As discussed in the Introduction, major depression represents the greatest non-fatal burden of disease for the humankind, with commensurate rise in spending on the antidepressants world-wide. We maintain that this must be accompanied by commensurate increase in evidence base to guide their wise clinical administration. For example, the total annual sales of antidepressants amount to 120 billion yen (1.3 billion US dollars), and we would like to advocate that at least 0.1% of this sum be spent on public-domain pragmatic research of their use for mood and anxiety disorders. Many urgent and critical clinical questions can be answered with this research funds only if the research can be simple and pragmatic enough. We hope that SUN(^_^)D can be a template for such future clinical trials, and that it ultimately can provide good evidence to improve the treatment guidelines for depression in the world.

List of abbreviations

5-HT: 5-hydroxytryptamine; BDI2: Beck Depression Inventory-II; C-CASA: Columbia Classification Algorithm of Suicide Assessment; CRC: Clinical Research Coordinator; CRO: Contract Research Organization; CYP: Cytochrome pigment; DALY: Disability-Adjusted Life Years; DSMB: Data Safety Monitoring Board; EDC: Electronic Data Capturing; FIBSER: Frequency, Intensity, and Burden of Side Effects Rating; MANGA: Meta-Analyses of New Generation Antidepressants; MAO: Monoamine oxidase; NICE: National Institute of Clinical Excellence; NaSSA: Noradrenergic and Specific Serotonergic Antidepressant; NNT: Number needed to treat; PHQ9: Personal Health Questionnaire-9; RCT: Randomized controlled trial; SMO: Site Management Organization; SNRI: Serotonin & Noradrenalin Reuptake Inhibitor; SSRI: Selective Serotonin Reuptake Inhibitor; STAR*D: Sequenced Treatment Alternatives to Relieve Depression; SUN ☒ D: Strategic Use of New generation antidepressants for Depression.

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Author details

[1]Department of Health Promotion and Human Behavior, Kyoto University Graduate School of Medicine/School of Public Health, Yoshida Konoe-cho, Sakyo-ku, Kyoto 606-8501 Japan. [2]Department of Psychiatry and Cognitive-Behavioral Medicine, Nagoya City University Graduate School of Medical Sciences, Mizuho-cho, Mizuho-ku, Nagoya 467-8601 Japan. [3]Department of Neuropsychiatry, Kochi Medical School, Kohasu, Okoh-cho, Nankokushi, Kochi 783-8505 Japan. [4]Department of Neuropsychopharmacology, National Institute of Mental Health, National Center of Neurology and Psychiatry, 4-1-1 Ogawa-Higashi, Kodaira, Tokyo 187-8553 Japan. [5]Department of Epidemiology and Biostatistics, Translational Medical Center, National Center of Mental Health, National Centre of Neurology and Psychiatry, 4-1-1 Ogawa-Higashi, Kodaira, Tokyo 187-8502 Japan. [6]Miki Clinic, 1-1-3 Hiranuma, Nishi-ku, Yokohama 220-0023 Japan. [7]Center for Suicide Prevention, National Institute of Mental Health, National Center of Neurology and Psychiatry, 4-1-1 Ogawa-Higashi, Kodaira, Tokyo 187-8553 Japan.

Authors' contributions

TAF conceived the study, TAF, MY, MI and NY prepared the original manuscript. TAF, TA, SS, MY, KM, NW, MI and NY participated in the refinement of the protocol. NY is the trial statistician. All authors critically reviewed and approved the final version of the manuscript.

Competing interests

TAF has received honoraria for speaking at CME meetings sponsored by Astellas, Dai-Nippon Sumitomo, Eli Lilly, GlaxoSmithKline, Janssen, Kyorin, MSD, Meiji, Otsuka, Pfizer, Shionogi and Yoshitomi. He is on advisory board for Sekisui Chemicals and Takeda Science Foundation. He has received royalties from Igaku-Shoin, Seiwa-Shoten, Nihon Bunka Kagaku-sha and American Psychiatric Publication. TA has received speaking fees and/or research funds from Astellas, Astra-Zeneca, Bristol-Meyers-Squib, Daiichi-Sankyo, Dainippon-Sumitomo, Eisai, GlaxoSmithKline, Janssen, Kyowa-Hakko-Kirin, Lilly, Meiji, Otsuka, Pfizer, Sanofi-Aventis, Shionogi and Yakult. NW has received speaking fees and/or research funds from Dainippon-Sumitomo, GlaxoSmithKline, Lilly, Otsuka, Pfizer, Asahi-Kasei and Shering-Plough. SS has received speaking fees and/or research funds from Astellas, Dainippon-Sumitomo, GlaxoSmithKline, Janssen, Lilly, Otsuka, Pfizer, Shering-Plough, Shionogi and Yoshitomi. MY and NY have no conflicts of interest to declare. NY received royalties from Seiwa-Shoten. MI has received a speaking fee from Lilly. KM has received speaking fees from Astellas, Dainippon-Sumitomo, GlaxoSmithKline, Janssen, Lilly, Meiji, Otsuka, Pfizer and Shering-Plough.

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The first 100 patients in the SUN(^_^)D trial (Strategic Use of New generation antidepressants for Depression): Feasibility and adherence examination from its pilot phase

Shinji Shimodera[1], Tadashi Kato[2], Hirotoshi Sato[3], Kazuhira Miki[4], Yoshihiro Shinagawa[5], Masaki Kondo[7], Hirokazu Fujita[1], Ippei Morokuma[1], Yoshio Ikeda[6], Tatsuo Akechi[7], Norio Watanabe[7], Mitsuhiko Yamada[8], Masatoshi Inagaki[8], Naohiro Yonemoto[9], Toshi A. Furukawa[10]*, For the SUN(^_^)D Investigators

Address:

[1] Department of Neuropsychiatry, Kochi Medical School, Kohasu, Okoh-cho, Nankokushi, Kochi 783-8505 Japan

[2] Aratama Kokorono Clinic, Suyama-cho, Mizuho-ku, Nagoya 467-0066 Japan

[3] Harimayabashi Clinic, Harimaya-cho, Kochi 780-0822 Japan

[4] Miki Clinic, 1-1-3 Hiranuma, Nishi-ku, Yokohama 220-0023 Japan

[5] Shiki Clinic, Hongo, Meitou-ku, Nagoya 465-0024 Japan

[6] Narumi Himawari Clinic, Narumi-cho, Midori-ku, Nagoya 458-0801 Japan

[7] Department of Psychiatry and Cognitive-Behavioral Medicine, Nagoya City University Graduate School of Medical Sciences, Mizuho-cho, Mizuho-ku, Nagoya 467-8601 Japan

[8] Department of Neuropsychopharmacology, National Institute of Mental Health, National Center of Neurology and Psychiatry, 4-1-1 Ogawa-Higashi, Kodaira, Tokyo 187-8553 Japan

[9] Department of Epidemiology and Biostatistics, Translational Medical Center, National Center of Mental Health, National Centre of Neurology and Psychiatry, 4-1-1 Ogawa-Higashi, Kodaira, Tokyo 187-8502 Japan

[10] Department of Health Promotion and Human Behavior, Kyoto University Graduate School of Medicine / School of Public Health, Yoshida Konoe-cho, Sakyo-ku, Kyoto 606-8501 Japan

Emails:

SS shimodes@kochi-u.ac.jp

TK tkato@spice.or.jp

HS harimayabashi.clinic@honey.ocn.ne.jp

KM k-miki@largo-yokohama.com

YS shinna2004@yahoo.co.jp

MK kondo-masaki@umin.ac.jp
HF fujitah@kochi-u.ac.jp
IM morokuma@kochi-u.ac.jp
TI tomato@mc.ccnw.ne.jp
TA takechi@med.nagoya-cu.ac.jp
NW noriow@med.nagoya-cu.ac.jp
MY mitsu@ncnp.go.jp
MI minagaki@ncnp.go.jp
NY yonemoto@ncnp.go.jp
TAF furukawa@kuhp.kyoto-u.ac.jp

* Corresponding author. Tel: +81-75-753-9491, Fax: +81-75-753-4641, Email: furukawa@kuhp.kyoto-u.ac.jp

Abstract

Background

Initial glitches and unexpected inconsistencies are unavoidable in the early stage of a large, multi-centre trial. Adaptively modifying its protocol and operational procedures to ensure its smooth running is therefore imperative. We started a large pragmatic, multi-centre, assessor-blinded, 25-week trial to investigate the optimal first- and second-line treatments of untreated episodes of nonpsychotic major depression in 2010 (Strategic Use of New generation antidepressants for Depression, abbreviated SUN(^_^)D) and would like to herein report its feasibility and adherence examinations among its first 100 participants.

Methods

We examined the participants' characteristics, their treatments allocated and received in each step of the trial, and the quality of the outcome assessments administered among the first 100 patients of SUN(^_^)D.

Results

Of 2743 first-visit patients visiting the first two collaborating centres between December 2010 and July 2011, 382 were judged potentially eligible, of whom 100 gave written informed consent. They represented the whole spectrum of mild to very severe depression. Of the 93 who had reached Week 3 by end of July 2011, one withdrew consent both for treatment and assessment, eight withdrew consent to treatment only and altogether 90 were successfully assessed for the primary outcomes (96.8%). Of the 72 who had reached Week 9, three withdrew consent to treatment but 70 were successfully interviewed (97.2%). Of the 32 who had reached Week 25, we have successfully followed up 29 (90.5%). The inter-rater reliability of the assessments was nearly perfect and its successful blinding was ascertained. Minor modifications and clarifications to the protocol were deemed necessary.

Discussion

Given the satisfactory feasibility and adherence to the study protocol and the minor modifications necessitated, we conclude that the data from the first 100 patients can be safely included towards the main study and that we can and will now speed up the study by recruiting more collaborating centres and clinics/hospitals.

Trial registration: ClinicalTrials.gov identifier: NCT01109693

Introduction

A randomised clinical trial starts after its protocol and operational procedures are fixed and written down in detail. Like any industrial product, however, it cannot escape some malfunctioning glitches and unexpected inconsistencies especially in its early stages. Adaptively modifying the protocol and operational procedures to ensure its smooth running is therefore imperative.

No guidelines exist, however, on how to implement this crucial step in the conduct of a clinical trial. One often used method is to run a pilot study, separately from and before the formal study [1, 2]. A drawback to this approach is that the data from this sample cannot in principle be merged into the full dataset, especially if only limited aspects of the whole protocol are to be implemented and evaluated in the pilot study or if the randomisation is broken. Moreover, limiting the scope of the pilot study to avoid wasting valuable patient resources may ironically mean that the whole study procedures cannot be tested out in the pilot phase and that the same problem of initial adjustments may have to be worked through de novo only after the full-scale formal study is initiated.

The Strategic Use of New generation antidepressants for Depression, or SUN(^_^)D for short, is a large pragmatic multi-centre, assessor-blinded, parallel-group trial to examine the optimal first-line and second-line treatments of heretofore untreated episodes of nonpsychotic unipolar major depression [3]. It first compares the rapid titration strategy up to the maximum tolerable dosage versus the titration up to the minimum effective dosage of a selective serotonin-reuptake inhibitor (SSRI) antidepressant in the first line treatment of depression in a cluster-randomised design. When the first-line treatment fails to achieve remission, it then attempts to compare three second-line treatment strategies, namely to augment the SSRI with a noradrenergic and specific serotonergic antidepressant (NaSSA), to switch from SSRI to NaSSA, or to continue several more weeks with SSRI, in an individually randomised comparison. The study will enroll 2000 adult patients with untreated major depressive episodes seeking treatment at psychiatric clinics and hospitals at a number of regional centres from all over Japan.

In this large pragmatic psychiatric trial, we opted to include the feasibility examination in the main study itself. Namely we decided to implement the whole study procedure from the very beginning but at a limited number of regional centres, to examine the feasibility of the original protocol as well as the adherence of both the patients and the doctors to the protocol, and to modify, if necessary, the protocol and operational procedures as we enter the first patients into the study [3]. The current report gives the

results of the feasibility and adherence examination among our first 100 patients and detail the required amendments to the SUN(^_^)D study protocol.

Methods

Ethics

The original study protocol was approved by the Institutional Review Board (IRB) at Nagoya City University Hospital in April 2010, by the Ethics Committee at Kyoto University Graduate School of Medicine in August 2010, and by the Ethics Committee at Kochi University Medical School in October 2010. The pilot phase of the SUN(^_^)D started its recruitment at two regional centres in Nagoya and Kochi on December 6, 2010, with the centre in Kyoto serving as the central office. Eligible patients provided written informed consent after full disclosure and explanation of the purpose and procedures of the study.

This trial has been registered at ClinicalTrials.gov as NCT01109693.

Procedures

The full details of the procedures of the study are given in the published protocol [3] and we briefly present the overall flow of the trial, the participants' eligibility criteria and the outcome measures here.

Figure 1 presents the overall procedure of the trial. The participants' eligibility criteria are listed in Table 1. We chose sertraline as the first-line SSRI treatment because it was found to offer the best balance between efficacy and tolerability among the currently marketed anti-depressant drugs in Japan according to the recent multiple-treatments meta-analysis of 12 new generation antidepressants [4]. The optimum titration strategy, however, has never been systematically examined in the literature. In Step I, therefore, eligible and consenting patients will either receive sertraline titrated up to 50 mg/d or up to 100 mg/d unless prohibited by adverse effects for three weeks. We employed the cluster randomisation design for Step I, i.e. the participating sites were randomised either to 50 mg/ or 100 mg/d arms.

When sertraline failed as first-line treatment to achieve remission, one natural choice is to switch to the antidepressant found to be the most efficacious, albeit with reduced acceptability, in the same meta-analysis, namely mirtazapine [4]. Because this NaSSA has a different neurochemical profile than SSRI and has been found to work in synergy when combined with SSRI in a number of trials [5-7], another option is to augment SSRI with mirtazapine. These two second-line options are to be compared with continuing with sertraline for six more weeks in Step II. If patients have remitted on

first-line treatment, they are to continue with their first-line treatment in Step II. Step III is a 16-week extension to Steps I & II, in which the doctors and the patients are free to continue their Step II treatments or to choose whatever treatments they deem appropriate. This represents the important continuation phase in the treatment of major depression, because almost every patient is advised to receive this continuation treatment [8]. In Step III we therefore aim to examine which first- and second-line treatments will be continued to sustain remission.

The primary outcome measures include the Patient Health Questionnaire-9 (PHQ-9) [9] and the Frequency, Intensity and Burden of Side Effects Rating (FIBSER), as assessed by the central raters at weeks 1, 3, 9 and 25. The assessment is conducted via telephone while blinded to the treatment status of the patients. The inter-rater and intra-rater reliability of the primary outcome measures was examined by having all the six raters to re-assess the audio recordings of 20 telephone interviews. The secondary outcomes included the Beck Depression Inventory-II [10], rated by the patients themselves.

As we had declared in the protocol [3], analyses of the pilot phase will be performed without knowledge of the allocated treatments and will involve no statistical comparison between randomised arms. Unless there is a major change in the study protocol, the participants in the pilot phase will therefore be included in the main study.

Analyses

In this study the focus is on how feasible the original protocol was and how adherent the doctors and the patients were in Steps I through III of the study. All the data had been provided to the researchers from the data center without any information linking the treatment allocations and assessment results. We first report the demographic and clinical characteristics of the screened as well as finally entered patients to examine the efficiency of our recruitment procedure as well as to ascertain if the intended types of patients have been recruited into the study. We then examine if the randomisation has been successful, if the treatments as stipulated in the protocol have been adhered to, and if the assessments have been made with satisfactory follow-up rates in each step of the trial.

The quality of the assessments is of paramount importance in a trial. We therefore examine the reliability of our primary outcomes and if their blinding has been successfully implemented in the study.

Finally we also report the important safety aspects among our first 100 patients.

Results

Participating sites

Two regional centres participated in the pilot phase of the SUN(^_^)D. One regional centre comprised of one general hospital and five private psychiatric clinics, while the other included four hospitals and two private psychiatric clinics (Table 2).

Participants

Altogether 2 743 first-visit patients visited the participating sites between December 6, 2010 and July 31, 2011. After standard psychiatric consultation and formal diagnosis with the help of the semi-structured interview PRIME-MD [9], 382 patients were judged to have been suffering from a major depressive episode in the past month and to have had no treatment. 100 of these were subsequently judged to meet all the eligibility criteria, provided written informed consent after full explanation of the purpose and procedures of the study, and entered the study (Figure 2).

Figure 3 depicts the monthly recruitment of the participants for the first 8 months of the study. We have been able to enter, on average, 12.5 patients per month. The number of participants recruited at each site is given in Table 2.

Table 3 describes the basic demographic characteristics of these participants. The subjects were approximately equally divided into both sexes, representing the whole age rage as specified in the protocol with peak age in the 40s. Slightly more than half had education at college or university or beyond. About half the subjects had some job at the time of the entry into the study but about a third were on sick leave.

Table 4 gives the clinical characteristics of the participants. The average age of onset of the depressive disorder for the participants was in their 30s, some 5 years earlier than their age at first visit. For half of the cohort, the index episode was their first major depressive episode, but the others had had up to four previous episodes. The median length of the episode before the hospital visit was 2.5 months, with a range between 0.5 to 120 months. The participants' depression scores were 18.9 on PHQ-9 and 33.0 on BDI-II on average, but varying between 8 to 27 and 14 to 52, respectively, thus representing the whole spectrum of mild to very severe depression [11].

Adherence to the protocol in Step I

Treatment allocation at beginning of Step I

Of the 100 initial participants, 16 were recruited at five sites allocated to the sertraline 50 mg/d arm and the remaining 84 at seven sites allocated to the sertraline 100 mg/d arm. This imbalance in the number of recruited patients is due to the one site which

recruited the largest number of patients.

Treatment received by end of Step I

Of the 100 patients who had provided their written informed consent at week 1 by the end of July (the observation period for this feasibility study), 93 would have reached their week 3 during this observation period. We now examine the treatments that these patients received in Step I.

Of this 93, 16 were in the sertraline 50 mg/d arm and 77 were in the sertraline 100 mg/d arm. None of the 16 patients allocated to sertraline 50 mg/d withdrew their consent and all reached the designated dosage by week 3.

Of the 77 allocated to 100 mg/d, one withdrew consent both to the protocol treatment and to further assessments and was therefore dropped from the study. Eight further patients withdrew consent to the protocol treatment by week 3 but consented to further assessments at weeks 3, 9 and 25: one got much better and decided to stop the medication, one decided to stop the drug because of side effects, one was hospitalized due to depressive stupor, one started working and could not come to the clinic at appointed times, two moved, and two for unknown reasons. Of the 68 patients allocated to sertraline 100 mg/d and whose consent to the treatment remained valid, 10 could not reach the intended dosage by week 3 and were on 75 mg/d only.

None received the prohibited concomitant treatments during Step I.

Assessment at end of Step I

Regardless of the treatments received, 93 patients should have received their week-3 assessments during the present study's observation period. Unfortunately, two of the eight patients who withdrew their consent to the protocol treatment but still agreed to further assessments were unreachable at week 3. Thus altogether three (one who withdrew consent to treatment and assessment, and two of the eight who withdrew consent to treatment but not to assessment) could not provide PHQ-9 and FIBSER assessments at week 3. The follow-up rate is 96.8% (90/93).

Adherence to the protocol in Step II

Treatment allocation at beginning of Step II

Of the 93 who reached their week 3 by end of July, nine had withdrawn consent to treatment and 84 patients were therefore randomisable at week 3. Seven of these scored 4 or less on PHQ-9 at week 3 and were therefore prescribed the same antidepressant in Step II as in Step I. The nine patients who had withdrawn their consent to treatment were provided the treatments of their and their doctors' choice.

77 patients were then randomised 1:1:1 either to continuation of sertraline, to

mirtazapine augmentation of sertraline, or to switching from sertraline to mirtazapine. The allocated numbers of patients were 26, 24 and 27, respectively, and the randomisation procedure seemed to be equally numbered and well balanced for the two stratification variables.

Treatment received by end of Step II

Of the 77 thus randomised at week 3, 62 would have reached week 9 by the end of July (the observation period for this feasibility study).

22 had been allocated to continuation of sertraline and should have reached week 9; only one of them dropped out of the treatment prematurely. 19 had been allocated to mirtazapine augmentation of sertraline and should have reached week 9; all of them received the protocol treatment (i.e. sertraline 50-100 mg/d plus mirtazapine 7.5 to 45 mg/d). 21 had been allocated to switching to mirtazapine; two stopped the treatment prematurely but all the others had been successfully switched to mirtazapine 15-45 mg/d. None received the prohibited concomitant treatments during Step II.

Assessment at end of Step II

Of the original 100 patients recruited into the study, 72 should have reached their week-9 assessment by end of July. In Step II three dropped out from the protocol treatment but none withdrew consent to further assessment (the one participant who withdrew consent to both the treatment and assessments in Step I had not reached his week-9 date by end of July). However, one patient who had been hospitalized in Step I and another who had been allocated to continuation of sertraline in Step II but stopped treatment prematurely despite medical advice were unreachable at week 9. The follow-up rate is therefore 70/72, or 97.2%.

Adherence to the protocol in Step III

Treatments received in Step III

This feasibility and adherence study did not examine closely the contents of the treatments provided to the patients in Step III because, according to our protocol, there are no prohibited co-interventions for this period and adherence to protocol treatments presents no concern in this Step. The contents of the treatments provided are being recorded in the dataset and, at end of week 25, 53% of the patients reported that they continued to be on the protocol treatment from Step II.

Assessment at end of Step III

Of the original 100 patients recruited into the study, 32 patients should have had their week 25 assessment by the end of July. So far we have been able to follow-up 29 of them (90.6%).

Primary outcomes

Inter-rater and intra-rater reliability of the primary outcomes

Table 5 shows ANOVA intra-class correlation coefficients for individual items of PHQ-9 and FIBSER, and for PHQ-9 total scores, based on the re-assessments by the six interviewers of 10 audio recordings of the telephone interviews. The inter-rater reliability among the six raters was perfect to nearly perfect.

The intra-rater (test-retest) reliability of the telephone assessments, that is the agreement between the interviewer's ratings during the telephone interview and those by the same interviewer when he/she listened to his/her own recordings one to two weeks later, was perfect for all the items.

Assessors' blindness to allocated treatments

The assessors' blindness to the allocated treatment was evaluated by tabulating their guessed treatments and the actually allocated treatments.

Table 6a presents such agreement for Step I allocations and Table 6b the same for Step II allocations. Because the assessors were blinded to the timing of the assessments, they sometimes made mixed guesses for both Step I and Step II. The agreement for the correct vs incorrect guesses for Step I treatments was a kappa of -0.19 (95%CI: -0.34 to -0.04), and that for Step II treatments was a kappa of -0.04 (-0.14 to 0.06).

Overall outcomes

Figure 3 presents the overall outcomes of our cohort as a group, undivided for the treatments allocations.

The number of remitters (PHQ-9=<4) were 10, 21 and 16 at week 3, 9 and 25, respectively. These figures would correspond to 10.8% (10/93), 29.2% (21/72) and 50.0% (16/32) of the intention-to-treat sample.

Adverse events and change in diagnoses

No serious adverse event has been reported among the first 100 patients in the first 8 months of the SUN(^_^)D trial.

Suicidality was assessed according to Columbia Classification Algorithm of Suicide Assessment (C-CASA) [12] at week 9 and at week 25 retrospectively by the treating psychiatrists. No case of completed suicide, suicide attempt or preparatory act toward imminent suicidal behavior was reported. Two patients expressed strong suicidal ideation to the doctor and/or the family.

One patient presented with depressive stupor and was hospitalized in Step I. One patient presented with a hypomanic episode in Step II. No other change in diagnosis has been reported.

Modifications to the original protocol and procedures

Through the initial pilot phase of SUN(^_^)D, only the following minor modifications to the protocol and the operational procedures were necessary.

1) We added repetitive transcranial magnetic stimulation (rTMS), light therapy and lamotrigine as prohibited treatments both before entry to the trial and in Steps I & II. We had overlooked rTMS and light therapy in the original protocol. Lamotrigine was newly brought into the Japanese market after the study was begun.
2) We explicated the eligibility criteria by adding "The major depressive episode is the focus of the treatment" because we encountered patients with major depressive episode comorbid with anxiety disorder, for whom the latter would clinically be the target condition of treatment. We reasoned such cases should be excluded from our trial.
3) We allowed more flexible titration schedules for Step I. In the original protocol there was only one anticipated titration schedule for the sertraline 100 mg/d arm, namely 50 mg/d at week 1 titrated up to 100 mg/d at week 2. In the revised protocol, any duration of any dosage was permitted at week 1, such as 75 mg/d for a week or 50 mg/d for 3 days plus 75 mg/d for 4 days, with the minimum requirement of reaching 100 mg/d at week 2.
4) We also accepted 7.5 mg/d of mirtazapine in Step II. In the original protocol, mirtazapine was to be prescribed between 15 and 45 mg/d.
5) A number of new reporting forms were prepared and updated in order to gather necessary information more systematically and more efficiently.

Discussion

We started the first large-scale pragmatic clinical trial of antidepressant treatment in Japan in December 2011. It is an assessor-blinded, parallel-group, multi-centre trial that aims to enroll 2000 patients with heretofore untreated unipolar major depressive episodes in order to find out the optimum first- and second-line antidepressant treatment strategies. The current study reports on the feasibility and adherence of its study protocol and operational procedures among its first 100 patients.

Patient enrollment and characteristics

At its 12 psychiatric clinics and hospitals at two centres in Nagoya and Kochi, we screened approximately 2700 first-visit patients, of whom approximately 400 were judged possibly eligible and 100 finally entered the study after providing written informed consent, over the course of its initial eight months. We consider that this is a respectable figure and calculate that, if we can liaise with six more centres associated each with five clinics or hospitals in the main study, we would be able to enroll 8 centres * 6 patients/month * 36 months = ca. 1800 patients in 3 years.

If we can continue with the 1 out of 4 recruitment rate and the sample characteristics as shown in Tables 3 and 4, we can be confident that our cohort will be representative of mildly to very severely depressed patients seeking initial treatment for their untreated depressive episodes.

Randomisation

The randomisation for Step I was unbalanced between 50 mg/d and 100 mg/d arms due to the one very actively recruiting clinic. We reason first that this imbalance will slightly decrease the statistical power but will not undermine the internal validity of Step I. Moreover, we expect that the treatment allocation will eventually be balanced as we enter more participating centres and clinics in the main study.

The randomisation for Step II was well balanced among its three arms and its strata.

Treatment adherence

In Step I, of the 93 patients who should have reached the end of this step, nine (9.7%) withdrew their consent to the protocol treatment. Of the remaining 84, 74 (88.1%) received the treatments as required by the protocol.

In Step II, of the 62 patients who had been randomised to one of the three treatment arms and should have reached the end of this step, only three (4.8%) withdrew consent to the protocol treatments. When continued on any one of the three arms, no protocol deviation occurred.

Between 5-10% voluntary withdrawal rate from the assigned treatments and between 0-10% deviation from the protocol treatment if continued are acceptable figures in a large pragmatic trial [13, 14].

Follow-up assessments

In the study protocol we sharply distinguish between withdrawal from the protocol treatments and that from the follow-up assessments, and invite the patients the

cooperate with the follow-up assessments even when they voluntarily choose to withdraw from the assigned treatments. As a result, we have so far been able to successfully assess 96.8%, 97.2% and 90.6% of the intention-to-treat sample at week 3, 9 and 25, respectively. We accept that the follow-up rate at week 25 needs to be improved. In this study we have been able to establish the inter-rater and intra-rater (test-retest) reliability of our primary outcomes and also to ascertain the successful blinding of the assessments thus made.

Safety

We encountered no unexpected or concerning safety issues among our first 100 patients.

Conclusion

Based on the present feasibility and adherence examinations of the pilot study phase of SUN(^_^)D study, we conclude that the study protocol [3_ENREF_3] can be implemented as originally envisaged with some minor modifications only and that the data from the first 100 patients can therefore be safely and validly included towards the main study. We will continue with the pilot phase of the study as we had originally set out in the protocol until the first 200 patients finish their 25-week follow-ups but we are now confident that we can speed up recruitment of collaborating centres and clinics/hospitals, thereby accelerating not only the pilot phase but also the entire study itself.

Competing interests

SS has received speaking fees and/or research funds from Astellas, Dainippon-Sumitomo, GlaxoSmithKline, Janssen, Lilly, MSD, Otsuka, Pfizer, Shering-Plough, Shionogi and Yoshitomi.
KM has received speaking fees from Astellas, Dainippon-Sumitomo, GlaxoSmithKline, Janssen, Lilly, Meiji, Otsuka, Pfizer and Shering-Plough.
YS has received a speaking fee from Meiji.
MK has received speaking fees from Lilly and Otsuka.
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TA has received speaking fees and/or research funds from Astellas, Astra-Zeneca, Bristol-Meyers-Squib, Daiichi-Sankyo, Dainippon-Sumitomo, Eisai, GlaxoSmithKline, Janssen, Kyowa-Hakko-Kirin, Lilly, Meiji, Otsuka, Pfizer, Sanofi-Aventis, Shionogi, Yakult, MSD, Novartis Pharma and Chugai.

NW has received speaking fees and/or research funds from Dainippon-Sumitomo, GlaxoSmithKline, Lilly, Otsuka, Pfizer, Asahi-Kasei and Shering-Plough.
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All the other authors have no competing interests to declare.

Authors' contributions

TAF conceived the study. SS and TAF prepared the original manuscript. TK, HS, KM, YS, TI collaborated in data collection, these authors along with TA, NW, MY, MI and NY participated in the refinement of the manuscript. NY is the trial statistician. All authors critically reviewed and approved the final version of the manuscript.

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The SUN(^_^)D Investigators include:

- Tatsuo Akechi, Norio Watanabe, Yumi Nakano, Masaki Kondo (Nagoya City University, Nagoya)
- Tadashi Kato (Aratama Kokorono Clinic, Nagoya)
- Yoshihiro Shinagawa (Shiki Clinic, Nagoya)
- Yoshio Ikeda (Narumi Himawari Clinic, Nagoya)
- Yoshiyuki Itakura (Itakura Clinic, Nagoya)
- Kazuhira Miki (Miki Mental Clinic, Yokohama)
- Shinji Shimodera, Hirokazu Fujita, Ippei Morokuma, Mikako Fuji (Kochi University, Kochi)
- Chisato Ichikawa (Chikamori Daini Hospital, Kochi)
- Ryosuke Fujito (Fujito Hospital, Kochi)
- Takashi Ito (Ito Clinic, Kochi)
- Hirotoshi Sato (Harimayabashi Clinic, Kochi)
- Mitsuhiko Yamada, Masatoshi Inagaki, Naohiro Yonemoto (National Center for

Neurology and Psychiatry, Tokyo)

- Toshi A. Furukawa (Kyoto University, Kyoto)

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