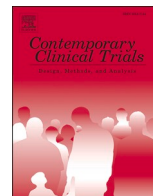




Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Full Length Article



Japanese Project for Telepsychiatry Evaluation during COVID-19: Treatment Comparison Trial (J-PROTECT): Rationale, design, and methodology

Taishiro Kishimoto^{a,*}, Shotaro Kinoshita^{a,b}, Shogyoku Bun^{c,d}, Yasunori Sato^e, Momoko Kitazawa^c, Toshiaki Kikuchi^c, Mitsuhiro Sado^c, Akihiro Takamiya^c, Masaru Mimura^c, Takashi Nakamae^f, Yoshinari Abe^f, Tetsufumi Kanazawa^g, Yasuo Kawabata^g, Hiroaki Tomita^{h,i}, Koichi Abe^h, Akitoyo Hishimoto^j, Takeshi Asami^j, Akira Suda^j, Yoshinori Watanabe^k, Toru Amagai^l, Kei Sakuma^m, Hisashi Kida^{c,m}, Michitaka Funayamaⁿ, Hiroshi Kimura^{o,p}, Aiko Sato^p, Shuichiro Fujiwara^q, Kiichiro Nagao^r, Naoya Sugiyama^s, Maki Takamiya^t, Hideyuki Kodama^t, Takaharu Azekawa^u, On Behalf of the J-PROTECT Collaborators

^a Hills Joint Research Laboratory for Future Preventive Medicine and Wellness, Keio University School of Medicine, #7F Roppongi Hills, North Tower 6-2-31 Roppongi, Minato-ku, Tokyo 106-0032, Japan

^b Graduate School of Medicine, International University of Health and Welfare, 4-1-26 Akasaka, Minato-ku, Tokyo 107-8402, Japan

^c Department of Neuropsychiatry, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan

^d Sato Hospital, 948-1 Kunugizuka, Nanyo, Yamagata 999-2221, Japan

^e Department of Preventive Medicine and Public Health, Keio University School of Medicine, 35 Shinanomachi, Shinjuku, Tokyo 160-8582, Japan

^f Department of Psychiatry, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, 465 Kajii-cho, Kawaramachi-Hirokoji, Kamigyo, Kyoto, Kyoto 602-8566, Japan

^g Department of Neuropsychiatry, Osaka Medical and Pharmaceutical University, 2-7 Daigaku-machi, Takatsuki, Osaka 569-8686, Japan

^h Department of Psychiatry, Tohoku University Hospital, 1-1 Seiry-Machi, Aoba-ku, Sendai, Miyagi 980-8573, Japan

ⁱ Department of Psychiatry, Tohoku University Graduate School of Medicine, 1-1 Seiry-Machi, Aoba-ku, Sendai, Miyagi 980-8573, Japan

^j Department of Psychiatry, Yokohama City University Graduate School of Medicine, 3-9 Fukuura, Kanazawa-ku, Yokohama, Kanagawa 236-0004, Japan

^k Himorogi Psychiatric Institute, Ichigaya-Asukara Bldg. 1F2F, 2-31-3 Ichigayatamachi, Shinjuku, Tokyo 162-0843, Japan

^l Amagai Mental Clinic, Kitami Bldg. 3F, 1-4-20 Kamiooka-nishi, Konan, Yokohama, Kanagawa 233-0002, Japan

^m Asaka Hospital, 45 Kyotan, Sasagawa, Asakamachi, Koriyama, Fukushima 963-0198, Japan

ⁿ Department of Neuropsychiatry, Ashikaga Red Cross Hospital, 284-1 Yobe, Ashikaga, Tochigi 326-0843, Japan

^o Department of Psychiatry, Gakuji-kai Kimura Hospital, 6-19, Higashi Honcho, Chuo-ku, Chiba, Chiba 260-0004, Japan

^p Department of Psychiatry, School of Medicine, International University of Health and Welfare, 4-3, Kozunomori, Narita, Chiba 286-8686, Japan

^q Kanazawabunko Yell Clinic, Kanazawa Bunko Park Homes 102, Kamariyahigashi, Kanazawa, Yokohama, Kanagawa 236-0042, Japan

^r Neyagawa Sanatorium, 2370-6 Neyagawakoen, Neyagawa, Osaka, Osaka 572-0854, Japan

^s Numazu Chuo Hospital, 24-1 Nakase-cho, Numazu, Shizuoka 410-8575, Japan

^t Takamiya Hospital, 1931 Omachikou, Yoshimura, Miyazaki, Miyazaki 880-0841, Japan

^u Shioiri Mental Clinic, 2-7-1 Shioiri, Yokosuka, Kanagawa, 238-0042, Japan

Abbreviations: COVID-19, the 2019 novel coronavirus disease; J-PROTECT, Japanese Project for Telepsychiatry Evaluation during COVID-19: Treatment Comparison Trial; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; FTF, face-to-face treatment; jRCT, Japan Registry of Clinical Trials; OCD, Obsessive–Compulsive Disorder; SF-36 MCS, Medical Outcomes Study 36-Item Short-Form Health Survey Mental Component Summary; SF-36, Medical Outcomes Study 36-Item Short-Form Health Survey; WAI, Working Alliance Inventory; CSQ, Client Satisfaction Questionnaire; EQ-5D, EuroQol 5 Dimension; HAMD, Hamilton Depression Rating Scale; HAMA, Hamilton Anxiety Rating Scale; YBOCS, Yale-Brown Obsessive Compulsive Scale; EDC, Electronic Data Capture; ePRO, electronic Patient-Reported Outcome; QOL, Quality Of Life; MMRM, Mixed-effects Model for Repeated Measurements; PRECIS2, Pragmatic-Explanatory Continuum Indicator Summary-2.

* Corresponding author at: Hills Joint Research Laboratory for Future Preventive Medicine and Wellness, Keio University School of Medicine, #7F Roppongi Hills, North Tower 6-2-31 Roppongi, Minato-ku, Tokyo 106-0032, Japan.

E-mail address: taishiro-k@mti.biglobe.ne.jp (T. Kishimoto).

<https://doi.org/10.1016/j.cct.2021.106596>

Received 22 June 2021; Received in revised form 7 October 2021; Accepted 7 October 2021

Available online 13 October 2021

1551-7144/© 2021 Published by Elsevier Inc.

ARTICLE INFO

Keywords:

Telepsychiatry
 Depression
 Anxiety disorder
 Obsessive-compulsive disorder
 Master protocol

ABSTRACT

Introduction: The COVID-19 pandemic has had a profound impact on the mental health of people around the world. Anxiety related to infection, stress and stigma caused by the forced changes in daily life have reportedly increased the incidence and symptoms of depression, anxiety disorder and obsessive-compulsive disorder. Under such circumstances, telepsychiatry is gaining importance and attracting a great deal of attention. However, few large pragmatic clinical trials on the use of telepsychiatry targeting multiple psychiatric disorders have been conducted to date.

Methods: The targeted study cohort will consist of adults (>18 years) who meet the DSM-5 diagnostic criteria for either (1) depressive disorders, (2) anxiety disorders, or (3) obsessive-compulsive and related disorders. Patients will be assigned in a 1:1 ratio to either a “telepsychiatry group” (at least 50% of treatments to be conducted using telemedicine, with at least one face-to-face treatment [FTF] within six months) or an “FTF group” (all treatments to be conducted FTF, with no telemedicine). Both groups will receive the usual treatment covered by public medical insurance. The study will utilize a master protocol design in that there will be primary and secondary outcomes for the entire group regardless of diagnosis, as well as the outcomes for each individual disorder group.

Discussion: This study will be a non-inferiority trial to test that the treatment effect of telepsychiatry is not inferior to that of FTF alone. This study will provide useful insights into the effect of the COVID-19 pandemic on the practice of psychiatry.

Trial Registration: jRCT1030210037, Japan Registry of Clinical Trials (jRCT).

1. Introduction

The 2019 novel coronavirus disease (COVID-19) pandemic, which is raging worldwide, has had significant direct and indirect impacts on mental health. The incidence of symptoms, such as anxiety, depression, and obsessive-compulsive disorder (OCD), in the general population is reportedly higher than during pre-pandemic times as a result of the effects of lockdowns and other restrictions on going out, sudden unemployment, and frequent exposure to related topics through news associated with the COVID-19 pandemic [1,2]. People infected with COVID-19 also reportedly have a higher risk of developing psychiatric disorders, and people with a history of psychiatric disorders have a higher diagnosis rate of COVID-19 infection [3]. This situation suggests that psychiatric care is becoming increasingly important under the COVID-19 pandemic.

However, during the COVID-19 pandemic, patients may refrain from visiting hospitals because of fears of infection, and hospitals may stop performing outpatient consultations. According to a survey conducted by WHO in 130 countries, 93% of the countries surveyed reported obstacles to providing psychiatric and mental health services [4]. Under these circumstances, it is important to find ways to continue the provision of psychiatric care. In past epidemics of infectious diseases, telemedicine has been used to prevent infection among healthcare workers by using the telephone and video calls to conduct consultations [5]. During the recent pandemic, telemedicine has attracted attention as a way of continuing medical care while preventing infection, and its use has rapidly expanded due to deregulation in many countries [6]. According to the WHO survey mentioned earlier, 70% of 130 countries have introduced telepsychiatry to overcome interruptions in psychiatric care and other problems caused by COVID-19 [4].

In psychiatry, outpatient care is mainly conducted in the form of in-person conversations; therefore, doctor-to-patient telemedicine, in which patients are treated remotely via videophone, is easy to apply in this field. For this reason, telemedicine was popular in the field of psychiatry even before the COVID-19 pandemic [7]. There have also been many studies comparing the effectiveness of telepsychiatry with face-to-face (FTF) treatment, and telepsychiatry can reportedly provide equivalent or better treatment effects, patient satisfaction, and improved medication adherence, compared with FTF treatment [8–10]. However, most of the existing studies have focused on only a single disorder, such as depression or PTSD, or on experimental trials that differ from real-world clinical practice, and few large pragmatic trials examining multiple psychiatric disorders have been reported worldwide.

As COVID-19 is expected to take some time to fully resolve, verifying whether telemedicine is as effective as FTF treatment in real-world

clinical practice for the treatment of depression, anxiety, and OCD in existing clinical settings is of great importance, particularly since increases in the diagnosis or exacerbation of these conditions have been reported in response to the circumstances created by the COVID-19 pandemic.

2. Method

2.1. Design overview

Patients will be assigned in a 1:1 ratio to either a “telepsychiatry group” (at least 50% of treatments to be conducted by telemedicine, with at least one FTF within six months) or an “FTF group” (all treatments to be FTF, with no telemedicine). Patients in telepsychiatry arm will meet with their psychiatrist from their private places such as home or office using a smartphone, tablet or PC. Both groups will receive the usual treatment covered by public medical insurance. The interval between treatments will be at the discretion of the psychiatrist in charge. This study will have a master protocol with primary and secondary outcomes for the entire group as well as outcomes for each individual disorder group.

The main objective of this study will be to show that the telepsychiatry group is non-inferior to the FTF group after 6 months of practice in patients with depressive disorder, anxiety disorder, or OCD and related disorders.

2.2. Participants

This study will be a multi-site, prospective randomized controlled trial. Participants will be recruited at 17 medical institutions that provide psychiatric services in 11 different prefectures in Japan. Patient recruitment will be conducted at the following locations and medical institutions: Tokyo (Keio University Hospital, Himorogi Psychiatric Institute); Kanagawa (Yokohama City University Hospital, Shioiri Mental Clinic, Amagai Mental Clinic, Kanazawabunko Yell Clinic); Fukushima (Asaka Hospital); Miyagi (Tohoku University Hospital); Kyoto (University Hospital Kyoto Prefectural University of Medicine); Osaka (Osaka Medical and Pharmaceutical University Hospital, Neyagawa Sanatorium); Tochigi (Ashikaga Red Cross Hospital); Yamagata (Sato Hospital); Miyazaki (Takamiya Hospital); Shizuoka (Numazu Chuo Hospital); and Chiba (International University of Health and Welfare University Narita Hospital, Gakuji-kai Kimura Hospital).

The inclusion criteria for participants will be as follows: 1) patients who meet the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [11] criteria for depressive disorders, anxiety

disorders, or OCD and related disorders and are outpatients at a participating medical institution; 2) patients who are 18 years old or older at the time of obtaining consent; 3) patients who need continuous treatment for the next 6 months or more (at the discretion of the attending physician); 4) patients who have a smart phone or PC and have access to video calling over the Internet (even if it is only available with family support); 5) patients whose psychiatric conditions are stable enough to receive telepsychiatry by clinical judgement of the attending physician; 6) patients whose psychiatric conditions are stable enough to have sufficient capacity provide consent by clinical judgement of the attending physician; and 7) patients who have provided written consent to participate in the study. For patients who are minors (less than 20 years of age), written consent must be obtained from the patient and his/her guardian. Exclusion criteria include: 1) patients who are likely to require unscheduled or urgent treatments at the hospital in addition to regular treatments because of emergent suicidal ideation, anxiety or agitation; and 2) patients who have difficulty managing an emergency visit by themselves when their psychiatric conditions deteriorate (e.g., the hospital is located far away). Researchers will obtain written informed consent from all the participants. The participants will be able to leave the study at any time. Diagnoses will be based on clinical judgement with consideration of the DSM-5 criteria, since this is the usual practice in Japan.

2.3. Randomization

Patients who have given their consent to participate in this study will be randomly assigned in a 1:1 ratio to the “Telepsychiatry group” or the “FTF group” for treatment during the study period. In this study, to avoid inter-institutional differences and biases in the types of disorders among the groups, randomization process is carried out by a blinded, independent third party using a modified minimization method with a biased-coin assignment [12], balanced for age group (60 years old or older, or younger), gender (male or female), target disorder, and participating institution. In addition, the allocation results will not be disclosed to the central evaluator to minimize bias.

2.4. Assessment schedule

The assessment schedule is presented in Table 1. After randomization, participants will be assessed with the Medical Outcomes Study 36-Item Short-Form Health Survey Mental Component Summary (SF-36 MCS) at baseline and at weeks 12 and 24. The duration of each patient’s participation in the study is estimated to be approximately 6 to 7 months, including the allowance period for the prescribed visits.

2.5. Primary outcomes

The primary outcome is the SF-36 MCS measured at baseline and at weeks 12 and 24. We will examine whether these changes differ between the Telepsychiatry and FTF groups. The SF-36 is a scientific and reliable measure of Health Related Quality of Life; this measure can also be used to calculate a Mental Component Summary, which focuses on mental items [13]. We decided to use the SF-36 MCS because the present study targets multiple psychiatric disorders. The SF-36 MCS is a self-administered rating scale to which patients respond via a dedicated application.

2.6. Secondary outcome

The secondary outcomes are the following 12 items: 1) overall Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) score (assessed at baseline and at weeks 12 and 24); 2) dropout rate (in the Telepsychiatry group, if the patient stops telepsychiatry and switches to FTF only, the patient will be considered to have dropped out of the Telepsychiatry group); 3) Working Alliance Inventory (WAI) scores

as treatment alliance [14]; 4) Client Satisfaction Questionnaire (CSQ) scores as satisfaction [15]; 5) adverse events; 6) costs (Self-administered questionnaire on costs associated with medical treatments, etc.); 7) EQ-5D (EuroQol 5 Dimension) as another measure of Health Related Quality of Life [16]; 8) degree of anxiety about COVID-19; 9) comments about telepsychiatry (or central evaluation by telemedicine); 10) for the depressive disorder group, Hamilton Depression Rating Scale (HAMD) [17]; 11) for the anxiety disorder group, the Hamilton Anxiety Rating Scale (HAMA) [18]; and 12) for the OCD and related disorders group, the Yale-Brown Obsessive Compulsive Scale (YBOCS) [19].

2.7. Sample size

The primary outcome of the study is health-related quality of life as assessed using the SF36-MCS, which will be evaluated at baseline and at weeks 12 and 24. The sample size is based on previous psychiatric intervention studies (including psychotherapy and electroconvulsive therapy interventions, but not studies comparing telepsychiatry and FTF), in which the evaluation period was 6 months [20–25]. In existing studies, the mean SF-36 MCS ranged from 30 to 50 and the standard deviation from 9 to 14.

In the present study, assuming that the SF-36 MCS of the telemedicine and FTF groups at 6 months is 45 (no difference between the two groups), with a standard deviation of 12, and a non-inferiority margin of 5, the required number of patients in each group would be 92 under the conditions of 80% power and a one-sided significance level of 2.5%.

In this study, the dropout rate is expected to be low because the primary psychiatrist who have been treating the patients up to the time of the study will continue to be in charge of the treatment regardless of whether the patients are treated in the Telepsychiatry group or in the FTF group. Assuming a dropout rate of about 10%, the total number of patients will be 200, or 100 in each group.



2.8. Data collection and management

Data on the SF-36 MCS, overall SF-36 score, treatment alliance, satisfaction, cost, EQ-5D, and degree of anxiety about COVID-19 will be collected as self-administered patient-reported outcome measures. We will construct and operate a system to store these data directly using electronic data capture (EDC) and an electronic patient-reported outcome (ePRO). We will use “cubeCDMS” by CRScube Inc. for EDC and “cubePro” by CRScube Inc. for ePRO. The participants will install the ePRO application on their smartphones, etc., access the questionnaire included in the application, and enter and transmit the data. For the HAMD, HAMA, and YBOCS, remote centralized ratings performed through a video camera feed will be used. Evaluators are required to have completed a total of at least 30 h of training on these evaluation items, and the evaluator will assess the examinees through a video camera feed at the time of each visit. In addition, as an optional part of the study, both FTF evaluations and centralized ratings for HAMD, HAMA, and YBOCS will be performed for patients who are willing to participate, so as to validate the centralized ratings.

2.9. Statistical analysis

The analyses of the primary and secondary outcomes will be performed in full analysis set (FAS), which will include all patients who completed at least one SF-36 MCS assessment during the study period, do not present any serious violation of the study protocol such as the inappropriate procurement of consent or a breach of the inclusion and exclusion criteria, and whose data were collected after treatment commencement. For the baseline characteristics, summary statistics will comprise frequencies and proportions for categorical variables, and means and standard deviations for continuous variables. The patient characteristics will be compared using a chi-square test for categorical variables, and a *t*-test or Wilcoxon rank sum test for continuous

Table 1
Schedule for data collection and evaluations during the study's observation period.

Medical care (FTF or telepsychiatry)	 After obtaining consent, patients will be assigned to either the FTF group or the Telepsychiatry group, and they will continue to receive treatment for 6 months. (The interval between treatments will be determined by the attending physician.)		
	Visit 1	Visit 2	Visit 3
	Baseline	12 Weeks (3 Months)	24 Weeks (6 Months)
Patient background	●		
SF-36	○	○	○
Working Alliance Inventory (WAI)		○	○
Client Satisfaction Questionnaire (CSQ)		○	○
Adverse events			
Costs (Self-administered questionnaire on costs associated with medical visits, etc.)	○	○	○
EQ-5D	○	○	○
Degree of anxiety about COVID-19	○	○	○
Comments about telepsychiatry			○
HAMD (Depressive disorders only)	☆	☆	☆
HAMA (Anxiety disorders only)	☆	☆	☆
YBOCS (OCD and related disorders only)	☆	☆	☆

●: Both groups receive FTF treatment.

○: In both groups, the evaluation was conducted using input from smartphones and tablets (via ePRO).

☆: For each disorder group, outcomes unique to each disorder will be investigated. A centralized evaluation system will be adopted in which patients and evaluators will be connected remotely. For patients with partial cooperation, both face-to-face evaluation and telemedicine with central evaluation will be conducted for the purpose of verifying the reliability of the outcomes of each disorder group.

- : Both groups receive FTF treatment.
- : In both groups, the evaluation was conducted using input from smartphones and tablets (via ePRO).
- ☆: For each disorder group, outcomes unique to each disorder will be investigated. A centralized evaluation system will be adopted in which patients and evaluators will be connected remotely. For patients with partial cooperation, both face-to-face evaluation and telemedicine with central evaluation will be conducted for the purpose of verifying the reliability of the outcomes of each disorder group.

variables.

For the primary analysis, aimed at comparing treatment effects, the least square mean and its 95% confidence interval (CI) will be estimated using a mixed-effects model for repeated measurements (MMRM). No imputation of missing data was performed. The MMRM model will include the treatment effect, treatment-by-time interaction, and baseline SF-36 MCS. An unstructured covariance matrix will be assumed to model the within-patient variance and estimation was performed by restricted maximum likelihood method. Based on this model, the result of the SF-36 MCS during each 6-month period will be expressed as a point estimate of group differences for whole groups and a one-sided confidence interval with significance level of 2.5%. Non-inferiority will be demonstrated if the upper boundary of this confidence interval does not exceed the non-inferiority margin of 5.

The secondary analysis will be performed in the same manner as the primary analysis. All comparisons will be planned and all p values will be two sided. p Values < 0.05 will be considered statistically significant. All statistical analyses will be performed using the SAS software version 9.4 (SAS Institute, Cary, NC, USA). The statistical analysis plan (SAP) will be developed by the principal investigator and the biostatistician before completion of patient recruitment and data fixation.

3. Results

The trial began in April 2021. Recruitment goals are on target to date, and the trial is projected to be completed in March 2023. The trial is registered at jRCT1030210037.

4. Discussion

The J-PROTECT study is an important study in both the psychiatric and telemedicine fields, as the COVID-19 outbreak is far from under control. The wide practice of telemedicine in this field is meaningful as an effective countermeasure against infection and to prove that telepsychiatry is effective for the treatment of psychiatric disorders that can worsen during a pandemic. As mentioned above, many studies comparing telepsychiatry with FTF treatment have focused on specific disorders or specific treatments, such as CBT, but few studies have examined multiple disorders simultaneously. For example, O'Reilly et al. randomly assigned 495 outpatients to FTF treatment or telepsychiatry and followed them for up to 4 months; they reported that telepsychiatry provided the same clinical outcome and satisfaction as FTF treatment, but at a lower cost [26]. In another study, De Las Cuevas et al. randomly assigned 140 outpatients to FTF treatment or telepsychiatry with a 24-week follow-up period and reported that the efficacy of telepsychiatry was comparable to that of FTF treatment [27]. The novelty of the present study is that it will be the first pragmatic trial of telepsychiatry in Japan, a country that provides universal health insurance that allows free access to medical services with relatively low cost. Since the degree and content of telepsychiatry regulation varies in each country [6], showing that telepsychiatry is equally effective in different regulatory and cultural settings will be important to promote its use appropriately. Also, the most important feature of this study is that patients in telepsychiatry arm can access their own psychiatrist and receive treatment at home or in their own office. Currently, the most popular way for patients to have Telepsychiatry conducted is through their own smartphones, tablets, or PCs. Most of the previous RCTs in telepsychiatry have been conducted under special circumstances, such as setting up a dedicated line between clinics and having a patient visit one clinic and be seen by a psychiatrist at another clinic. However, this

study tested non-inferiority using methods used in real-world clinical practice, and there have been few such RCTs to date.

In considering the study design, several issues needed to be taken into account. First, the rationale for selecting SF-36 MCS as the primary outcome in this study was that it was necessary to establish an outcome that encompassed depressive disorder, anxiety disorder, and OCD and related disorders and that was in use at many psychiatric clinical studies as a health-related quality of life (QOL), which is a superordinate concept for the severity of all illnesses [20–25]. Next, the reason why we set the percentage of telemedicine in the telepsychiatry group to be more than 50% is to allow room for the use of both FTF and telepsychiatry depending on the patient's condition, just as in regular medical care. The Japanese government regulations and guidelines require that telemedicine be combined with regular FTF care [28]. And, we have taken care to make this study pragmatic. We used the Pragmatic-Explanatory Continuum Indicator Summary-2 (PRECIS-2) as a tool to assess the degree of pragmaticity of the study. PRECIS-2 consists of nine domains (eligibility, recruitment, setting, organisation, flexibility [delivery], flexibility [adherence], follow up, primary outcome and primary analysis), each of which is given a score out of five, with higher scores being more pragmatic [29]. The results are summarized in Fig. 1 [30], which shows that the present study design is highly pragmatic. The reasons for the scoring are reported in Table 2.

The limitations of this study are as follows. First, we targeted three disorder groups, namely depressive disorders, anxiety disorders, and OCD and related disorders. In addition to targeting three disorders in one trial, the demographic characteristics of the participants may vary over a wide range. This may lead to difficulty in finding a comparative effect size of telemedicine; however, this is an inherent difficulty of pragmatic trials, and limiting participation to a specific patient population may limit the generalizability of the results. Related to this point, IT literacy might be the largest modulator of the results, and since Japan is a world-leading aging society, this fact is of particular consideration. Elderly people generally experience more hurdles to telemedicine because of IT literacy issues [31]. By randomizing the whole population, we reduce the risk of the impact of this possible modulator. At the same time, by asking the participants regarding their impressions or hurdles regarding telemedicine utilization in a free-answer format, we hope to gather information that will enable us to help elderly or low-IT literacy patients to take advantage of telemedicine in the future. In addition, although the three disorder groups covered by this study can be said to

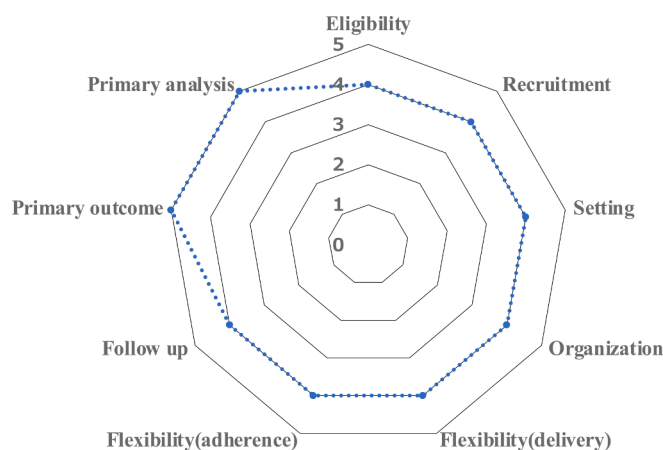


Fig. 1. Pragmatism wheel according to PRECIS-2 tool.

Table 2
PRECIS2 scoring.

Items	Score	Rationale
Eligibility	4	Although there are some exclusion criteria, these are similar to the criteria for patients who should not be introduced to telepsychiatry in clinical practice.
Recruitment	4	Since participants are recruited during regular outpatient clinics, there are not many extra efforts. Instructions given to patients who are new to telemedicine are similar in scope to those that occur in actual clinical practice.
Setting	4	This study involved medical institutions with diverse attributes from across the country.
Organisation	4	Consultations will be conducted by the usual outpatient physicians and staff at the same medical facilities as usual, but some additional resources will be required for symptom assessment by psychologists and other procedures to be conducted during the course of the study.
Flexibility (delivery)	4	The content of treatment is the same as that of regular medical treatment. The number of times telepsychiatry is performed can be flexibly adjusted.
Flexibility (adherence)	4	The content of medical treatment is the same as usual, and the use of devices and systems during telepsychiatry is also the same as usual. However, it may be necessary to remind the patient about the input of evaluation using ePRO.
Follow up	4	The number of treatments by the physician is the same as for normal medical care. There will be no increase in consultation time compared to normal, but there will be additional opportunities for symptom assessment outside of the consultation.
Primary outcome	5	Primary outcome is relevant to participants.
Primary analysis	5	The analyses of the primary outcome will be performed in full analysis set (FAS), which includes all patients who took at least one SF-36 MCS assessment during the study, do not present any serious violation of the study protocol, and have data collected after treatment commencement.

represent a large number of patients in psychiatric outpatient clinics, they do not cover all psychiatric disorders, such as schizophrenia, eating disorders, and PTSD. The comparison of telepsychiatry and FTF in diseases not covered in this study is a subject for future research. Finally, the implementation of this study may be affected by the status of the COVID-19 pandemic. If the pandemic becomes serious, there is a risk that hospitals will suspend FTF treatment or that patients will refuse to come to the hospital for fear of the risk of infection. In any case, we will implement an appropriate combination of telepsychiatry and FTF treatment, while prioritizing the interests of the patients.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of the National Center of Neurology and Psychiatry and the participating medical facilities. Researchers will obtain written informed consent from all the participants. Participants are able to leave the study at any time.

Funding

This research is supported by the Japan Agency for Medical Research and Development (AMED) under Grant Number JP21dk0307098. The funding source did not participate in the design of this study and will not have any hand in the study's execution, analyses, or submission of results.

Japan Agency for Medical Research and Development (AMED) 20F Yomiuri Shimbu Bldg. 1-7-1 Otemachi, Chiyoda-ku, Tokyo 100-0004 Japan Tel: +81-3-6870-2200, Fax: +81-3-6870-2241, Email: jimu-ask@amed.go.jp.

Authors' contributions

All authors critically revised the manuscript, and approved the manuscript to be published, and agree to be accountable for all aspects of the work in ensuring the questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CRediT authorship contribution statement

Taishiro Kishimoto: Conceptualization, Methodology, Writing – review & editing, Funding acquisition. **Shotaro Kinoshita:** Conceptualization, Methodology, Writing – original draft. **Shogyoku Bun:** Methodology, Investigation, Writing – review & editing. **Yasunori Sato:** Methodology, Formal analysis. **Momoko Kitazawa:** Methodology, Writing – review & editing. **Toshiaki Kikuchi:** Methodology, Investigation. **Mitsuhiro Sado:** Methodology, Investigation. **Akihiro Takamiya:** Methodology, Investigation. **Masaru Mimura:** Supervision. **Takashi Nakamae:** Methodology, Investigation. **Yoshinari Abe:** Methodology, Investigation. **Tetsufumi Kanazawa:** Methodology, Investigation. **Yasuo Kawabata:** Methodology, Investigation. **Hiroaki Tomita:** Methodology, Investigation. **Koichi Abe:** Methodology, Investigation. **Akitoyo Hishimoto:** Methodology, Investigation. **Take-shi Asami:** Methodology, Investigation. **Akira Suda:** Methodology, Investigation. **Yoshinori Watanabe:** Methodology, Investigation. **Toru Amagai:** Methodology, Investigation. **Kei Sakuma:** Methodology, Investigation. **Hisashi Kida:** Methodology, Investigation. **Michitaka Funayama:** Methodology, Investigation. **Hiroshi Kimura:** Methodology, Investigation. **Aiko Sato:** Methodology, Investigation. **Shuichiro Fujiwara:** Methodology, Investigation. **Kiichiro Nagao:** Methodology, Investigation. **Naoya Sugiyama:** Methodology, Investigation. **Maki Takamiya:** Methodology, Investigation. **Hideyuki Kodama:** Methodology, Investigation. **Takaharu Azekawa:** Methodology, Investigation.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

- T. Kishimoto: Research grant funding, Micin.
- T. Nakamae: Provided with a telemedicine system, Medley.
- Y. Abe: Provided with a telemedicine system, Medley.

Acknowledgements

The authors are grateful to Dr. Kazunari Yoshida, Dr. Toshiro Horigome, Dr. Mayu Fujikawa, Ms. Kumiko Hiza, Ms. Hiromi Mikami, Dr. Saki Hattori, Dr. Masao Takaishi, Dr. Satoshi Tsujimura, Dr. Hajime Tamura, Ms. Junko Suzuki, Ms. Keiko Komiya, Dr. Anri Watanabe, Dr. Yoshihiro Matsumoto, Ms. Satoko Kimura, Ms. Haruka Okamoto, Dr. Kyosuke Sawada, Ms. Yuka Oba, Ms. Shii Sagae, Dr. Kiyoji Nagao, Mr. Ryuhei Terashi, Ms. Sumako Onishi, Ms. Mayumi Hiruma, Ms. Junko Kannari, Ms. Kanako Sasao, Ms. Ayumi Konishi, Ms. Nobuko Haga, Dr. Nobuhiko Noguchi, Dr. Kosuke Hino, Dr. Yuya Igarashi, Dr. Kenichi Goto for supporting data collection and management in this study.

References

- [1] J. Xiong, O. Lipsitz, F. Nasri, L.M.W. Lui, H. Gill, L. Phan, D. Chen-Li, M. Iacobucci, R. Ho, A. Majeed, R.S. McIntyre, Impact of COVID-19 pandemic on mental health in the general population: a systematic review, *J. Affect. Disord.* 277 (2020 Dec 1) 55–64, <https://doi.org/10.1016/j.jad.2020.08.001>.
- [2] L. Jelinek, S. Moritz, F. Miegel, U. Voderholzer, Obsessive-compulsive disorder during COVID-19: turning a problem into an opportunity? *J. Anxiety Disord.* 77 (2021 Jan) 102329, <https://doi.org/10.1016/j.janxdis.2020.102329>.
- [3] M. Taquet, S. Luciano, J.R. Geddes, P.J. Harrison, Bidirectional associations between COVID-19 and psychiatric disorder: retrospective cohort studies of 62354 COVID-19 cases in the USA, *Lancet Psychiatry* 8 (2) (2021 Feb) 130–140, [https://doi.org/10.1016/S2215-0366\(20\)30462-4](https://doi.org/10.1016/S2215-0366(20)30462-4).

- [4] World Health Organization, The Impact of COVID-19 on Mental, Neurological and Substance Use Services: Results of a Rapid Assessment, URL: <https://apps.who.int/iris/rest/bitstreams/1310579/retrieve> (accessed: 2021/9/9).
- [5] S. Keshvardoust, K. Bahaadinbeigi, F. Fatehi, Role of Telehealth in the management of COVID-19: lessons learned from previous SARS, MERS, and Ebola outbreaks, *Telemed. J. E Health* 26 (7) (2020 Jul) 850–852, <https://doi.org/10.1089/tmj.2020.0105>.
- [6] S. Kinoshita, K. Cortright, A. Crawford, Y. Mizuno, K. Yoshida, D. Hilty, D. Guinart, J. Torous, C.U. Correll, D.J. Castle, D. Rocha, Y. Yang, Y.T. Xiang, P. Kølbaek, D. Dines, M. El Shami, P. Jain, R. Kallivayalil, M. Solmi, A. Favaro, N. Veronese, S. Seedat, S. Shin, G. Salazar de Pablo, C.H. Chang, K.P. Su, H. Karas, J.M. Kane, P. Yellowlees, T. Kishimoto, Changes in telepsychiatry regulations during the COVID-19 pandemic: 17 countries and regions' approaches to an evolving healthcare landscape, *Psychol. Med.* (2020 Nov 27) 1–8, <https://doi.org/10.1017/S0033291720004584> (Epub ahead of print).
- [7] World Health Organization, Telemedicine: Opportunities and Developments in Member States: Report on the Second Global Survey on eHealth 2009, URL: http://www.who.int/goe/publications/goe_telemedicine_2010.pdf (accessed: 2021/9/9).
- [8] A. Salmoiraghi, S. Hussain, A systematic review of the use of telepsychiatry in acute settings, *J. Psychiatr. Pract.* 21 (5) (2015 Sep) 389–393, <https://doi.org/10.1097/PRA.0000000000000103>.
- [9] S. Hubley, S.B. Lynch, C. Schneck, M. Thomas, J. Shore, Review of key telepsychiatry outcomes, *World J. Psychiatry* 6 (2) (2016 Jun 22) 269–282, <https://doi.org/10.5498/wjp.v6.i2.269>.
- [10] S.A. Basit, N. Mathews, M.E. Kunik, Telemedicine interventions for medication adherence in mental illness: a systematic review, *Gen. Hosp. Psychiatry* 62 (2020 Jan-Feb) 28–36, <https://doi.org/10.1016/j.genhosppsych.2019.11.004>.
- [11] American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders, 5th edition*, American Psychiatric Publishing, Arlington, VA, 2013.
- [12] B. Efron, Forcing a sequential experiment to be balanced, *Biometrika* 58 (3) (1971 Dec) 403–417, <https://doi.org/10.2307/2334377>.
- [13] J.E. Ware, M. Kosinski, S.D. Keller, SF-36 Physical and Mental Health Summary Scales: A User's Manual, The Health Institute, New England Medical Center, Boston, Mass, 1994.
- [14] O. Horvath Adam, S. Leslie, Greenberg. Development and validation of the Working Alliance Inventory, *J. Couns. Psychol.* 36 (2) (1989) 223.
- [15] D.L. Larsen, C.C. Attkisson, W.A. Hargreaves, T.D. Nguyen, Assessment of client/patient satisfaction: development of a general scale, *Eval Program Plann* 2 (3) (1979) 197–207, [https://doi.org/10.1016/0149-7189\(79\)90094-6](https://doi.org/10.1016/0149-7189(79)90094-6).
- [16] Brooks R with the EuroQol Group, EuroQol: the current state of play, *Health Policy* 37 (1) (1996) 53–72, [https://doi.org/10.1016/0168-8510\(96\)00822-6](https://doi.org/10.1016/0168-8510(96)00822-6).
- [17] M. Hamilton, A rating scale for depression, *J. Neurol. Neurosurg. Psychiatry* 23 (1) (1960) 56–62, <https://doi.org/10.1136/jnnp.23.1.56>.
- [18] M. Hamilton, The assessment of anxiety states by rating, *Br. J. Med. Psychol.* 32 (1) (1959) 50–55, <https://doi.org/10.1111/j.2044-8341.1959.tb00467.x>.
- [19] W.K. Goodman, L.H. Price, S.A. Rasmussen, C. Mazure, R.L. Fleischmann, C.L. Hill, G.R. Heninger, D.S. Charney, The Yale-Brown obsessive compulsive scale. I. Development, use, and reliability, *Arch. Gen. Psychiatry* 46 (11) (1989) 1006–1011, <https://doi.org/10.1001/archpsyc.1989.01810110048007>.
- [20] J.C. Fortney, J.M. Pyne, S.B. Mouden, D. Mittal, T.J. Hudson, G.W. Schroeder, D. K. Williams, C.A. Bynum, R. Mattox, K.M. Rost, Practice-based versus telemedicine-based collaborative care for depression in rural federally qualified health centers: a pragmatic randomized comparative effectiveness trial, *Am. J. Psychiatry* 170 (4) (2013 Apr) 414–425, <https://doi.org/10.1176/appi.ajp.2012.12050696>.
- [21] M.B. Connolly Gibbons, R. Gallop, D. Thompson, D. Luther, K. Crits-Christoph, J. Jacobs, S. Yin, P. Crits-Christoph, Comparative effectiveness of cognitive therapy and dynamic psychotherapy for major depressive disorder in a community mental health setting: a randomized clinical noninferiority trial, *JAMA Psychiatry* 73 (9) (2016 Sep 1) 904–911, <https://doi.org/10.1001/jamapsychiatry.2016.1720>.
Erratum in: *JAMA Psychiatry*. 2017 Jan 1;74(1):107.
- [22] W.V. McCall, S.H. Lisanby, P.B. Rosenquist, M. Dooley, M.M. Husain, R.G. Knapp, G. Petrides, M.V. Rudorfer, R.C. Young, S.M. McClintock, M. Mueller, J. Prudic, R. M. Greenberg, R.D. Weiner, S.H. Bailine, N.A. Youssef, L. McCloud, C.H. Kellner, CORE/PRIDE Work Group, Effects of continuation electroconvulsive therapy on quality of life in elderly depressed patients: a randomized clinical trial, *J. Psychiatr. Res.* 97 (2018 Feb) 65–69, <https://doi.org/10.1016/j.jpsychires.2017.11.001>.
- [23] K. Lovell, P. Bower, J. Gellatly, S. Byford, P. Bee, D. McMillan, C. Arundel, S. Gilbody, L. Gega, G. Hardy, S. Reynolds, M. Barkham, P. Mottram, N. Lidbetter, R. Pedley, J. Molle, E. Peckham, J. Knopp-Hoffer, O. Price, J. Connell, M. Heslin, C. Foley, F. Plummer, C. Roberts, Low-intensity cognitive-behaviour therapy interventions for obsessive-compulsive disorder compared to waiting list for therapist-led cognitive-behaviour therapy: 3-arm randomised controlled trial of clinical effectiveness, *PLoS Med.* 14 (6) (2017 Jun 27), e1002337, <https://doi.org/10.1371/journal.pmed.1002337>.
- [24] B.L. Rollman, B.H. Belpap, S. Mazumdar, K.Z. Abebe, J.F. Karp, E.J. Lenze, H. C. Schulberg, Telephone-delivered stepped collaborative Care for Treating Anxiety in primary care: a randomized controlled trial, *J. Gen. Intern. Med.* 32 (3) (2017 Mar) 245–255, <https://doi.org/10.1007/s11606-016-3873-1>.
- [25] F. Bennebroek Evertsz, Sprangers MAG, K. Sitnikova, Stokkers PCF, C.Y. Ponsioen, Bartelsman JFWM, A.A. van Bodegraven, S. Fischer, Depla ACTM, R.C. Mallant, R. Sanderman, H. Burger, Bockting CLH, Effectiveness of cognitive-behavioral therapy on quality of life, anxiety, and depressive symptoms among patients with inflammatory bowel disease: a multicenter randomized controlled trial, *J. Consult. Clin. Psychol.* 85 (9) (2017 Sep) 918–925, <https://doi.org/10.1037/ccp0000227>.
- [26] R. O'Reilly, J. Bishop, K. Maddox, L. Hutchinson, M. Fisman, J. Takhar, Is telepsychiatry equivalent to face-to-face psychiatry? Results from a randomized controlled equivalence trial, *Psychiatr. Serv.* 58 (6) (2007 Jun) 836–843, <https://doi.org/10.1176/ps.2007.58.6.836>.
- [27] Cuevas C. De Las, M.T. Arredondo, M.F. Cabrera, H. Sulzenbacher, U. Meise, Randomized clinical trial of telepsychiatry through videoconference versus face-to-face conventional psychiatric treatment, *Telemed. J. E Health* 12 (3) (2006 Jun) 341–350, <https://doi.org/10.1089/tmj.2006.12.341>.
- [28] Ministry of Health, Labour and Welfare, The Guidelines for Appropriate Operation of Online Medicine [in Japanese], <https://www.mhlw.go.jp/content/000534254.pdf>, 2021 (accessed: 2021/9/9).
- [29] K. Loudon, S. Treweek, F. Sullivan, P. Donnan, K.E. Thorpe, M. Zwarenstein, The PRECIS-2 tool: designing trials that are fit for purpose, *BMJ* 350 (2015), h2147, <https://doi.org/10.1136/bmj.h2147>.
- [30] PRECIS Toolkit. <https://www.precis-2.org/Help/Documentation/ToolkitDownload>, 2021 (accessed: 2021/9/9).
- [31] E. Hargittai, A.M. Piper, M.R. Morris, From internet access to internet skills: digital inequality among older adults, *Univ. Access Inf. Soc.* 18 (2019) 881–890, <https://doi.org/10.1007/s10209-018-0617-5>.