authors have read and approved the final manuscript.

Funding: This work is supported by the Fundamental study on effective community services for people with severe mental disorders and their families.

Competing interests: None declared.

Patient Consent: Obtained.

Ethics approval: Research Committee of the Graduate School of Medicine and the Faculty of Medicine at the University of Tokyo, Japan.

REFERENCES

1. Awad AG, Voruganti LN. The burden of schizophrenia on caregivers: a review. *Pharmacoecon Open* 2008;26:149–62. doi:10.2165/00019053-200826020-00005

2. Saunders JC. Families living with severe mental illness: a literature review. *Issues Ment Health Nurs* 2003;24:175–98. doi:10.1080/01612840305301

3. Shah AJ, Wadoo O, Latoo J. Psychological distress in carers of people with mental disorders. *British Journal of Medical Practitioners* 2010;3:a327.

4. Gopinath PA, Chaturvedi S. Distress behaviour of schizophrenics at home. *Acta Psychiatr Scand* 1992;86:185–8. doi:10.1111/j.1600-0447.1992.tb03249.x

5. McAuliffe R, O'Connor L, Meagher D. Parents' experience of living with and caring for an adult son or daughter with schizophrenia at home in Ireland: a qualitative study. *J Psychiatr Ment Health Nurs* 2014;21:145–53. doi:10.1111/jpm.12065

6. Sin J, Gillard S, Spain D, *et al.* Effectiveness of psychoeducational interventions for family carers of people with psychosis: a systematic review and meta-analysis. *Clin Psychol Rev* 2017;56:13–24. doi:10.1016/j.cpr.2017.05.002

7. Sin J, Jordan CD, Barley EA, *et al.* Psychoeducation for siblings of people with severe mental illness. *Cochrane Database Syst Rev* 2015;5:Cd010540. doi:10.1002/14651858.CD010540.pub2

8. Dixon L, McFarlane WR, Lefley H, *et al.* Evidence-based practices for services to families of people with psychiatric disabilities. *Psychiatr Serv* 2001;52:903–10. doi:10.1176/appi.ps.52.7.903

9. Birchwood M, Smith J, Cochrane R. Specific and non-specific effects of educational intervention for families living with schizophrenia. A comparison of three methods. *Br J Psychiatry* 1992;160:806–14. doi:10.1192/bjp.160.6.806

10. Lehman AF, Steinwachs DM. Patterns of usual care for schizophrenia: initial results from the Schizophrenia Patient Outcomes Research Team (PORT) Client Survey. *Schizophr Bull* 1998;24:11–20; discussion 20–32. doi:10.1093/oxfordjournals.schbul.a033303

11. Oshima I, Mino Y, Nakamura Y, *et al.* Implementation and dissemination of family psychoeducation in Japan: nationwide survey on psychiatric hospitals in 1995 and 2001. *Journal of Social Policy & Social Work* 2007;11:5–16.

12. Rummel-Kluge C, Kissling W. Psychoeducation in schizophrenia: new developments and approaches in the field. *Curr Opin Psychiatry* 2008;21:168–72. doi:10.1097/YCO.0b013e3282f4e574

13. Harvey C. Family psychoeducation for people living with schizophrenia and their families. *BJPsych Adv* 2018;24:9–19. doi:10.1192/bja.2017.4

14. Fadden G, Heelis R. 2011. The Meriden Family Programme: lessons learned over 10 years. *J Ment Health* 2011;20:79–88. doi:10.3109/09638237.2010.492413 [published online first: 2 September 2010].

15. McFarlane WR, Dixon L, Lukens E, *et al.* Family psychoeducation and schizophrenia: a review of the literature. *J Marital Fam Ther* 2003;29:223–45.

16. Okpokoro U, Adams CE, Sampson S. Family intervention (brief) for schizophrenia. *Cochrane Database Syst Rev* 2014;3:Cd009802. doi:10.1002/14651858.CD009802.pub2

17. Pitschel-Walz G, Leucht S, Bauml J, *et al.* The effect of family interventions on relapse and rehospitalization in schizophrenia—a meta-analysis. *Schizophr Bull* 2001;27:73–92. doi:10.1093/oxfordjournals.schbul.a006861.

18. Smith JV, Birchwood MJ. Specific and non-specific effects of educational intervention with families living with a schizophrenic relative. *Br J Psychiatry* 1987;150:645–52. doi:10.1192/bjp.150.5.645.

19. Devaramane V, Pai NB, Vella SL. The effect of a brief family intervention on primary carer's functioning and their schizophrenic relatives levels of psychopathology in India. *Asian J Psychiatr* 2011;4:183–7. doi:10.1016/j.ajp.2011.06.004

20. Sharif F, Shaygan M, Mani A. Effect of a psycho-educational intervention for family members on caregiver burdens and psychiatric symptoms in patients with schizophrenia in Shiraz, Iran. *BMC Psychiatry* 2012;12:48. doi:10.1186/1471-244x-12-48

21. Huang XY, Ma WF, Shih HH, *et al.* Roles and functions of community mental health nurses caring for people with schizophrenia in Taiwan. *J Clin Nurs* 2008;17:3030–40. doi:10.1111/j.1365-2702.2008.02426.x

22. Setoya N, Kayama M, Tsunoda A, *et al.* A survey of the family care provided in psychiatric home-visit nursing and related characteristics of clients. *Japanese Bulletin of Social Psychiatry* 2011;20:17–25.

23. Chan AW, Tetzlaff JM, Altman DG, *et al.* SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158:200–7. doi:10.7326/0003-4819-158-3-201302050-00583

24. Mueser, K. T., Bond, G. R., Drake, R. E., & Resnick, S. G. (1998). Models of community care for severe mental illness: a review of research on case management. Schizophr Bull, 24(1), 37-74. doi:10.1093/oxfordjournals.schbul.a033314

25. Varghese M, Shah A, Kumar GSU, *et al.* Family intervention and support in schizophrenia: a manual on family intervention for the mental health professional, version 2. Bangalore, India: National Institute of Mental Health and Neurosciences.

26. Batalden M, Batalden P, Margolis P, *et al.* Coproduction of healthcare service. *BMJ Qual Safe* 2016;25:509–17. doi:10.1136/bmjqs-2015-004315

27. Ferriter M, Huband N. Experiences of parents with a son or daughter suffering from schizophrenia. *J Psychiatr Ment Health Nurs* 2003;10:552–60. doi:10.1046/j.1365-2850.2003.00624.x

28. Menezes NM, Arenovich T, Zipursky RB. A systematic review of longitudinal outcome studies of first-episode psychosis. *Psychol Med* 2006;36:1349–62. doi:10.1017/s0033291706007951

29. Amaresha AC, Venkatasubramanian G. Expressed emotion in schizophrenia: an overview. *Indian J Psychol Med* 2012;34:12–20. doi:10.4103/0253-7176.96149

30. Arai Y, Kudo K, Hosokawa T, *et al.* Reliability and validity of the Japanese version of the Zarit Caregiver Burden interview. *Psychiatry Clin Neurosci* 1997;51:281–7. doi:10.1111/j.1440-1819.1997.tb03199.x

31. Sakurai K, Nishi A, Kondo K, *et al.* Screening performance of K6/K10 and other screening instruments for mood and anxiety disorders in Japan. *Psychiatry Clin Neurosci* 2011;65:434–41. doi:10.1111/j.1440-1819.2011.02236.x

32. Sakano Y, Tohjoh M. The General Self-Efficacy Scale (GSES): scale development and validation. *Japanese Journal of Behavior Therapy* 1986;12:73–82.

33. Awata S, Bech P, Yoshida S, *et al.* Reliability and validity of the Japanese version of the World Health Organization-Five Well-Being Index in the context of detecting depression in diabetic patients. *Psychiatry Clin Neurosci* 2007;61:112–9. doi:10.1111/j.1440-1819.2007.01619.x

34. Maeda M, OM, Renri T, *et al.* It is as a result of disease drug knowledge degree investigation (Knowledge of Illness and Drugs Inventory, KIDI) for a person with IIB-29 schizophrenia and the family. *Japanese Bulletin of Social Psychiatry* 1994;2:173–4.

35. Setoya Y, N. Y., Kurita H. Utility of the Japanese version of the BASIS-32 in inpatients in psychiatric hospital. *Japanese Journal of Clinical Psychiatry* 2002;31:571–5.

36. Campbell MK, Piaggio G, Elbourne DR, *et al.* Consort 2010 statement: extension to cluster randomised trials. *BMJ* 2012;345:e5661. doi:10.1136/bmj.e5661

37. Faul F, Erdfelder E, Buchner A, *et al.* Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. *Behav Res Methods* 2009;41:1149–60. doi:10.3758/brm.41.4.1149

38. Faul F, Erdfelder E, Lang AG, *et al.* G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods* 2007;39:175–91.

39. Campbell MK, Elbourne DR, Altman DG. CONSORT statement: extension to cluster randomised trials. *BMJ* 2004;328:702–8. doi:10.1136/bmj.328.7441.702

Table 1. Outline of the brief family psychoeducation program

Session number	Session aim	Content
I	General knowledge about schizophrenia	Definition, causes, symptoms, prognosis, pharmacological treatment, psychosocial rehabilitation. Activity: Let's review the knowledge gained in this session.
II	How to cope with people with schizophrenia using problem-solving skills	How to cope with hallucinations and delusions; signs of recurrence and how to prevent recurrence; how to cope when the disease gets worse; what to do with people with schizophrenia when they stay at home all day; how to respond to people with schizophrenia who do not want to take their medication; what to do when domestic violence is imminent, is happening, or has happened; how to get involved when self-injury or suicide is suspected. Activity: Let's learn how to apply problem-solving skills.
III	Handling communication and emotions	Understanding the feelings of people with schizophrenia, expressed emotion theory, basic knowledge about communication, and lecture about desirable and undesirable communication with people with schizophrenia. Activity: Let's practice conversations using real cases.
IV	Family recovery	Thinking about the family's recovery, importance of living one's own life, taking care of the family's physical and mental health needs, proper stress management, and experiences and messages from members of the Family Association. Activity: Let's identify social resources in the community and recognise the importance of connecting with many supporters around families.

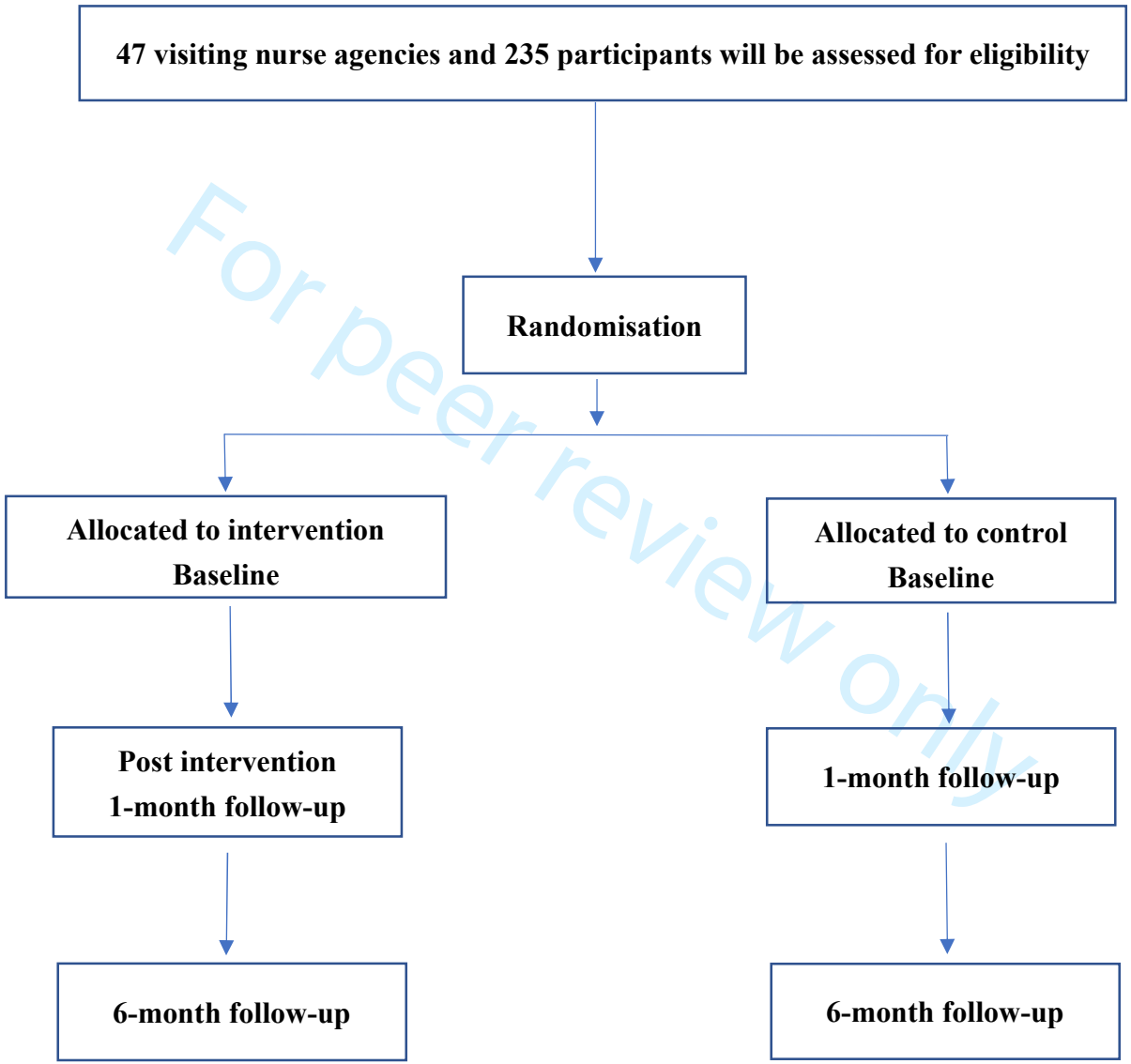
This intervention program consists of four 60-minute modules completed over 1 month.

Table 2. Outcome measures

	Outcome measure	Baseline	1-month follow-up	6-month follow-up
Caregivers	Zarit Burden Interview (ZBI-22)	✓	✓	✓
	K6	✓	✓	✓
	General Self-Efficacy Scale (GSES)	✓	✓	✓
	WHO-5	✓	✓	✓
	Knowledge of Illness and Drug Inventory (KIDI)	✓	✓	✓
People with schizophrenia	Behavior and Symptom Identification Scale (BASIS-32)	✓	✓	✓
	WHO-5	✓	✓	✓
	Hospitalisation during the past 6 months	✓	–	✓

Figure 1

Figure 1. Study flow chart



SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	ItemNo	Description	
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	P2
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	NA
Funding	4	Sources and types of financial, material, and other support	P15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	P1
	5b	Name and contact information for the trial sponsor	NA
	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	NA
	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)	NA
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	P4-6

	6b	Explanation for choice of comparators	P4-6
Objectives	7	Specific objectives or hypotheses	P6
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)	P6
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	P6-7
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)	P6-7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	P7-9
	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)	P7-9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	P7-9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	P7-9
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	P10-12
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)	P6-7

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	P12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	P6-7
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	P7
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	P7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	P7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	P7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	P7
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	P13

	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	P13
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	P13
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	P12-13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	P12-13
	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)	P12-13
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	P13
	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	NA
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	NA
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	P13-P14
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)	NA
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	P6-7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	P13
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	P15
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	P16
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	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	P14
	31b	Authorship eligibility guidelines and any intended use of professional writers	P14
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	P14

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	See supplementary file
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*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.