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

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

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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

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

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

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43 Practical implementation strategies for a brief FPE program need to be
44 considered in addition to a scientific evaluation of the effects. Brief FPE programs
45 provided by visiting nurses appear to be a potentially feasible and sustainable way of
46 implementing FPE in a Japanese clinical setting. Visiting nurses routinely visit clients
47 with schizophrenia and their family members. They have already built rapport with
48 clients and family members and would be able to respond according to their needs,
49 which means they could seamlessly provide highly individualized brief FPE.²¹ In
50 addition, the system of visiting nurses could easily be applied because the number of
51 visiting nurses has been increasing recently in Japan. From a cost perspective, it would
52 be possible to make family support a reimbursable service under national health
53 insurance to cover psychiatric visiting nurse consultancy fees.²² Taken together, brief
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6 FPE provided by visiting nurses could overcome the poor implementation rate and
7 become effective family interventions in the community setting in Japan. The purpose
8 of this study is to clarify, through a cluster randomised controlled trial (cRCT), whether
9 visiting nurses providing brief FPE to families caring for people with schizophrenia will
10 alleviate family burden.
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13 14 **METHODS AND ANALYSIS**

15 **Trial design**

16 This study is a two-arm, parallel-group cRCT. The randomisation procedure is
17 conducted at the cluster level (visiting nurse agencies). Visiting nurse agencies will be
18 randomly assigned to the intervention or control (treatment as usual (TAU)) group in a
19 1:1 ratio. Data will be collected at the individual level. Analyses to evaluate the efficacy
20 of the intervention program will be conducted at the individual level, taking into
21 consideration cluster-level effects. The study protocol was registered in the University
22 Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN-CTR
23 ID, UMIN000038044). This protocol was reported according to the Standard Protocol
24 Items: Recommendations for Interventional Trials (SPIRIT) guidelines.²³
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32 **Setting and site selection at the cluster level**

33 Figure 1 shows the participant flow chart for this study. We recruited 47 visiting nurse
34 agencies in four prefectures in Japan, namely Tokyo, Saitama, Kanagawa, and Chiba
35 prefectures. All the participating visiting nurse agencies are managed by one
36 organisation. The corresponding author (NY) explained the purpose of this study to the
37 organisation and asked the organisation to recruit 47 visiting nurse agencies.
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40 To be included, a visiting nurse agency must have been mainly providing services
41 for psychiatric patients or clients, not elderly people or those with other physical
42 diseases, for at least 1 year. In each agency, visiting nurses care for at least two people
43 with schizophrenia who live with their family. There are no exclusion criteria at the
44 cluster level.
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50 **Participant eligibility criteria and recruitment procedure at the individual level**

51 At the individual level, we set the following inclusion criteria for a caregiver of a person
52 with schizophrenia: 1) is the primary caregiver; 2) aged over 20 years; 3) is a family
53 member of the person with schizophrenia such as a parent, sibling, spouse, or child; and
54 4) lives with the person with schizophrenia. There are no exclusion criteria for
55 caregivers. In addition, the inclusion criteria for people with schizophrenia are as
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6 follows: 1) diagnosis of schizophrenia based on the International Statistical
7 Classification of Diseases and Related Health Problems, 10th revision and 2) use of
8 visiting nurse services.
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10 In each agency, potential participants (caregivers of people with schizophrenia
11 and people with schizophrenia) will be randomly extracted using a recruitment sequence
12 table. The recruitment sequence table will be created using a random number generation
13 method with the Stata statistical software program, version 15. Based on the recruitment
14 sequence table, consent acquisition will be performed by visiting nurses who have
15 attended a lecture on study design and ethical considerations. The study will include
16 only caregivers who voluntarily agree to participate in the study. The average cluster
17 size will be approximately five caregivers. Visiting nurse agencies will be allocated
18 randomly to the intervention or control group. The intervention program will last one
19 month. The study has three planned assessment points including baseline assessment
20 prior to the intervention (T1), immediately after the completion of the intervention (1-
21 month follow-up assessment, T2), and 6 months after the baseline assessment (6-month
22 follow-up assessment, T3) in both the intervention and control groups.
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30 31 **Intervention program**

32 The intervention program is a single-family intervention conducted by psychiatric
33 visiting nurses. It is based on the Family Intervention and Support in Schizophrenia: A
34 Manual on Family Intervention for the Mental Health Professional.²⁴ This program was
35 developed through discussions and collaborations among members of the Family
36 Association of Schizophrenia, psychiatric visiting nurses, FPE experts, psychiatrists,
37 psychiatric nurses, clinical psychologists, and mental health social workers based on the
38 concept of coproduction and Patient and Public Involvement (PPI).²⁵ During the
39 development process, we tried to avoid long sentences, enlarged the characters, and
40 used visually appealing drawings. The program consists of four sessions that last 60
41 minutes each using the above tool. It will be completed over a period of a month.
42 Psychiatric visiting nurses will provide appropriate information using this intervention
43 tool and advice to the family about living problems based on their own nursing clinical
44 experience.
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52 Before the intervention, we will provide the intervention team of psychiatric
53 visiting nurses with a 1-day lecture. The lecture will consist of three parts. First, a
54 caregiver of a person with schizophrenia will talk about their life problems and what
55 they want visiting nurses to do; this is expected to increase the motivation of visiting
56 nurses. Second, basic communication training will be conducted through role-playing.
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6 Visiting nurses, who will be brief FPE providers, will be in groups of three. They will
7 each play the role of a visiting nurse, caregiver, and evaluator. They will practice
8 listening to caregivers. Third, the primary investigator (NY) will equip them with basic
9 knowledge about FPE and explain the contents of this intervention tool and the points
10 the primary investigator wants to emphasise. Through these trainings, we expect to
11 improve the motivation, knowledge, and skills of the visiting nurses in providing the
12 brief FPE program.
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16 Table 1 shows the contents of the intervention tool. Session I covers general
17 knowledge about schizophrenia: definition, causes, symptoms, prognosis,
18 pharmacological treatment, and psychosocial rehabilitation. Regarding definition and
19 causes, visiting nurses will stress that schizophrenia is a brain disease that can manifest
20 in anyone using the diathesis-stress model and the dopamine hypothesis. It is important
21 to provide the family with a biological explanation about the aetiology of schizophrenia
22 because there might be family members who think people become schizophrenic
23 because of family relationships.²⁶ In addition to an explanation of the symptoms
24 themselves, visiting nurses will describe how people with schizophrenia have
25 difficulties living their own lives due to their symptoms. Visiting nurses will explain the
26 disease course such as the prodromal phase, acute phase, and recovery phase. Next,
27 visiting nurses will explain the characteristics of each phase and what to do during each
28 phase. In terms of prognosis, visiting nurses will address that over 70% of people can
29 recover if they receive appropriate pharmacological therapy.²⁷ Concerning medication,
30 visiting nurses will appreciate the idea that people with schizophrenia usually do not
31 want to take medication. Visiting nurses will talk about the necessity, safety, and
32 reasons for adherence to pharmacological therapy. In addition, the side effects of
33 antipsychotic medications will be described clearly, using relevant pictures. Finally,
34 visiting nurses will give an outline of psychosocial therapy. At the end, participants will
35 answer questions with dichotomous answers—“yes” or “no”—to confirm what they
36 have learned from the session.
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48 Session II deals with how to cope with people with schizophrenia and problem-
49 solving skills. The contents of this session include how to cope with hallucinations and
50 delusions; signs of recurrence; how to prevent recurrences; how to cope when the
51 disease gets worse; what to do with people with schizophrenia when they stay at home
52 all day; how to respond to people with schizophrenia who do not want to take their
53 medication; how to respond when domestic violence is imminent, is occurring, or has
54 occurred; and how to get involved when self-injury or suicide is suspected. Finally,
55 visiting nurses will explain problem-solving skills. In the routine clinical setting, the
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6 family will work on matters that are causing trouble in daily life using problem-solving
7 skills.
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10 Session III includes communication and emotions: understanding the feelings of
11 people with schizophrenia, expressed emotion (EE) theory, basic knowledge and skills
12 about communication, and a lecture on desirable and undesirable communication with
13 people with schizophrenia. In the first section, visiting nurses will describe the
14 importance of understanding that people with schizophrenia are likely to have a
15 pessimistic view about their future. In the second section on EE theory, visiting nurses
16 will appreciate that it is natural for a family to have high EE with poor knowledge and
17 lack of support about mental illness.²⁸ Of note, visiting nurses are not forcing family
18 members to play the role of supporter. When family members hear the explanation of
19 high EE, many might feel that they are responsible for their burden. Visiting nurses will
20 emphasise that both families and people with schizophrenia should think about positive
21 and constructive communication to ensure mutual independence. In the third section on
22 basic knowledge about communication and the lecture of desirable and undesirable
23 communication with patients, caregivers will practice conversations using real cases and
24 will be given time to consider better communication strategies.
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31 Session IV focuses on the family's recovery. Topics include thinking about the
32 family's recovery, the importance of living one's own life, taking care of the family's
33 physical and mental health needs, proper stress management, experiences and messages
34 from members of the Family Association, and identifying available social resources in
35 the community. During this session, visiting nurses will stress that people with
36 schizophrenia and family members each have their own lifestyle and individual goals.
37 Visiting nurses will also encourage family members to live their own lives using a
38 variety of social resources instead of working hard to take care of a person with
39 schizophrenia. In addition, visiting nurses expect that the family will improve their
40 physical and mental health by acquiring knowledge on self-care and stress management
41 skills. Furthermore, visiting nurses will introduce the experiences of three members of
42 the Family Association who have taken care of a person with schizophrenia. It is
43 expected that others' similar experiences will help family members understand that they
44 are not the only people experiencing such a hard time and relieve their feelings of
45 sadness or hopelessness. Finally, visiting nurses will explain the social resources
46 available in the community for family members and confirm the importance of
47 connecting with many supporters around them.
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58 **Control group**

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6 Visiting nurse agencies in the control group will offer TAU. Caregivers enrolled in the
7 control group will be put on a waiting list to receive the same intervention program after
8 completing the 6-month follow-up assessment.
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10 11 **Outcomes**

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13 Table 2 shows an overview of the outcome measures. Outcome measures will be
14 assessed baseline assessment prior to the intervention (T1), immediately after the
15 completion of the intervention (1-month follow-up assessment, T2), and 6 months after
16 the baseline assessment (6-month follow-up assessment, T3).
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19 20 **Primary outcome for caregivers**

21 Zarit burden interview (ZBI-22)

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

35 K6

36 K6 is used to measure non-clinical depression and anxiety disorders as part of a self-
37 administered questionnaire. It consists of six items answered on a five-point Likert
38 scale. Scores thus range from 0 to 24, with higher scores representing higher degrees of
39 non-clinical depression and anxiety disorder. The Japanese versions of the K6 have
40 essentially equivalent screening performance as the original English versions.³⁰
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46 General Self Efficacy Scale (GSES)

47 GSES is a measurement of self-efficacy in daily living. It includes 16 items with
48 dichotomous questions. The higher the score, the better the self-efficacy, in general.
49 GSES had high test-retest reproducibility and internal consistency. Construct validity
50 has been confirmed.³¹
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55 WHO-5

56 WHO-5 is used to measure subjective quality of life based on positive mood (good
57 spirits and relaxation), vitality (being active and waking up fresh and rested), and
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6 general interest (being interested in things). It consists of five items rated on a six-point
7 Likert scale. Higher scores mean higher well-being. The Japanese version of WHO-5
8 has adequate internal consistency. It was also confirmed to have external concurrent
9 validity and external discriminatory validity.³²
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13 Knowledge of Illness and Drug Inventory (KIDI)

14 KIDI is used to assess knowledge regarding mental illness and the effects of
15 medications on mental illness. There are two sub-scales: 10 items assessing knowledge
16 of mental illness and 10 items assessing knowledge of the effects of antipsychotic
17 drugs. This inventory consists of a self-reported inventory where respondents are asked
18 to select the correct answer from three choices, with higher scores representing greater
19 knowledge. KIDI is frequently used to assess knowledge about mental disorders and
20 treatments in Japan.³³
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27 **Primary outcome for people with schizophrenia**

28 Behavior and Symptoms Identification Scale (BASIS-32)

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

46 WHO-5

47 WHO-5 is used to measure subjective quality of life based on positive mood (good
48 spirits and relaxation), vitality (being active and waking up fresh and rested), and
49 general interest (being interested in things). WHO-5 comprises five items rated on a six-
50 point Likert scale. Higher scores mean higher well-being. The Japanese version of
51 WHO-5 has adequate internal consistency. It was also confirmed to have external
52 concurrent validity and external discriminatory validity.³²
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58 Hospitalisation by 6-month follow-up

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6 This is a question with a dichotomous answer (yes or no) about whether the patient has
7 been hospitalised during the past 6 months. The answer will be provided by the
8 caregiver at baseline and the 6-month follow-up.
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10 11 **Sample size calculation**

12 The sample size required was calculated according to guidelines in the Consolidated
13 Standards of Reporting Trials (CONSORT) for cRCTs,³⁵ taking into account intra-class
14 correlations (ICCs). The effect size of a brief FPE program for individual caregiver
15 burden was estimated based on a previous pre-post test.¹⁹ The pre-post test concluded
16 that the standardised mean difference (d) of brief FPE on family burden was 0.46.
17 Sample size was estimated as 76 in each arm based on an alpha error probability of 0.05
18 and power (1- β) of 0.80, using G*Power version 3.1.9.2.^{36 37} cRCT should be multiplied
19 by design effect (1+[m-1] ρ), where m is the average cluster size and ρ is the ICC.³⁸ The
20 estimated ICC for the primary outcome in this study was set to 0.05 and the average
21 number of caregivers per cluster was set at five people. Assuming an attrition rate of
22 20%, the required sample size was 110 caregivers in each arm; thus, at least 44 visiting
23 nurse stations will be recruited.
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32 **Randomisation**

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

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

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

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

50 Ethical considerations

51 The authors assert that all procedures contributing to this work comply with the ethical
52 standards of the relevant national and institutional committees on human experimentation
53 and with the Helsinki Declaration of 1975, as revised in 2008. The study protocol was
54 approved by the Research Ethics Committee of the Graduate School of Medicine and the
55 Faculty of Medicine at the University of Tokyo, Japan (No. 2019065NI). We will obtain
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6 informed consent from all caregivers and patients. The consent form will inform
7 caregivers and patients that we guarantee protection of personal information and that the
8 data will be anonymous and used only for academic purposes. There are no competing
9 interests. This study is supported by fundamental study on effective community services
10 for people with severe mental disorders and their families.
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12

13 14 15 **Dissemination of the research findings**

16 The findings will be published in a scientific peer-reviewed journal according to the
17 CONSORT guidelines for cRCTs.³⁵ The participants will be informed of conference
18 presentations and publications.
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21 22 **Strengths and limitations**

23 The study has both strengths and limitations. First, the study will evaluate an
24 implementable brief FPE program that potentially reduces time, cost, and staffing
25 problems by incorporating the program into an existing mental health service system,
26 namely visiting nurse services. Second, this is the first cRCT of a brief FPE program, a
27 trial with a better study design. It will provide better evidence than past studies. Third,
28 based on the concept of coproduction and PPI,²⁵ the study was developed with
29 incorporation of a variety of views from caregivers, visiting nurses, and FPE experts.
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32 We recognise three limitations of this study. First, since the sampling method for
33 participating agencies was not random, there is a possibility of selection bias. Second,
34 since subjects provide data through a self-reported questionnaire, information bias or
35 random error is possible. Third, each visiting nurse may not be able to complete all four
36 sessions using the tool in the actual clinical setting, leading to the possibility of a high
37 attrition rate during implementation.
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44 45 **Acknowledgments**

46 The authors would like to thank the members of the *Mokuseikai* Family Association of
47 Schizophrenia for their invaluable advice on many aspects of the project.
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50 51 **Contributors**

52 NY is the principal investigator responsible for the initial draft of this manuscript and
53 organising and implementing the study. NY and KW calculated the sample size. NY,
54 KW, SY, and MA decided on the analytic strategy. All authors contributed to the
55 development of the intervention and study design. All authors have read and approved
56 the final manuscript.
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6 **Funding:** This work is supported by Fundamental study on effective community
7 services for people with severe mental disorders and their families.
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10 **Competing interests:** None declared.
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13 **Patient Consent:** Obtained.
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16 **Ethics approval:** Research Committee of the Graduate School of Medicine and the
17 Faculty of Medicine at the University of Tokyo, Japan.
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For peer review only

Table 1. Outline of the brief family psychoeducation program

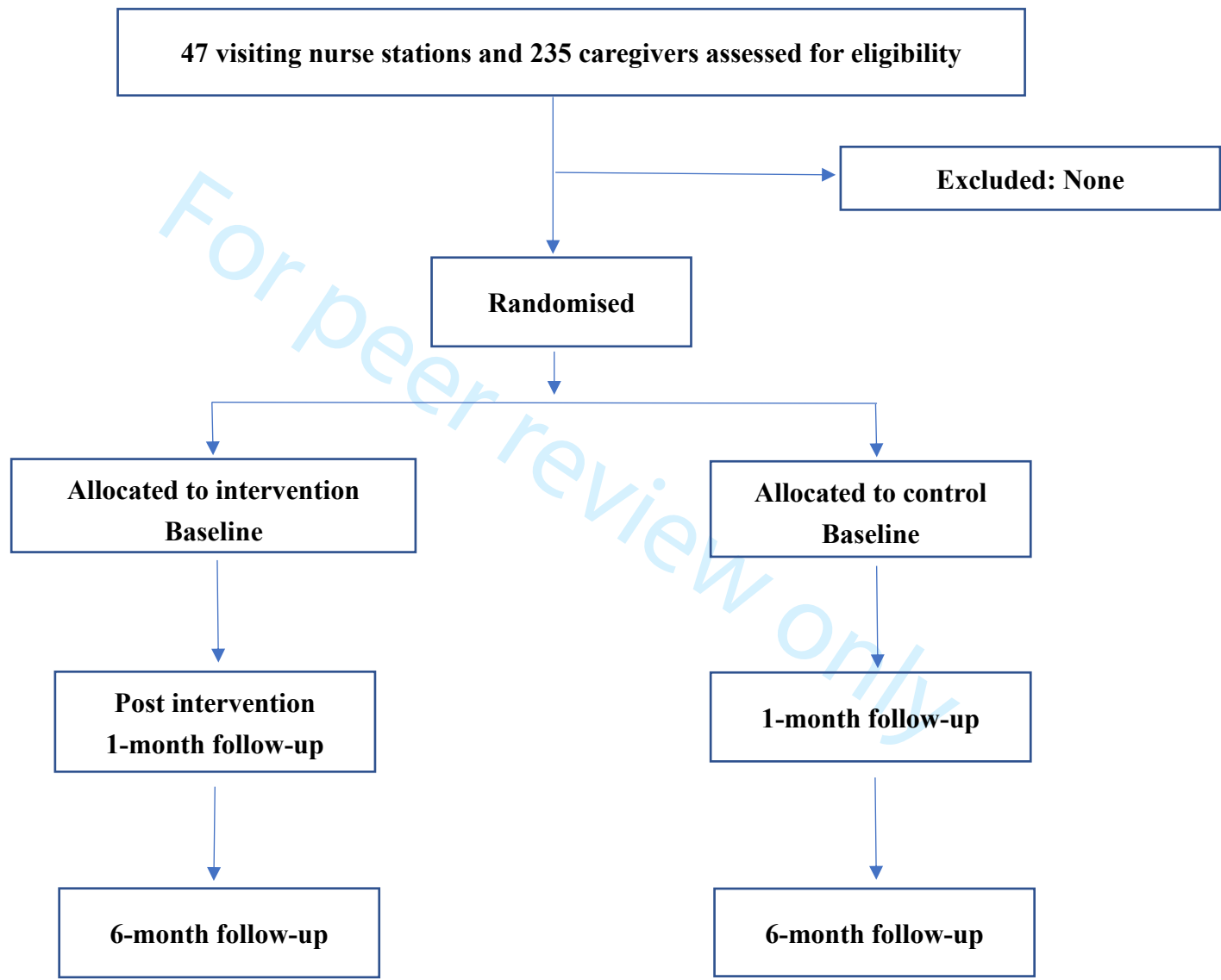
Session number	Session aim	Contents
I	General knowledge about schizophrenia	Definition, causes, symptoms, prognosis, pharmacological treatment, psychosocial rehabilitation. Work: Let's review the knowledge gained in this session.
II	How to cope with people with schizophrenia using problem-solving skills	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 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

1				
2	Objectives	7	Specific objectives or hypotheses	P5
3				
4	Trial design	8	Description of trial design including type of trial (eg,	P5
5			parallel group, crossover, factorial, single group),	
6			allocation ratio, and framework (eg, superiority,	
7			equivalence, noninferiority, exploratory)	
8				
9				
10	Methods: Participants, interventions, and outcomes			
11				
12	Study setting	9	Description of study settings (eg, community clinic,	P5-6
13			academic hospital) and list of countries where data will	
14			be collected. Reference to where list of study sites can	
15			be obtained	
16				
17	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If	P5-6
18			applicable, eligibility criteria for study centres and	
19			individuals who will perform the interventions (eg,	
20			surgeons, psychotherapists)	
21				
22				
23	Interventions	11a	Interventions for each group with sufficient detail to	P6-8
24			allow replication, including how and when they will be	
25			administered	
26				
27				
28		11b	Criteria for discontinuing or modifying allocated	P6-8
29			interventions for a given trial participant (eg, drug dose	
30			change in response to harms, participant request, or	
31			improving/worsening disease)	
32				
33		11c	Strategies to improve adherence to intervention	P6-8
34			protocols, and any procedures for monitoring	
35			adherence (eg, drug tablet return, laboratory tests)	
36				
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38		11d	Relevant concomitant care and interventions that are	P6-8
39			permitted or prohibited during the trial	
40				
41	Outcomes	12	Primary, secondary, and other outcomes, including the	P9-10
42			specific measurement variable (eg, systolic blood	
43			pressure), analysis metric (eg, change from baseline,	
44			final value, time to event), method of aggregation (eg,	
45			median, proportion), and time point for each outcome.	
46			Explanation of the clinical relevance of chosen efficacy	
47			and harm outcomes is strongly recommended	
48				
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50	Participant	13	Time schedule of enrolment, interventions (including	P5-6
51	timeline		any run-ins and washouts), assessments, and visits for	
52			participants. A schematic diagram is highly	
53			recommended (see Figure)	
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2	Sample size	14	Estimated number of participants needed to achieve	P10-11
3			study objectives and how it was determined, including	
4			clinical and statistical assumptions supporting any	
5			sample size calculations	
6				
7	Recruitment	15	Strategies for achieving adequate participant enrolment	P5-6
8			to reach target sample size	
9				

Methods: Assignment of interventions (for controlled trials)

Allocation:

14	Sequence	16a	Method of generating the allocation sequence (eg,	P11
15	generation		computer-generated random numbers), and list of any	
16			factors for stratification. To reduce predictability of a	
17			random sequence, details of any planned restriction	
18			(eg, blocking) should be provided in a separate	
19			document that is unavailable to those who enrol	
20			participants or assign interventions	
21				
22				
23				
24	Allocation	16b	Mechanism of implementing the allocation sequence	P11
25	concealment		(eg, central telephone; sequentially numbered, opaque,	
26	mechanism		sealed envelopes), describing any steps to conceal the	
27			sequence until interventions are assigned	
28				
29				
30	Implementation	16c	Who will generate the allocation sequence, who will	P11
31			enrol participants, and who will assign participants to	
32			interventions	
33				
34	Blinding	17a	Who will be blinded after assignment to interventions	P11
35	(masking)		(eg, trial participants, care providers, outcome	
36			assessors, data analysts), and how	
37				
38				
39		17b	If blinded, circumstances under which unblinding is	P11
40			permissible, and procedure for revealing a participant's	
41			allocated intervention during the trial	
42				

Methods: Data collection, management, and analysis

45	Data collection	18a	Plans for assessment and collection of outcome,	P11-12
46	methods		baseline, and other trial data, including any related	
47			processes to promote data quality (eg, duplicate	
48			measurements, training of assessors) and a description	
49			of study instruments (eg, questionnaires, laboratory	
50			tests) along with their reliability and validity, if known.	
51			Reference to where data collection forms can be found,	
52			if not in the protocol	
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56		18b	Plans to promote participant retention and complete	P11-12
57			follow-up, including list of any outcome data to be	
58			collected for participants who discontinue or deviate	
59			from intervention protocols	
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2	Data	19	Plans for data entry, coding, security, and storage,	P12
3	management		including any related processes to promote data quality	
4			(eg, double data entry; range checks for data values).	
5			Reference to where details of data management	
6			procedures can be found, if not in the protocol	
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9	Statistical	20a	Statistical methods for analysing primary and	P11-12
10	methods		secondary outcomes. Reference to where other details	
11			of the statistical analysis plan can be found, if not in the	
12			protocol	
13				
14		20b	Methods for any additional analyses (eg, subgroup and	P11-12
15			adjusted analyses)	
16				
17		20c	Definition of analysis population relating to protocol	P11-12
18			non-adherence (eg, as randomised analysis), and any	
19			statistical methods to handle missing data (eg, multiple	
20			imputation)	
21				
22				
23	Methods: Monitoring			
24				
25	Data monitoring	21a	Composition of data monitoring committee (DMC);	P12
26			summary of its role and reporting structure; statement	
27			of whether it is independent from the sponsor and	
28			competing interests; and reference to where further	
29			details about its charter can be found, if not in the	
30			protocol. Alternatively, an explanation of why a DMC is	
31			not needed	
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34		21b	Description of any interim analyses and stopping	NA
35			guidelines, including who will have access to these	
36			interim results and make the final decision to terminate	
37			the trial	
38				
39				
40	Harms	22	Plans for collecting, assessing, reporting, and	NA
41			managing solicited and spontaneously reported	
42			adverse events and other unintended effects of trial	
43			interventions or trial conduct	
44				
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46	Auditing	23	Frequency and procedures for auditing trial conduct, if	NA
47			any, and whether the process will be independent from	
48			investigators and the sponsor	
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51	Ethics and dissemination			
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53	Research ethics	24	Plans for seeking research ethics	P12
54	approval		committee/institutional review board (REC/IRB)	
55			approval	
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1				
2	Protocol	25	Plans for communicating important protocol	NA
3	amendments		modifications (eg, changes to eligibility criteria,	
4			outcomes, analyses) to relevant parties (eg,	
5			investigators, REC/IRBs, trial participants, trial	
6			registries, journals, regulators)	
7				
8				
9	Consent or	26a	Who will obtain informed consent or assent from	P5-6
10	assent		potential trial participants or authorised surrogates, and	
11			how (see Item 32)	
12				
13		26b	Additional consent provisions for collection and use of	NA
14			participant data and biological specimens in ancillary	
15			studies, if applicable	
16				
17	Confidentiality	27	How personal information about potential and enrolled	P12
18			participants will be collected, shared, and maintained in	
19			order to protect confidentiality before, during, and after	
20			the trial	
21				
22				
23	Declaration of	28	Financial and other competing interests for principal	P13
24	interests		investigators for the overall trial and each study site	
25				
26	Access to data	29	Statement of who will have access to the final trial	P12
27			dataset, and disclosure of contractual agreements that	
28			limit such access for investigators	
29				
30				
31	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and	NA
32	post-trial care		for compensation to those who suffer harm from trial	
33			participation	
34				
35	Dissemination	31a	Plans for investigators and sponsor to communicate	P13
36	policy		trial results to participants, healthcare professionals,	
37			the public, and other relevant groups (eg, via	
38			publication, reporting in results databases, or other	
39			data sharing arrangements), including any publication	
40			restrictions	
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44		31b	Authorship eligibility guidelines and any intended use of	P13
45			professional writers	
46				
47		31c	Plans, if any, for granting public access to the full	P13
48			protocol, participant-level dataset, and statistical code	
49				
50				
51	Appendices			
52	Informed consent	32	Model consent form and other related documentation	NA
53	materials		given to participants and authorised surrogates	
54				
55	Biological	33	Plans for collection, laboratory evaluation, and storage	NA
56	specimens		of biological specimens for genetic or molecular	
57			analysis in the current trial and for future use in	
58			ancillary studies, if applicable	
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Effects of brief family psychoeducation for caregivers of people with schizophrenia in Japan provided by visiting nurses: protocol for a cluster randomized controlled trial

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6 **1 Effects of brief family psychoeducation for caregivers of people with**
7 **2 schizophrenia in Japan provided by visiting nurses: protocol for a**
8 **3 cluster randomized controlled trial**
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1 **ABSTRACT**

2 **Introduction**

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

18 **Methods and analysis**

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

29 **Ethics and dissemination**

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

34 **Registration number**

35 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.

1 INTRODUCTION

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

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

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

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

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

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

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

4 **Hypothesis and aims**

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

10 **METHODS AND ANALYSIS**

11 **Trial design**

12 This study is a two-arm, parallel-group cRCT. The randomisation procedure will be
13 conducted at the cluster level (visiting nurse agencies). Visiting nurse agencies will be
14 randomly assigned to the intervention or control (treatment as usual (TAU)) group in a
15 1:1 ratio. Data will be collected at the individual level. Analyses to evaluate the efficacy
16 of the intervention program will be conducted at the individual level, taking into
17 consideration cluster-level effects. The study protocol was registered in the University
18 Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN-CTR
19 ID, UMIN000038044). This protocol has been reported according to the Standard
20 Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.²³ The
21 anticipated trial start date will be 1 October 2019 and the date of last follow-up date will
22 be 31 May 2020.

23 **Setting and site selection at the cluster level**

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

29 To be included, a visiting nurse agency must provide services mostly to
30 psychiatric patients or clients, not elderly people or those with physical diseases. In each
31 agency, visiting nurses care for at least two people with schizophrenia who live with
32 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

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

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

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

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

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

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

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

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

17 **Control group**

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

23 **Outcomes**

24 Table 2 shows an overview of the outcome measures. Outcome measures will be
25 assessed at baseline prior to the intervention (T1), immediately after the completion of
26 the intervention (1-month follow-up, T2), and 6 months after the baseline assessment
27 (6-month follow-up, T3).

29 **Primary outcome for caregivers**

30 Zarit Burden Interview (ZBI-22)

31 ZBI-22 will be used to measure caregiver burden. It consists of 22 items scored on a
32 five-point Likert scale from 0 (never) to 4 (nearly always), except for the final item on
33 global burden, which is rated from 0 (not at all) to 4 (extremely). The total score ranges
34 from 0 to 88, with higher scores indicating higher burden. The Japanese version of ZBI-
35 22 had a high test-retest reproducibility and internal consistency. Construct validity has
36 also been confirmed.²⁹

1 2 3 4 5 6 7 **2 Secondary outcome for caregivers**

8 **3 K6**

9
10 4 K6 will be used to measure sub-clinical depression and anxiety disorders as part of a
11 5 self-administered questionnaire. It consists of six items answered on a five-point Likert
12 6 scale. Scores range from 0 to 24, with higher scores representing higher degrees of sub-
13 7 clinical depression and anxiety disorder. The Japanese versions of the K6 have
14 8 essentially equivalent screening performance as the original English versions.³⁰
15 9

10 **10 General Self Efficacy Scale (GSES)**

11 11 GSES is a measurement of self-efficacy in daily living. It includes 16 items with
12 12 dichotomous questions. The higher the score, the better the self-efficacy, in general.
13 13 GSES had high test-retest reproducibility and internal consistency. Construct validity
14 14 has been confirmed.³¹
15 15

16 **16 WHO-5**

17 17 WHO-5 will be used to measure subjective quality of life based on positive mood (good
18 18 spirits and relaxation), vitality (being active and waking up fresh and rested), and
19 19 general interest (being interested in things). It consists of five items rated on a six-point
20 20 Likert scale. Higher scores mean higher well-being. The Japanese version of WHO-5
21 21 has adequate internal consistency. It has been confirmed to have external concurrent
22 22 validity and external discriminatory validity.³²
23 23

24 **24 Knowledge of Illness and Drug Inventory (KIDI)**

25 25 KIDI will be used to assess knowledge regarding mental illness and the effects of
26 26 medications on mental illness. There are two sub-scales: 10 items assessing knowledge
27 27 of mental illness and 10 items assessing knowledge of the effects of antipsychotic
28 28 drugs. This inventory consists of a self-reported inventory where respondents are asked
29 29 to select the correct answer from three choices, with higher scores representing greater
30 30 knowledge. KIDI is frequently used to assess knowledge about mental disorders and
31 31 treatments in Japan.³³
32 32

33 **33 Secondary outcomes in people with schizophrenia**

34 **34 Behavior and Symptom Identification Scale (BASIS-32)**

35 35 BASIS-32 is a commonly used measure in mental health. It includes 32 items on a five-
36 36 point Likert scale, where 0 indicates no difficulties and 4 indicates severe difficulties.

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6 1 The scale measures five factors: (1) relation to self and others (seven items); (2)
7 2 depression/anxiety (six items); (3) everyday life and role functioning (nine items); (4)
8 3 impulsive and addictive behaviour (six items); and (5) psychosis (four items). Factors 1,
9 4 2, 4, and 5 are assessed as the total score divided by the number of items answered
10 5 (mean score), while factor 3 is assessed based non the highest rating. Internal
11 6 consistency and construct validity of the Japanese version of BASIS-32 have been
12 7 demonstrated.³⁴
13 8

9 WHO-5

10 WHO-5 is used to measure subjective quality of life based on positive mood (good
11 11 spirits and relaxation), vitality (being active and waking up fresh and rested), and
12 12 general interest (being interested in things). WHO-5 comprises five items rated on a six-
13 13 point Likert scale. Higher scores mean higher well-being. The Japanese version of
14 14 WHO-5 has adequate internal consistency. It has been confirmed to have external
15 15 concurrent validity and external discriminatory validity.³²
16 16

17 Hospitalisation by 6-month follow-up

18 18 This is a question with a dichotomous answer (yes or no) about whether the patient has
19 19 been hospitalised during the past 6 months. The answer will be provided by the
20 20 caregiver at baseline and the 6-month follow-up.
21 21

22 **Sample size calculation**

23 23 The sample size required was calculated according to guidelines in the Consolidated
24 24 Standards of Reporting Trials (CONSORT) for cRCTs,³⁵ taking into account intra-class
25 25 correlations (ICCs). The effect size of a brief FPE program for individual caregiver
26 26 burden was estimated based on a previous pre-post test.¹⁹ The pre-post test concluded
27 27 that the standardised mean difference (d) of brief FPE on family burden was 0.46.
28 28 Sample size was estimated as 76 in each arm based on an alpha error probability of 0.05
29 29 and power (1- β) of 0.80, using G*Power version 3.1.9.2.^{36 37} cRCTs should be
30 30 multiplied by design effect (1+[m-1] ρ), where m is the average cluster size and ρ is the
31 31 ICC.³⁸ The estimated ICC for the primary outcome in this study was set to 0.05 and the
32 32 average number of caregivers per cluster was set at five people. Assuming an attrition
33 33 rate of 20%, the required sample size is 110 caregivers in each arm; thus, at least 44
34 34 visiting nurse agencies will be recruited.
35 35

36 **Quantitative analysis**

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

18 **Data monitoring**

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

25 **Patient and public involvement**

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

34 **Ethics and dissemination**

35 Ethical considerations

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5
6 1 The authors assert that all procedures contributing to this work comply with the ethical
7 2 standards of the relevant national and institutional committees on human experimentation
8 3 and with the Helsinki Declaration of 1975, as revised in 2008. The study protocol was
9 4 approved by the Research Ethics Committee of the Graduate School of Medicine and the
10 5 Faculty of Medicine at the University of Tokyo, Japan (No. 2019065NI). We will obtain
11 6 informed consent from all caregivers and patients. The consent form will inform
12 7 caregivers and patients that we guarantee protection of personal information and that the
13 8 data will be anonymous and used only for academic purposes. There are no competing
14 9 interests. This study is supported by fundamental study on effective community services
15 10 for people with severe mental disorders and their families.
16 11

12 **Dissemination of the research findings**

13 The findings will be published in a scientific peer-reviewed journal according to the
14 14 CONSORT guidelines for cRCTs.³⁵ The participants will be informed of conference
15 15 presentations and publications.
16 16

17 **Strengths and limitations**

18 18 The study has both strengths and limitations. First, the study will evaluate an
19 19 implementable brief FPE program that potentially reduces time, cost, and staffing
20 20 problems by incorporating the program into an existing mental health service system,
21 21 namely visiting nurse services. Second, this is the first cRCT of a brief FPE program, a
22 22 trial with a better study design. It will provide better evidence than past studies. Third,
23 23 based on the concept of coproduction and PPI,²⁵ the study incorporated a variety of
24 24 viewpoints from caregivers, visiting nurses, and FPE experts.

25 25 We recognise three limitations of this study. First, since the sampling method for
26 26 participating agencies was not random, there is a possibility of selection bias. Second,
27 27 since subjects will provide data through a self-reported questionnaire, information bias
28 28 or random error is possible. For example, the severity of symptoms in people with
29 29 schizophrenia that impact a caregiver's burden may not be accurately measured. Third,
30 30 we designed the study and intervention based on coproduction, but there are still
31 31 concerns about its feasibility in actual clinical settings. For example, participants might
32 32 not complete all four sessions due to the condition of people with schizophrenia, family
33 33 work, and family hospitalisation. These may lead to a high attrition rate during
34 34 implementation.
35 35

36 **Acknowledgments**

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2 Schizophrenia for their invaluable advice on many aspects of the project.

3 4 **Contributors**

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

10
11 **Funding:** This work is supported by Fundamental study on effective community
12 services for people with severe mental disorders and their families.

13
14 **Competing interests:** None declared.

15
16 **Patient Consent:** Obtained.

17
18 **Ethics approval:** Research Committee of the Graduate School of Medicine and the
19 Faculty of Medicine at the University of Tokyo, Japan.

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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

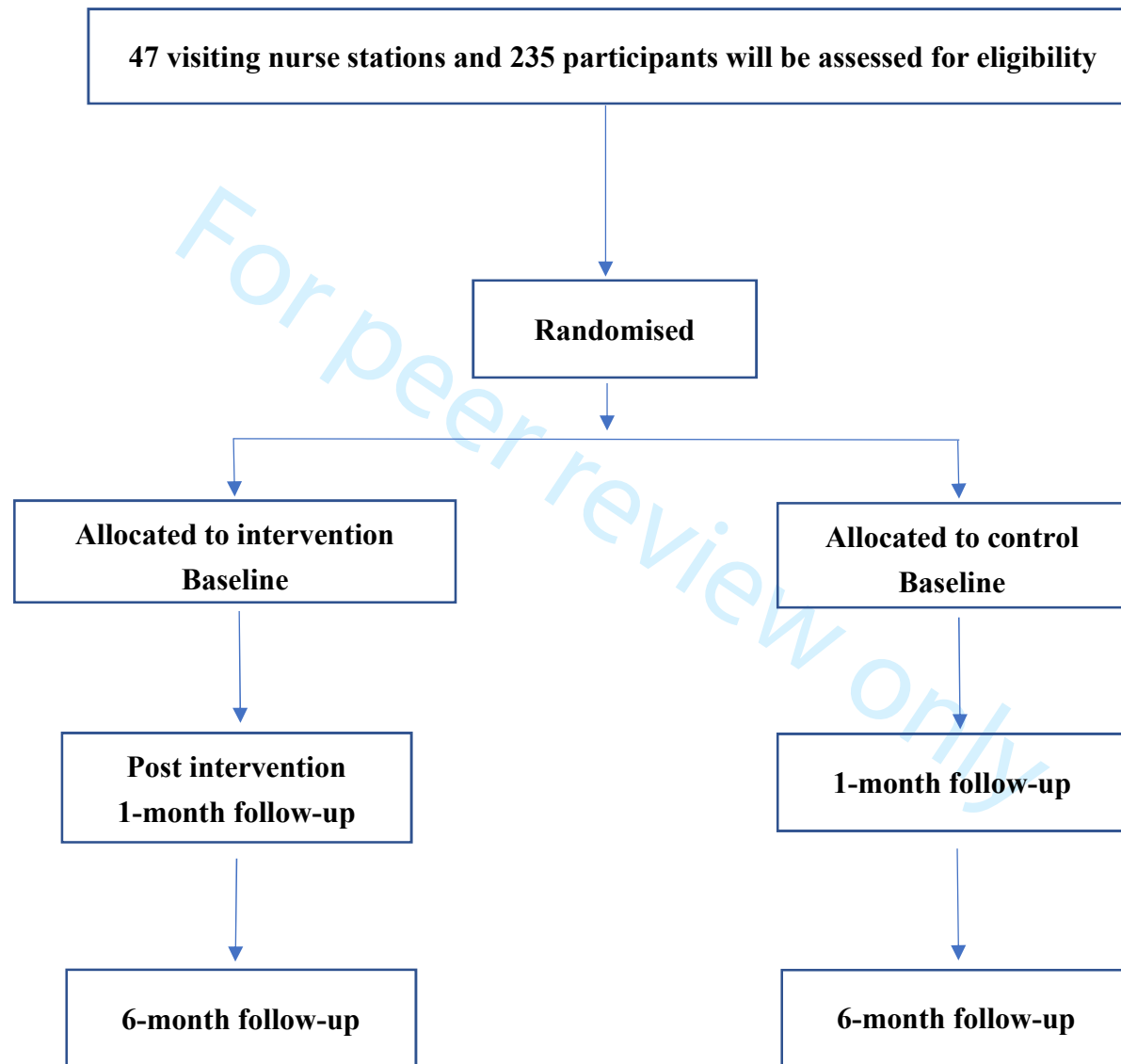
	Outcome measure	Baseline	1-month follow-up	6-month follow-up
Caregivers	Zarit Burden Interview (ZBI-22)	✓	✓	✓
	K6	✓	✓	✓
	General Self-Efficacy Scale (GSES)	✓	✓	✓
	WHO-5	✓	✓	✓
	Knowledge of Illness and Drug Inventory (KIDI)	✓	✓	✓
People with schizophrenia	Behavior and Symptom Identification Scale (BASIS-32)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

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Figure 1: Participant flow chart

For peer review only

Figure 1. Participant flow chart





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

1			
2		6b	Explanation for choice of comparators P4-6
3			
4	Objectives	7	Specific objectives or hypotheses P6
5			
6	Trial design	8	Description of trial design including type of trial (eg, P6 parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
7			
8			
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11			
12	Methods: Participants, interventions, and outcomes		
13			
14	Study setting	9	Description of study settings (eg, community clinic, P6-7 academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
15			
16			
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18			
19	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If P6-7 applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
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25	Interventions	11a	Interventions for each group with sufficient detail to P7-9 allow replication, including how and when they will be administered
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30		11b	Criteria for discontinuing or modifying allocated P7-9 interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
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35		11c	Strategies to improve adherence to intervention P7-9 protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
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40		11d	Relevant concomitant care and interventions that P7-9 are permitted or prohibited during the trial
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43	Outcomes	12	Primary, secondary, and other outcomes, including P10-12 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
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53	Participant	13	Time schedule of enrolment, interventions P6-7 timeline (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
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2	Sample size	14	Estimated number of participants needed to	P12
3			achieve study objectives and how it was	
4			determined, including clinical and statistical	
5			assumptions supporting any sample size	
6			calculations	
7				
8	Recruitment	15	Strategies for achieving adequate participant	P6-7
9			enrolment to reach target sample size	

Methods: Assignment of interventions (for controlled trials)

Allocation:

15				
16	Sequence	16a	Method of generating the allocation sequence (eg,	P7
17	generation		computer-generated random numbers), and list of	
18			any factors for stratification. To reduce	
19			predictability of a random sequence, details of any	
20			planned restriction (eg, blocking) should be	
21			provided in a separate document that is	
22			unavailable to those who enrol participants or	
23			assign interventions	
24				
25				
26	Allocation	16b	Mechanism of implementing the allocation	P7
27	concealment		sequence (eg, central telephone; sequentially	
28	mechanism		numbered, opaque, sealed envelopes), describing	
29			any steps to conceal the sequence until	
30			interventions are assigned	
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33	Implementation	16c	Who will generate the allocation sequence, who	P7
34			will enrol participants, and who will assign	
35			participants to interventions	
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38	Blinding	17a	Who will be blinded after assignment to	P7
39	(masking)		interventions (eg, trial participants, care providers,	
40			outcome assessors, data analysts), and how	
41				
42		17b	If blinded, circumstances under which unblinding is	P7
43			permissible, and procedure for revealing a	
44			participant's allocated intervention during the trial	
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Methods: Data collection, management, and analysis

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48				
49	Data collection	18a	Plans for assessment and collection of outcome,	P13
50	methods		baseline, and other trial data, including any related	
51			processes to promote data quality (eg, duplicate	
52			measurements, training of assessors) and a	
53			description of study instruments (eg,	
54			questionnaires, laboratory tests) along with their	
55			reliability and validity, if known. Reference to where	
56			data collection forms can be found, if not in the	
57			protocol	
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2		18b	Plans to promote participant retention and	P13
3			complete follow-up, including list of any outcome	
4			data to be collected for participants who	
5			discontinue or deviate from intervention protocols	
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7	Data	19	Plans for data entry, coding, security, and storage,	P13
8	management		including any related processes to promote data	
9			quality (eg, double data entry; range checks for	
10			data values). Reference to where details of data	
11			management procedures can be found, if not in the	
12			protocol	
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15	Statistical	20a	Statistical methods for analysing primary and	P12-13
16	methods		secondary outcomes. Reference to where other	
17			details of the statistical analysis plan can be found,	
18			if not in the protocol	
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21		20b	Methods for any additional analyses (eg, subgroup	P12-13
22			and adjusted analyses)	
23				
24		20c	Definition of analysis population relating to protocol	P12-13
25			non-adherence (eg, as randomised analysis), and	
26			any statistical methods to handle missing data (eg,	
27			multiple imputation)	
28				
29				
30	Methods: Monitoring			
31				
32	Data monitoring	21a	Composition of data monitoring committee (DMC);	P13
33			summary of its role and reporting structure;	
34			statement of whether it is independent from the	
35			sponsor and competing interests; and reference to	
36			where further details about its charter can be	
37			found, if not in the protocol. Alternatively, an	
38			explanation of why a DMC is not needed	
39				
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41		21b	Description of any interim analyses and stopping	NA
42			guidelines, including who will have access to these	
43			interim results and make the final decision to	
44			terminate the trial	
45				
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47	Harms	22	Plans for collecting, assessing, reporting, and	NA
48			managing solicited and spontaneously reported	
49			adverse events and other unintended effects of	
50			trial interventions or trial conduct	
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53	Auditing	23	Frequency and procedures for auditing trial	NA
54			conduct, if any, and whether the process will be	
55			independent from investigators and the sponsor	
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58	Ethics and dissemination			
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2	Research ethics	24	Plans for seeking research ethics	P13-P14
3	approval		committee/institutional review board (REC/IRB)	
4			approval	
5				
6	Protocol	25	Plans for communicating important protocol	NA
7	amendments		modifications (eg, changes to eligibility criteria,	
8			outcomes, analyses) to relevant parties (eg,	
9			investigators, REC/IRBs, trial participants, trial	
10			registries, journals, regulators)	
11				
12				
13	Consent or	26a	Who will obtain informed consent or assent from	P6-7
14	assent		potential trial participants or authorised surrogates,	
15			and how (see Item 32)	
16				
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18		26b	Additional consent provisions for collection and use	NA
19			of participant data and biological specimens in	
20			ancillary studies, if applicable	
21				
22	Confidentiality	27	How personal information about potential and	P13
23			enrolled participants will be collected, shared, and	
24			maintained in order to protect confidentiality	
25			before, during, and after the trial	
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28	Declaration of	28	Financial and other competing interests for	P15
29	interests		principal investigators for the overall trial and each	
30			study site	
31				
32	Access to data	29	Statement of who will have access to the final trial	P16
33			dataset, and disclosure of contractual agreements	
34			that limit such access for investigators	
35				
36				
37	Ancillary and	30	Provisions, if any, for ancillary and post-trial care,	NA
38	post-trial care		and for compensation to those who suffer harm	
39			from trial participation	
40				
41	Dissemination	31a	Plans for investigators and sponsor to	P14
42	policy		communicate trial results to participants,	
43			healthcare professionals, the public, and other	
44			relevant groups (eg, via publication, reporting in	
45			results databases, or other data sharing	
46			arrangements), including any publication	
47			restrictions	
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50				
51		31b	Authorship eligibility guidelines and any intended	P14
52			use of professional writers	
53				
54		31c	Plans, if any, for granting public access to the full	P14
55			protocol, participant-level dataset, and statistical	
56			code	
57				

Appendices

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

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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

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6 **1 Effects of brief family psychoeducation for caregivers of people with**
7 **2 schizophrenia in Japan provided by visiting nurses: protocol for a**
8 **3 cluster randomised controlled trial**
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1 **ABSTRACT**

2 **Introduction**

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

18 **Methods and analysis**

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

29 **Ethics and dissemination**

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

34 **Registration number**

35 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.

1 INTRODUCTION

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

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

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

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

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

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

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

3 4 **Hypothesis and aims**

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

10 11 **METHODS AND ANALYSIS**

12 **Trial design**

13 This study is a two-arm, parallel-group cRCT. The randomisation procedure will be
14 conducted at the cluster level (visiting nurse agencies). Visiting nurse agencies will be
15 randomly assigned to the intervention or control (treatment as usual (TAU)) group in a
16 1:1 ratio. Data will be collected at the individual level. Analyses to evaluate the efficacy
17 of the intervention program will be conducted at the individual level, taking into
18 consideration cluster-level effects. The study protocol was registered in the University
19 Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN-CTR
20 ID, UMIN000038044). This protocol has been reported according to the Standard
21 Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.²³ The
22 anticipated trial start date will be 18 September 2019 and the date of last follow-up will
23 be 31 May 2020.

24 25 **Setting and site selection at the cluster level**

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

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

35 36 **Randomisation at the cluster level**

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6 1 Visiting nurse agencies that meet the inclusion criteria will be randomly allocated to the
7 2 intervention group (brief FPE program) or the control group. Randomisation will be
8 3 stratified by the median of the average caseload of visiting nurses in each agency. We
9 4 used stratified randomisation based on this factor because the number of patients for
10 5 whom a visiting nurse can maintain service quality is generally fixed.²⁴ If a visiting
11 6 nurse has too many patients, family support will probably be neglected. A random
12 7 sequence table will be created by a researcher (HT) in another department at our
13 8 institution who is not involved in the study protocol development process. In addition,
14 9 another independent researcher (SY) who is not involved in intervention and analysis
15 10 will conduct the randomisation. SY will inform each visiting nurse agency of the
16 11 randomisation results. The primary investigator (NY) will be blinded through the entire
17 12 randomisation process.
18 13

14 **Participant eligibility criteria and recruitment procedure at the individual level**

15 At the individual level, we set the following inclusion criteria for a caregiver of a person
16 17 with schizophrenia: 1) is the primary caregiver; 2) aged over 20 years; 3) is a family
18 19 member of the person with schizophrenia such as a parent, sibling, spouse, or child; and
20 21 4) lives with the person with schizophrenia. There are no exclusion criteria for
22 23 caregivers. In addition, the inclusion criteria for people with schizophrenia are as
24 25 follows: 1) diagnosis of schizophrenia based on the International Statistical
26 27 Classification of Diseases and Related Health Problems, 10th revision and 2) receiving
28 29 services from visiting nurses.

30 31 As part of the recruitment procedure at the individual level, all potential
32 33 participants (caregivers of people with schizophrenia and people with schizophrenia) at
34 35 each agency will be listed. Second, a randomly ordered list will be created using a
36 37 random number generator in the Stata statistical software program, version 15, in order
38 39 to avoid selection bias at the individual level. Third, visiting nurses who have attended a
40 41 lecture on study design and ethical considerations will recruit participants in accordance
42 43 with the randomly ordered list until five participants have been recruited. The study will
44 45 include only participants who voluntarily agree to participate in the study.
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52 **Intervention program**

53 54 The intervention program is a single-family intervention conducted by psychiatric
55 56 visiting nurses. It is based on the Family Intervention and Support in Schizophrenia: A
57 58 Manual on Family Intervention for the Mental Health Professional.²⁵ This program was
59 60 developed through discussions and collaborations among members of the Family

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

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

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

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

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

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

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6 1 Session IV will focus on the family's recovery. Topics will include thinking about
7 2 the family's recovery, the importance of living one's own life, taking care of the
8 3 family's physical and mental health needs, proper stress management, experiences and
9 4 messages from members of the Family Association, and identifying available social
10 5 resources in the community. During this session, visiting nurses will stress that people
11 6 with schizophrenia and family members each have their own lifestyle and individual
12 7 goals. Visiting nurses will also encourage family members to live their own lives using
13 8 a variety of social resources instead of only working hard to take care of a person with
14 9 schizophrenia. In addition, visiting nurses expect that family members will improve
15 10 their physical and mental health by acquiring knowledge on self-care and stress
16 11 management skills. Furthermore, visiting nurses will introduce the experiences of three
17 12 members of the Family Association who have taken care of a person with
18 13 schizophrenia. It is expected that others' similar experiences will help family members
19 14 understand that they are not the only people experiencing such a hard time and relieve
20 15 their feelings of sadness or hopelessness. Finally, visiting nurses will explain the social
21 16 resources available in the community for family members and confirm the importance
22 17 of connecting with many supporters around them.
23 18

19 **Control group**

20 Caregivers enrolled in the control group will receive usual care from visiting nurses.
21 They will be put on a waiting list to receive the same intervention program after
22 completing the 6-month follow-up assessment. They will not receive any type of
23 psychoeducation or supportive therapies.
24

25 **Outcomes**

26 Table 2 shows an overview of the outcome measures. Outcome measures will be
27 assessed at baseline prior to the intervention (T1), immediately after the completion of
28 the intervention (1-month follow-up, T2), and 6 months after the baseline assessment
29 (6-month follow-up, T3).
30

31 **Primary outcome for caregivers**

32 Zarit Burden Interview (ZBI-22)

33 ZBI-22 will be used to measure caregiver burden. It consists of 22 items scored on a
34 five-point Likert scale from 0 (never) to 4 (nearly always), except for the final item on
35 global burden, which is rated from 0 (not at all) to 4 (extremely). The total score ranges
36 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)

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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 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} 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

1 Ethical considerations

2 The authors assert that all procedures contributing to this work comply with the ethical
3 standards of the relevant national and institutional committees on human
4 experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The
5 study protocol was approved by the Research Ethics Committee of the Graduate School
6 of Medicine and the Faculty of Medicine at the University of Tokyo, Japan (No.
7 2019065NI). We will obtain informed consent from all caregivers and patients. The
8 consent form will inform caregivers and patients that we guarantee protection of
9 personal information and that the data will be anonymous and used only for academic
10 purposes. There are no competing interests. This study is supported by fundamental
11 study on effective community services for people with severe mental disorders and their
12 families.

14 Dissemination of the research findings

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

19 **Strengths and limitations**

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

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

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

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8 9 **Contributors**

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

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18
19 **Competing interests:** None declared.

20
21 **Patient Consent:** Obtained.

22
23 **Ethics approval:** Research Committee of the Graduate School of Medicine and the
24 Faculty of Medicine at the University of Tokyo, Japan.

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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.

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

2 **Table 2. Outcome measures**

3

4

	Outcome measure	Baseline	1-month follow-up	6-month follow-up
5	Caregivers			
6	Zarit Burden Interview (ZBI-22)	✓	✓	✓
7				
8	K6	✓	✓	✓
9				
10	General Self-Efficacy Scale (GSES)	✓	✓	✓
11				
12	WHO-5	✓	✓	✓
13				
14	Knowledge of Illness and Drug Inventory (KIDI)	✓	✓	✓
15				
16				
17				
18				
19				
20	People with schizophrenia			
21	Behavior and Symptom Identification Scale (BASIS-32)	✓	✓	✓
22				
23	WHO-5	✓	✓	✓
24				
25	Hospitalisation during the past 6 months	✓	–	✓
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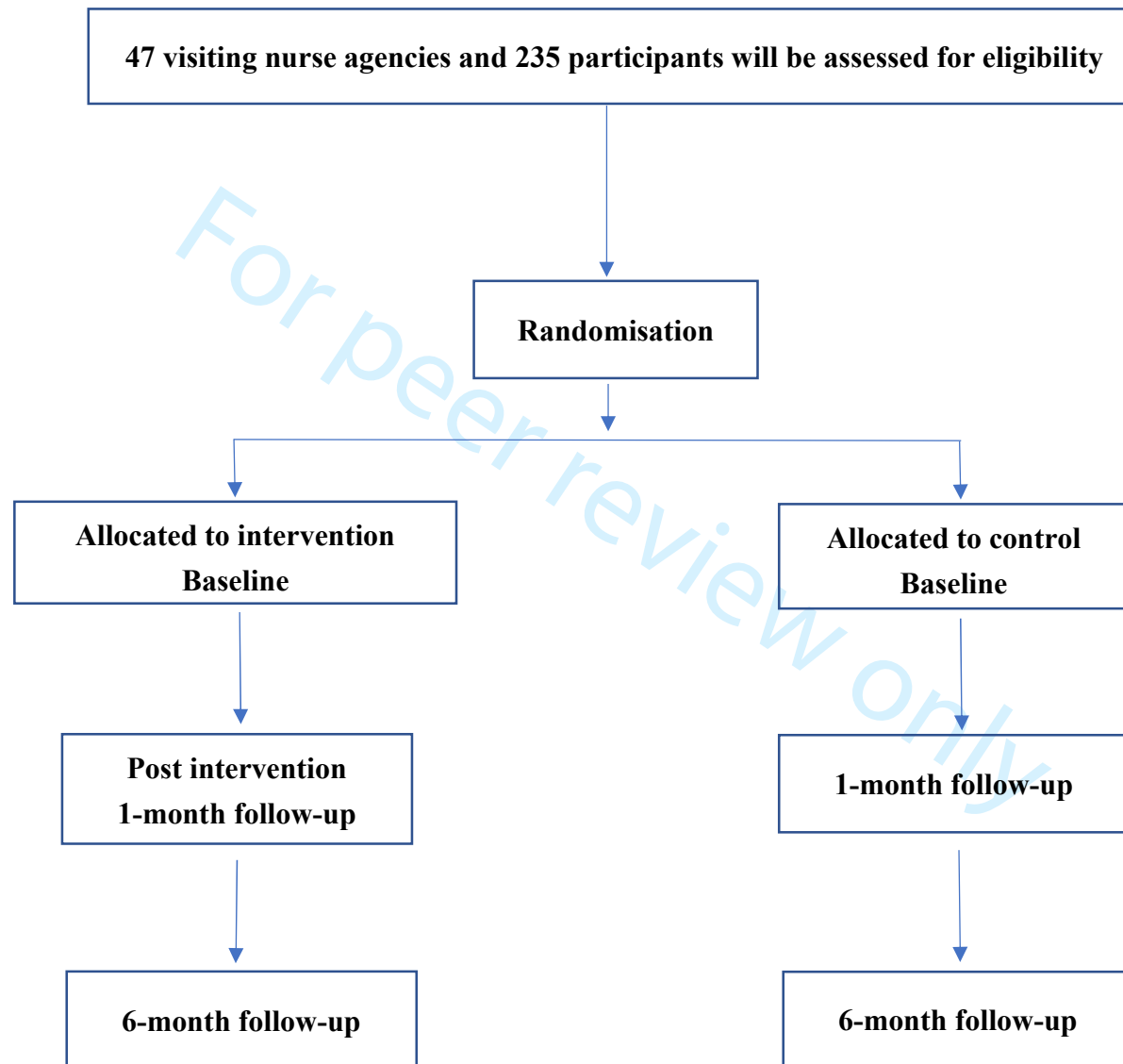
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Figure 1

For peer review only

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

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Primary Subject Heading:	Mental health
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Keywords:	Brief family psychoeducation, schizophrenia, caregivers, visiting nurses

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6 **1 Effects of brief family psychoeducation for caregivers of people with**
7 **2 schizophrenia in Japan provided by visiting nurses: protocol for a**
8 **3 cluster randomised controlled trial**
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1 **ABSTRACT**

2 **Introduction**

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

17

18 **Methods and analysis**

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

28

29 **Ethics and dissemination**

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

33

34 **Registration number**

35 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.

1 INTRODUCTION

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

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

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

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

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

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

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

3 4 **Hypothesis and aims**

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

10 11 **METHODS AND ANALYSIS**

12 **Trial design**

13 This study is a two-arm, parallel-group cRCT. The randomisation procedure will be
14 conducted at the cluster level (visiting nurse agencies). Visiting nurse agencies will be
15 randomly assigned to the intervention or control (treatment as usual (TAU)) group in a
16 1:1 ratio. Data will be collected at the individual level. Analyses to evaluate the efficacy
17 of the intervention program will be conducted at the individual level, taking into
18 consideration cluster-level effects. The study protocol was registered in the University
19 Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN-CTR
20 ID, UMIN000038044). This protocol has been reported according to the Standard
21 Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.²³ The
22 anticipated trial start date will be 18 September 2019 and the date of last follow-up will
23 be 31 May 2020.

24 25 **Setting and site selection at the cluster level**

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

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

35 36 **Randomisation at the cluster level**

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6 1 Visiting nurse agencies that meet the inclusion criteria will be randomly allocated to the
7 2 intervention group (brief FPE program) or the control group. Randomisation will be
8 3 stratified by the median of the average caseload of visiting nurses in each agency. We
9 4 used stratified randomisation based on this factor because the number of patients for
10 5 whom a visiting nurse can maintain service quality is generally fixed.²⁴ If a visiting
11 6 nurse has too many patients, family support will probably be neglected. A random
12 7 sequence table will be created by a researcher (HT) in another department at our
13 8 institution who is not involved in the study protocol development process. In addition,
14 9 another independent researcher (SY) who is not involved in intervention and analysis
15 10 will conduct the randomisation and will inform each visiting nurse agency of the
16 11 randomisation results. The primary investigator (NY) will be blinded through the entire
17 12 randomisation process.
18 13

14 **Participant eligibility criteria and recruitment procedure at the individual level**

15 15 At the individual level, we set the following inclusion criteria for a caregiver of a person
16 16 with schizophrenia: 1) is the primary caregiver; 2) aged over 20 years; 3) is a family
17 17 member of the person with schizophrenia such as a parent, sibling, spouse, or child; and
18 18 4) lives with the person with schizophrenia. There are no exclusion criteria for
19 19 caregivers. In addition, the inclusion criteria for people with schizophrenia are as
20 20 follows: 1) diagnosis of schizophrenia based on the International Statistical
21 21 Classification of Diseases and Related Health Problems, 10th revision and 2) receiving
22 22 services from visiting nurses.

23 23 As part of the recruitment procedure at the individual level, all potential
24 24 participants (caregivers of people with schizophrenia and people with schizophrenia) at
25 25 each agency will be listed. Second, a randomly ordered list will be created using a
26 26 random number generator in the Stata statistical software program, version 15, in order
27 27 to avoid selection bias at the individual level. Third, each visiting nurse, after attending
28 28 a lecture on study design and ethical considerations, will recruit participants in
29 29 accordance with the randomly ordered list until five participants have been recruited.
30 30 The study will include only participants who voluntarily agree to participate in the
31 31 study.
32 32

33 **Intervention program**

34 34 The intervention program consists of a single-family intervention conducted by
35 35 psychiatric visiting nurses. It is based on the Family Intervention and Support in
36 36 Schizophrenia: A Manual on Family Intervention for the Mental Health Professional.²⁵

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

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

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

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

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

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

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6 1 Session IV will focus on the family's recovery. Topics will include thinking about
7 2 the family's recovery, the importance of living one's own life, taking care of the
8 3 family's physical and mental health needs, proper stress management, experiences and
9 4 messages from members of the Family Association, and identifying available social
10 5 resources in the community. During this session, visiting nurses will stress that people
11 6 with schizophrenia and family members each have their own lifestyle and individual
12 7 goals. Visiting nurses will also encourage family members to live their own lives using
13 8 a variety of social resources instead of only working hard to take care of a person with
14 9 schizophrenia. In addition, visiting nurses expect that family members will improve
15 10 their physical and mental health by acquiring knowledge on self-care and stress
16 11 management skills. Furthermore, visiting nurses will introduce the experiences of three
17 12 members of the Family Association who have taken care of a person with
18 13 schizophrenia. It is expected that others' similar experiences will help family members
19 14 understand that they are not the only people experiencing such a hard time and relieve
20 15 their feelings of sadness or hopelessness. Finally, visiting nurses will explain the social
21 16 resources available in the community for family members and confirm the importance
22 17 of connecting with many supporters around them.
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33 **Control group**

34 20 Caregivers enrolled in the control group will receive usual care from visiting nurses.
35 21 They will be put on a waiting list to receive the same intervention program after
36 22 completing the 6-month follow-up assessment. They will not receive any type of
37 23 psychoeducation or supportive therapies.
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42 **Outcomes**

43 26 Table 2 shows an overview of the outcome measures. Outcome measures will be
44 27 assessed at baseline prior to the intervention (T1), immediately after the completion of
45 28 the intervention (1-month follow-up, T2), and 6 months after the baseline assessment
46 29 (6-month follow-up, T3).
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51 **Primary outcome for caregivers**

52 32 Zarit Burden Interview (ZBI-22)

53 33 ZBI-22 will be used to measure caregiver burden. It consists of 22 items scored on a
54 34 five-point Likert scale from 0 (never) to 4 (nearly always), except for the final item on
55 35 global burden, which is rated from 0 (not at all) to 4 (extremely). The total score ranges
56 36 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)

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1 BASIS-32 is a commonly used measure in mental health. It includes 32 items on a five-
2 point Likert scale, where 0 indicates no difficulties and 4 indicates severe difficulties.
3 The scale measures five factors: (1) relation to self and others (seven items); (2)
4 depression/anxiety (six items); (3) everyday life and role functioning (nine items); (4)
5 impulsive and addictive behaviour (six items); and (5) psychosis (four items). Factors 1,
6 2, 4, and 5 are assessed as the total score divided by the number of items answered
7 (mean score). Factor 3 is assessed based on the highest rating. Internal consistency and
8 construct validity of the Japanese version of BASIS-32 have been demonstrated.³⁵

10 WHO-5

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

18 Hospitalisation by 6-month follow-up

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

23 **Sample size calculation**

24 The sample size required was calculated according to guidelines in the Consolidated
25 Standards of Reporting Trials (CONSORT) for cRCTs,³⁶ taking into account intra-class
26 correlations (ICCs). The effect size of a brief FPE program for individual caregiver
27 burden was estimated based on a previous pre-post test.¹⁹ The pre-post test concluded
28 that the standardised mean difference (d) of brief FPE on family burden was 0.46.
29 Sample size was estimated as 76 in each arm based on an alpha error probability of 0.05
30 and power (1- β) of 0.80, using G*Power version 3.1.9.2.^{37 38} For cRCTs, this value
31 should be multiplied by design effect (1+[m-1] ρ), where m is the average cluster size
32 and ρ is the ICC.³⁹ The estimated ICC for the primary outcome in this study was set to
33 0.05 and the average number of caregivers per cluster was set at 5. Assuming an
34 attrition rate of 20%, the required sample size is 110 caregivers in each arm. Thus, at
35 least 44 visiting nurse agencies will be recruited.

1 **Quantitative analysis**

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

18 **Data monitoring**

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

24 **Patient and public involvement**

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

32 **Ethics and dissemination**

33 Ethical considerations

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1 The authors assert that all procedures contributing to this work comply with the ethical
2 standards of the relevant national and institutional committees on human
3 experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The
4 study protocol was approved by the Research Ethics Committee of the Graduate School
5 of Medicine and the Faculty of Medicine at the University of Tokyo, Japan (No.
6 2019065NI). We will obtain informed consent from all caregivers and patients. The
7 consent form will inform caregivers and patients that we guarantee protection of
8 personal information and that the data will be anonymous and used only for academic
9 purposes. There are no competing interests. This study is supported by the fundamental
10 study on effective community services for people with severe mental disorders and their
11 families.

13 Dissemination of the research findings

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

18 **Strengths and limitations**

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

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

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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.

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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.

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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.

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

2 **Table 2. Outcome measures**

3

4

	Outcome measure	Baseline	1-month follow-up	6-month follow-up
5	Caregivers			
6	Zarit Burden Interview (ZBI-22)	✓	✓	✓
7				
8	K6	✓	✓	✓
9				
10	General Self-Efficacy Scale (GSES)	✓	✓	✓
11				
12	WHO-5	✓	✓	✓
13				
14	Knowledge of Illness and Drug Inventory (KIDI)	✓	✓	✓
15				
16				
17				
18				
19				
20	People with schizophrenia			
21	Behavior and Symptom Identification Scale (BASIS-32)	✓	✓	✓
22				
23	WHO-5	✓	✓	✓
24				
25	Hospitalisation during the past 6 months	✓	–	✓
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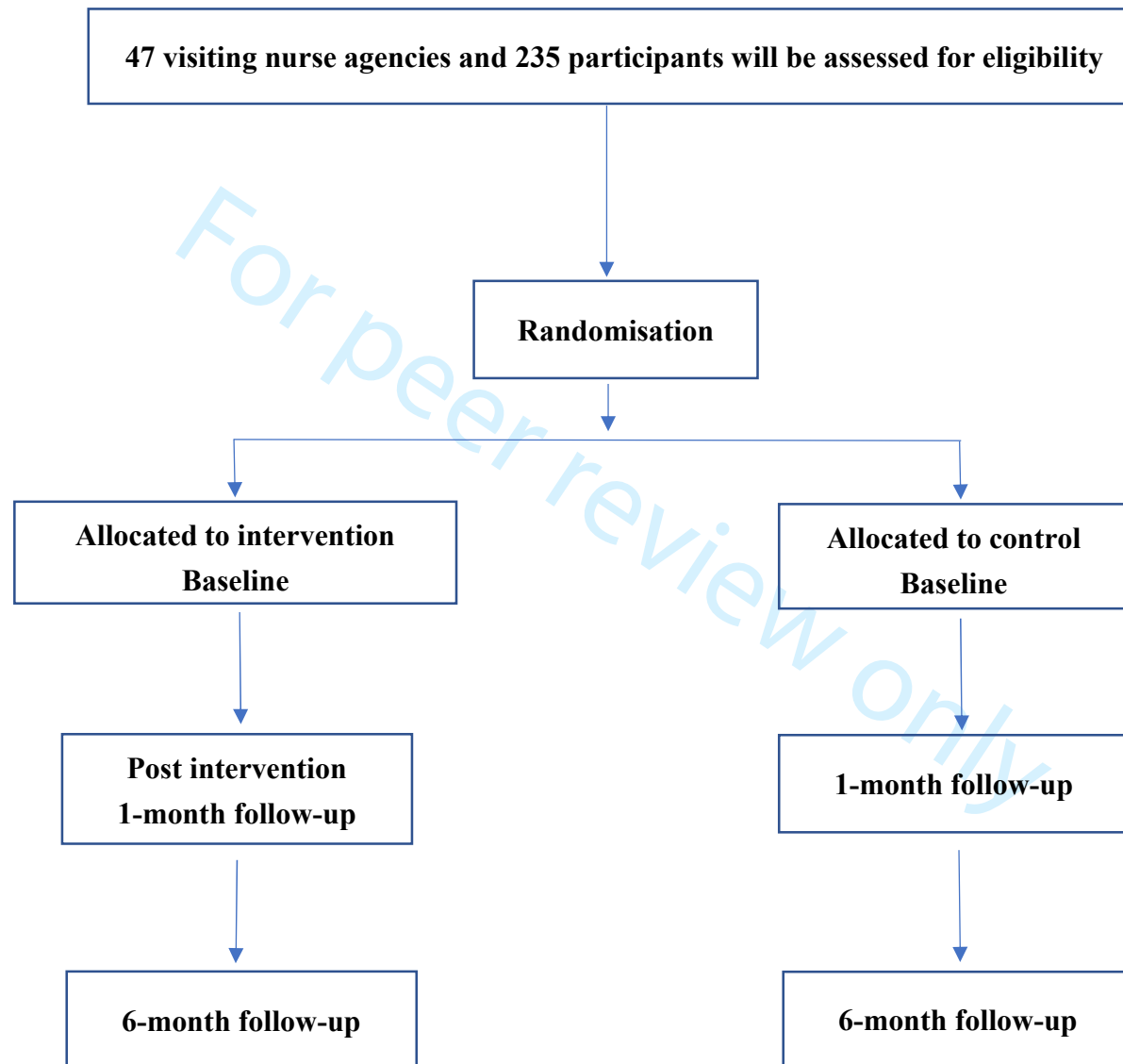
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Figure 1

For peer review only

Figure 1. Study flow chart





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

1			
2		6b	Explanation for choice of comparators P4-6
3			
4	Objectives	7	Specific objectives or hypotheses P6
5			
6	Trial design	8	Description of trial design including type of trial (eg, P6 parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
7			
8			
9			
10			
11			
12	Methods: Participants, interventions, and outcomes		
13			
14	Study setting	9	Description of study settings (eg, community clinic, P6-7 academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
15			
16			
17			
18			
19	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If P6-7 applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
20			
21			
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23			
24			
25	Interventions	11a	Interventions for each group with sufficient detail to P7-9 allow replication, including how and when they will be administered
26			
27			
28			
29			
30		11b	Criteria for discontinuing or modifying allocated P7-9 interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
31			
32			
33			
34			
35		11c	Strategies to improve adherence to intervention P7-9 protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
36			
37			
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39			
40		11d	Relevant concomitant care and interventions that P7-9 are permitted or prohibited during the trial
41			
42			
43	Outcomes	12	Primary, secondary, and other outcomes, including P10-12 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
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53	Participant	13	Time schedule of enrolment, interventions P6-7 timeline (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
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2	Sample size	14	Estimated number of participants needed to	P12
3			achieve study objectives and how it was	
4			determined, including clinical and statistical	
5			assumptions supporting any sample size	
6			calculations	
7				
8	Recruitment	15	Strategies for achieving adequate participant	P6-7
9			enrolment to reach target sample size	

Methods: Assignment of interventions (for controlled trials)

Allocation:

15				
16	Sequence	16a	Method of generating the allocation sequence (eg,	P7
17	generation		computer-generated random numbers), and list of	
18			any factors for stratification. To reduce	
19			predictability of a random sequence, details of any	
20			planned restriction (eg, blocking) should be	
21			provided in a separate document that is	
22			unavailable to those who enrol participants or	
23			assign interventions	
24				
25				
26	Allocation	16b	Mechanism of implementing the allocation	P7
27	concealment		sequence (eg, central telephone; sequentially	
28	mechanism		numbered, opaque, sealed envelopes), describing	
29			any steps to conceal the sequence until	
30			interventions are assigned	
31				
32				
33	Implementation	16c	Who will generate the allocation sequence, who	P7
34			will enrol participants, and who will assign	
35			participants to interventions	
36				
37				
38	Blinding	17a	Who will be blinded after assignment to	P7
39	(masking)		interventions (eg, trial participants, care providers,	
40			outcome assessors, data analysts), and how	
41				
42		17b	If blinded, circumstances under which unblinding is	P7
43			permissible, and procedure for revealing a	
44			participant's allocated intervention during the trial	
45				

Methods: Data collection, management, and analysis

47				
48				
49	Data collection	18a	Plans for assessment and collection of outcome,	P13
50	methods		baseline, and other trial data, including any related	
51			processes to promote data quality (eg, duplicate	
52			measurements, training of assessors) and a	
53			description of study instruments (eg,	
54			questionnaires, laboratory tests) along with their	
55			reliability and validity, if known. Reference to where	
56			data collection forms can be found, if not in the	
57			protocol	
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2		18b	Plans to promote participant retention and	P13
3			complete follow-up, including list of any outcome	
4			data to be collected for participants who	
5			discontinue or deviate from intervention protocols	
6				
7	Data	19	Plans for data entry, coding, security, and storage,	P13
8	management		including any related processes to promote data	
9			quality (eg, double data entry; range checks for	
10			data values). Reference to where details of data	
11			management procedures can be found, if not in the	
12			protocol	
13				
14				
15	Statistical	20a	Statistical methods for analysing primary and	P12-13
16	methods		secondary outcomes. Reference to where other	
17			details of the statistical analysis plan can be found,	
18			if not in the protocol	
19				
20				
21		20b	Methods for any additional analyses (eg, subgroup	P12-13
22			and adjusted analyses)	
23				
24		20c	Definition of analysis population relating to protocol	P12-13
25			non-adherence (eg, as randomised analysis), and	
26			any statistical methods to handle missing data (eg,	
27			multiple imputation)	
28				
29				
30	Methods: Monitoring			
31				
32	Data monitoring	21a	Composition of data monitoring committee (DMC);	P13
33			summary of its role and reporting structure;	
34			statement of whether it is independent from the	
35			sponsor and competing interests; and reference to	
36			where further details about its charter can be	
37			found, if not in the protocol. Alternatively, an	
38			explanation of why a DMC is not needed	
39				
40				
41		21b	Description of any interim analyses and stopping	NA
42			guidelines, including who will have access to these	
43			interim results and make the final decision to	
44			terminate the trial	
45				
46				
47	Harms	22	Plans for collecting, assessing, reporting, and	NA
48			managing solicited and spontaneously reported	
49			adverse events and other unintended effects of	
50			trial interventions or trial conduct	
51				
52				
53	Auditing	23	Frequency and procedures for auditing trial	NA
54			conduct, if any, and whether the process will be	
55			independent from investigators and the sponsor	
56				
57				
58	Ethics and dissemination			
59				
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1				
2	Research ethics	24	Plans for seeking research ethics	P13-P14
3	approval		committee/institutional review board (REC/IRB)	
4			approval	
5				
6	Protocol	25	Plans for communicating important protocol	NA
7	amendments		modifications (eg, changes to eligibility criteria,	
8			outcomes, analyses) to relevant parties (eg,	
9			investigators, REC/IRBs, trial participants, trial	
10			registries, journals, regulators)	
11				
12				
13	Consent or	26a	Who will obtain informed consent or assent from	P6-7
14	assent		potential trial participants or authorised surrogates,	
15			and how (see Item 32)	
16				
17				
18		26b	Additional consent provisions for collection and use	NA
19			of participant data and biological specimens in	
20			ancillary studies, if applicable	
21				
22	Confidentiality	27	How personal information about potential and	P13
23			enrolled participants will be collected, shared, and	
24			maintained in order to protect confidentiality	
25			before, during, and after the trial	
26				
27				
28	Declaration of	28	Financial and other competing interests for	P15
29	interests		principal investigators for the overall trial and each	
30			study site	
31				
32	Access to data	29	Statement of who will have access to the final trial	P16
33			dataset, and disclosure of contractual agreements	
34			that limit such access for investigators	
35				
36				
37	Ancillary and	30	Provisions, if any, for ancillary and post-trial care,	NA
38	post-trial care		and for compensation to those who suffer harm	
39			from trial participation	
40				
41	Dissemination	31a	Plans for investigators and sponsor to	P14
42	policy		communicate trial results to participants,	
43			healthcare professionals, the public, and other	
44			relevant groups (eg, via publication, reporting in	
45			results databases, or other data sharing	
46			arrangements), including any publication	
47			restrictions	
48				
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50				
51		31b	Authorship eligibility guidelines and any intended	P14
52			use of professional writers	
53				
54		31c	Plans, if any, for granting public access to the full	P14
55			protocol, participant-level dataset, and statistical	
56			code	
57				

Appendices

1 2 3 4 5	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	See supplementary file
6 7 8 9 10	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.

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