Electronic Health Record Nested Pragmatic Randomized Controlled Trial of a Reminder System for Serum Lithium Level Monitoring in Patients with Mood Disorder: KONOTORI study protocol

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Study protocol

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Abstract

Background: The weaknesses of classical explanatory randomized controlled trials (RCTs) include limited generalizability, high cost, and time burden. Pragmatic RCTs nested within electronic health records (EHRs) can be useful to overcome such limitations. Serum lithium level monitoring has often been underutilized in real-world practice in Japan. This trial aims to evaluate the effectiveness of the EHR-nested reminder system for serum lithium level monitoring in the maintenance of therapeutic lithium concentration and in the improvement of the quality of care for patients on lithium maintenance therapy. Methods: The Kyoto tOyooka Nested cOntrolled Trial Of Reminders (KONOTORI trial) is an EHR-nested, parallel-group, stratified permuted block randomized controlled trial. Screening, random allocation, reminder output, and outcome collection will be conducted automatically by the EHR-nested trial program. Patients with a mood disorder taking lithium carbonate for maintenance therapy will be randomly allocated to the two-step reminder system for serum lithium level monitoring or to usual care. The primary outcome is achievement of therapeutic serum lithium concentration between 0.4 and 1.0 mEq/L after 18 months. Discussion: The KONOTORI trial uses EHRs to enable the efficient conduct of a pragmatic trial of the reminder system for lithium monitoring. This may contribute to improved quality of care for patients on lithium maintenance therapy.

Background

Background and rationale

1. **Limitations of classical explanatory randomized control trials and the potential of electronic health record nested randomized control trial**

Randomized control trials (RCTs) have been the gold standard to evaluate the benefits and harms of interventions. However, problems with the classical “explanatory” RCTs have been reported.(1) First, the generalizability of the results of explanatory RCTs is usually limited because only ideal patients are included owing to their stringent eligibility criteria.(2) In addition, the recruitment of adequate numbers of participants is becoming increasingly difficult because of the expense and the time burden on clinicians.(3)

Pragmatic trials have been proposed to increase the generalizability by conducting RCTs under routine clinical practice conditions rather than in specialized environments.(4) For the past few decades, electronic health records (EHRs) have been used widely for observational pharmacoepidemiology and clinical studies.(5, 6) Recently, some pragmatic RCTs, which are called EHR-nested RCTs, have used EHRs to assess the effectiveness of various interventions.(7-11) EHR-nested RCT aims to increase the feasibility of RCTs by using an EHR to reduce trial costs, time burden, and human resources.(12, 13) The use of EHRs may allow pragmatic RCTs to be conducted in the routine care settings. In addition, EHR-nested systems were shown to increase the referral and recruitment of participants in some studies.(14, 15) Although the benefits of EHR-nested RCTs have continued to emerge, most of these studies have

been conducted in the US and UK, and the feasibility of EHR-nested RCTs in other clinical environments is still uncertain.(3, 9, 11, 16)

2. **Mood disorder and lithium carbonate**

The World Health Organization reported that major depression is the third most common cause of years lost due to disability and the 16th most common cause of disability-adjusted life years.(17) Behind alcohol abuse, major depressive disorder is the second most frequent psychiatric disorder in Japan, with a lifetime prevalence of 5.7%. Bipolar disorder is rare compared with major depressive disorder; the lifetime prevalence of bipolar I disorder is 0.4%.(18)

Lithium carbonate is a mood stabilizer used for the maintenance treatment of bipolar disorder and recurrent unipolar depression.(19, 20) Owing to its narrow therapeutic range, regular serum lithium level monitoring is strongly recommended: every week in the acute phase and every 3 months during the subsequent maintenance phase.(21-23) However, the rates of monitoring vary greatly in different countries, from 30% to 65%.(24, 25) In 2012, the Pharmaceutical and Medical Devices Agency (PMDA) in Japan warned against poor utilization of serum lithium level monitoring, because 52% of patients who were prescribed lithium carbonate had not been monitored for their serum lithium level.(26) However, despite the regulatory alerts, a recent study revealed serum lithium levels were monitored at least once a year for only 15% of patients.(27) After substantial literature search, we found no study was found about the intervention to improve the adherence of lithium monitoring.

Objective

The purpose of the Kyoto tOyooka Nested cOntrolled Trial Of Reminders (KONOTORI trial) is to examine whether the EHR-nested reminder system for serum lithium level monitoring is feasible in routine clinical practice in Japan, and whether it can help to achieve therapeutic serum lithium concentration and improve outcomes for patients on lithium maintenance therapy.

Methods/design

Trial design

The trial is an open-label, parallel-group, single-center, superiority randomized controlled trial to evaluate the effectiveness of an EHR-nested reminder system for serum lithium level monitoring. The trial program in the EHR system automatically prompts for eligibility screening, conducts the random allocation, outputs reminders, and collects outcomes.

Participants, interventions, and outcomes

Study setting

The trial is being conducted at the outpatient clinic of a psychiatry department at Toyooka hospital, which is a tertiary care community hospital with 518 beds in Toyooka City, Hyogo, Japan, which has a population of 85,000. All physicians participating in the trial are psychiatrists. The trial program covers the entire EHR system in Toyooka Hospital but the reminder itself works only at the department of psychiatry.

Participants

Eligibility criteria

Participants will be recruited in accordance with the eligibility criteria described below.

Inclusion criteria

The participant must fulfill all the following:

1. Age ≥18 years on the day of informed consent
2. Has recurrent major depression, bipolar I disorder, or bipolar II disorder according to Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5)
3. Has been taking lithium carbonate for 6 months or longer
4. Has been judged by the treating physician to need a prescription of lithium carbonate for the next 18 months

Exclusion criteria

The participant must not meet any of the following criteria:

1. Prescribed lithium carbonate for an indication other than mood disorders
2. A primary diagnosis of schizophrenia
3. Judged to have an imminent high risk of suicide by the treating physician
4. Suspected to have lithium intoxication
5. Women who are pregnant or breastfeeding
6. Cohabiting family members of study staff personnel
7. Inability to understand written Japanese

8. Contraindications for lithium carbonate
9. Participating in another clinical trial
10. Currently hospitalized
11. Terminal physical disease
12. No serum lithium concentration available within 7 days of informed consent
13. No appointment between 4 and 8 months after informed consent
14. Written informed consent is unavailable
15. Judged as inappropriate for participation by the treating physician

(Conditions 12 and 13 may be confirmed after informed consent, but before randomization.)

Interventions

The trial program outputs two-step reminders of serum lithium level monitoring to the treating physician as specified by the algorithm. When a participant in the intervention group visits the outpatient clinic between 4 and 8 months after the last lithium monitoring or at the study registration, reminder A will be sent to the treating physician. If the participant visits within 8 months after reminder A, reminder B will be sent. After reminder B has been sent and the participant visits the clinic thereafter, reminder A will be sent another time. No reminder will be sent if the participant receives the lithium monitoring within 4 months, visits the outpatient clinic after 8 months or later, or the participant in the control group. ~~(Table 1).~~

We anticipate that the two-step reminders will improve both the physician's awareness and the participant's adherence.

- Reminder A

The text of reminder A is as follows: "Please notify the participant of the need for a blood test for serum lithium level at the next outpatient visit. If the next visit will be 8 months or further from the previous blood test, please notify the participant of the need to conduct a blood test today. The participant and the treating physician can decide whether to conduct the blood test."

- Reminder B

The text of reminder B is as follows: "Please notify the participant the need for a blood test for serum lithium level today. The participant and the treating physician can decide whether to conduct the blood test."

Control

Participants in control group receive usual care without reminders.

Concurrent treatment and concerns about contamination

There are no restrictions on concurrent treatments in the trial.

Outcomes

At the first scheduled visit, between 18 and 24 months after informed consent, the program will output a reminder for the final evaluation. The treating physician will conduct a blood test within 7 days of the visit.

Primary outcome

The primary outcome is the achievement of therapeutic serum lithium concentration between 0.4 and1.0 mEq/L after 18 months from informed consent. If a participant withdraws during the follow-up period or the result of the final blood test is not available, he/she will be regarded as not having achieved the primary outcome, because unavailability for the final serum lithium measurement strongly implicates that the patients is not adherent. However, the validity of this assumption will be tested in a sensitivity analysis using multiple imputation (See statistical analyses).

Secondary outcomes

1) The number of blood tests for serum lithium concentration in the 18 months period after the date of informed consent.

2) Exacerbation of major depression or bipolar disorder in the 18 months period from the date of informed consent, defined by at least one of the following: hospitalization; increase in lithium dose; addition of antipsychotics or mood stabilizer (valproic acid, carbamazepine, lamotrigine); or addition of, or increase in, antidepressants.

3) Proportion of days covered (PDC) of lithium carbonate prescription during the 18 months from informed consent.(28)

4) Thyroid-stimulating hormone (TSH) $\geq$ 1.0μIU/mL after 18 months.

5) Estimated glomerular filtration rate (eGFR) < 60 mL/min per 1.73 m^2 after 18 months.

Participant timeline

The timeline for the study participants is shown in Figure 1 and the enrollment, intervention and assessment schedule is shown in Figure 2.

Screening by the trial program

The trial program automatically screens candidates who fulfill all of the following criteria from the EHR every morning:

1. Age ≥18 years
2. Have active diagnostic codes of mood disorders (F30.x, F31.x, F32.x, F33.x, F34.x, F38.x, and F39.x) by International Classification of Diseases (ICD), 10^{th}
3. First prescription of lithium carbonate more than 6 months previously
4. Lithium carbonate was prescribed more than twice in the previous 6 months
5. No results of serum lithium concentration available within the previous 4 months

The algorithm that combined lithium prescription more than twice and the prescription period longer than 180 days ensure lithium continuation over 180 days, because the maximum prescription period is 90 days in Japan. The participant will not be screened if he/she has been already registered as “not eligible”, “refused participation”, or “withdrawal after participation”.

Eligibility check and registration

Primary Care Evaluation of Mental Disorders (PRIME-MD) is a semi-structured diagnostic tool to assist primary care physicians in the diagnosis of common mental disorders based on DSM-5.(29) The treating physician conducts the PRIME-MD and confirms the diagnosis of depression, bipolar I, or bipolar II. If the candidate meets the eligibility criteria and written informed consent is obtained, the treating physician registers the participant through the EHR. If the candidate is not eligible, refuses participation, or withdraws after participation, the treating physician enters the status through EHR. The treating physician will conduct a baseline blood test within 7 days of informed consent. If the candidate does not receive the baseline blood test or a result for serum lithium level is not available within 7 days, he/she will be excluded from the study.

Sample size calculation

We estimated the sample size using Real World Data (RWD) database (Health, Clinic, Education, Information Evaluation Institute/Real World Data, Co., Ltd). Toyooka Hospital provides anonymized patient data to the database, which includes about 19 million patient's data from 170 institutions in Japan. In RWD database, 1,464 patients were prescribed lithium carbonate in a 6 months period. Of those, the serum lithium level was kept between 0.4 mEq/L and 1.0 mEq/L for 818 (55.9%) patients. Although RWD database includes patients from Toyooka Hospital, number of patients in Toyooka Hospital is unclear because numbers of patients in each hospital were not provided to the researcher.

In the trial, we assumed that 80% of participants in the intervention group and 55% of patients in the control group will achieve the goal. As 54 participants are needed for each group, assuming a dropout rate of 10%, a total of 120 participants is required to detect this difference with a type I error of 5% and a type II error of 10% using a two-sided chi-square test.

Assignment of intervention

Randomization

The participants will be stratified into nine strata in accordance with the following two conditions in EHR, and automatically randomized by the trial program at their first scheduled visit between 4 and 8 months from informed consent, using permuted block randomization.(30)

- Diagnosis based on PRIME-MD (major depression, bipolar I disorder, or bipolar II disorder)
- Lithium blood level (between 0.4 mEq/L and 1.0 mEq/L; < 4.0 mEq/L; or > 1.0 mEq/L)

Allocation sequence generation and concealment

Random allocation sequence is generated by an independent trial statistician (ST) but will not be notified to other researchers and participants. The allocation sequence is stored in the trial program and then concealed from other researchers.

Masking

Allocation status will not be masked to the treating physician and the participant. Allocation status will be masked to the data manager, the trial statistician, and the steering committee until the steering

committee finalizes the interpretation report with masked data.

Stopping rules for participants and trial

Stopping trial intervention

If the participant meets any of the following conditions, the treating physician will stop the trial intervention and record the date and the reason. However, the participant is not considered to have dropped out of the study at this stage and will receive the protocol assessments.

1) The participant wishes to withdraw from the trial intervention and/or lithium carbonate.

2) The treating physician judges that it is difficult to continue the trial intervention and/or lithium carbonate owing to the occurrence of serious adverse events.

3) The treating physician judges that the trial intervention and/or lithium carbonate should be stopped for clinical reasons other than serious adverse events.

4)The Steering Committee judges that the trial intervention or lithium carbonate should be stopped for any reason.

Stopping assessment

If the participant withdraws their consent to the protocol assessments, the participant will be excluded from analyses regardless of whether he/she continues the trial intervention and/or lithium carbonate.

The participant will be excluded from analyses if, after informed consent, it is found that the participant did not meet the eligibility criteria. In this case, the participant will not be considered to have stopped the trial intervention or the protocol assessments.

Stopping criteria for the trial

The Steering Committee will stop the trial upon advice or orders from the Ethics Committee if any of the following conditions are met.

1) Any serious problem in the quality, safety, and efficacy of the trial intervention and/or lithium carbonate.

2) When changing orders to the study protocol from the Ethics Committee is unacceptable.

The decision to stop the trial, and the reason for this, will be reported to the Ethics Committee and research staff as soon as possible.

Data collection and management

All the patient data is stored in the EHR and the password-protected trial program on a local server stores the information about screening, randomization and intervention automatically. After the trial completion, researchers extract anonymized patient data from the trial program and EHR, check the data quality, and finalize the data set manually.

Statistical analysis

All analyses will be conducted based on the intention-to-treat principle. The primary outcome will be analyzed from the full analysis set with a logistic regression analysis and reported with the odds ratio, p-value, and 95% confidence interval. The model includes the primary diagnosis based on PRIME-MD (major depression, bipolar I disorder, or bipolar II disorder) and baseline serum lithium level (0.4 mEq/L to 1.0 mEq/L; < 0.4 mEq/L; or > 1.0 mEq/L). The validity of our assumption equating missing the final serum lithium measurement with not achieving the primary outcome will be examined in a sensitivity analysis using multiple imputation. Secondary analyses and subgroup analyses will be conducted to supplement the primary analysis and explore a deeper understanding of the study questions. As secondary and subgroup analyses are exploratory, we will not adjust the significance level for multiple testing. All statistical tests will be two-sided and p values of < 0.05 will be considered statistically significant. The details of the statistical analysis will be decided within the statistical analysis plan, which will be reviewed and approved by the trial statistician and become publicly available before outcomes of the last participant are registered and therefore while the treatment allocation is still unknown. No interim analyses will be conducted in this trial.

Monitoring

Data monitoring

The data manager, in conjunction with the clinical management team, conducts weekly central monitoring and annually on-site monitoring in the trial. In the central monitoring, we monitored the number of screened, eligible, included and allocated patients by the weekly central monitoring. In addition, the data manager conducts on-site monitoring every 6 months after registration of the first case to check the logistics, like informed consent document.

Site audit

No formal site auditing will be conducted, because the trial comprises only a minimally invasive intervention.

Harms

Adverse events are defined as follows: any undesirable or unintended signs including anomalies in clinical laboratory evaluations, symptoms, or diseases that occurred to participants, regardless of the causal relationship with the treatment. The treating physician will provide and/or arrange appropriate treatments, including hospital admission if necessary. Because adverse events, including toxicities of lithium carbonate, are monitored as part of routine care, study specific monitoring will not be required.

When a serious adverse event occurs, the treating physician must take all the necessary and appropriate measures to ensure the safety of the participant. The treating physician must also notify the principal investigator and report to the chief study investigator at Toyooka Hospital within 24 hours. The principal investigator must notify the Ethics Committee of the Graduate School of Medicine, Kyoto University Graduate School of Medicine within 72 hours. The chief study investigator at Toyooka Hospital must report to its own IRB and, if it concerns an unforeseeable serious adverse event, must report to the Ministry of Health, Labour and Welfare (MHLW). A serious adverse event is defined as one that may lead to death or to continuous severe impairment, depending on the patient's conditions and circumstances.

Foreseeable adverse events

No adverse events are foreseeable for the trial intervention itself, except for the potential burden and complications of blood tests. All drugs, including lithium carbonate, are within the approved dosages and indications by the MHLW.

The foreseeable side effects of lithium carbonate, as described in the package insert, are as follows:

Major side effects: Tremor (4.6%), dry mouth (2.4%), and diarrhea (1.2%). Serious side effects: Lithium intoxication (unknown frequency); malignant syndrome (unknown frequency); sick sinus syndrome and bradycardia (unknown frequency); nephrotic diabetes insipidus (unknown frequency); acute kidney injury, interstitial nephritis, and nephrotic syndrome (unknown frequency); hypothyroidism and thyroiditis (unknown frequency); hyperparathyroidism (frequency unknown); and dementia and impaired consciousness (frequency unknown).

Ethics and dissemination

Adherence to the study protocol

All researchers participating in the trial will place the safety and human rights of the participants at the highest priority and will adhere to the study protocol, as long as it does not compromise their safety and human rights.

Regulations to be adhered to

All researchers participating in the trial will abide by the Declaration of Helsinki and its amendments, as well as the Ethical guidelines for medical and health research involving human subjects (2017 revision, Ministry of Education, Culture, Sports, Science and Technology, and MHLW).

Approval by the institutional review boards

The trial has been approved by the Ethics Committee of the Kyoto University Graduate School of Medicine (registration number: C1401) and the Institutional Review Boards of Toyooka Hospital (registration number: 180).

Protocol amendments

Any changes to the study protocol will be reported to the Ethics Committee of the Kyoto University Graduate School of Medicine for approval. If approval is granted, approval for the study protocol change will subsequently be sought from the Institutional Review Board of Toyooka Hospital. Changes will then be disseminated to the research staff, and, where necessary to the study participants.

Informed Consent

Procedures for informed consent

The treating physician must make sure that the participant has understood the contents of the trial and must obtain written informed consent from the participant. The treating physician must seek re-consent when the research protocol is revised, or a new invasion or any possible disadvantage is applied to the participant who has already consented.

Confidentiality

All researchers and contractors of the trial must strictly manage participants' personal information in adherence with the Ethics Guideline for Clinical Research and Act on the Protection of Personal Information. The data manager will delete site-specific patient IDs and add study-specific patient IDs at the time of data retrieval from Toyooka Hospital. Before the data manager retrieves the data, the data manager and the chief study investigator at Toyooka Hospital will ensure the data anonymity. The chief study investigator will keep the correspondence table up to date, including both the study-specific and the site-specific patient IDs at Toyooka Hospital. The data manager and the trial statistician will have access to only anonymized data but will not have access to the participants' personal information. The media will be stored in a locked cabinet in the office of Department of Pharmacoepidemiology, School of Public Health, Department of Pharmacoepidemiology, Graduate School of Medicine/School of Public Health, Kyoto University, for 10 years after the publication of the main results and will then be discarded.

Access to the data

All members of the Steering Committee will have full access to all the final dataset.

Ancillary and post-trial care

All participants will receive standard care during and after the trial.

Exemption of medical expenses and rewards

As all the diagnostic tests and treatments in the trial are within the approved dosage and administration by the MHLW, medical expenses will be covered in the usual way through the participant's health insurance and copayment. Participants will not receive any reward or exemption for any tests or treatments.

Compensation for adverse events

As all the diagnostic tests and treatments in the trial are conducted in accordance with the indications and dosage approved by the MHLW, the costs of care for any adverse events will be covered by the participant's health insurance and copayment. We will not contract private health insurance for clinical research because the trial involves only a minimally invasive intervention.

Dissemination policy

The protocol will be published in an English academic journal and presented at a scientific conference. The synopsis will be available from the website of Department of Health Promotion and Human Behavior, Department of Pharmacoepidemiology, Graduate School of Medicine/School of Public Health, Kyoto University, and Toyooka Hospital. The trial results will be disseminated through academic journals and conference presentations. A summary of study results will be disseminated on the website listed above for dissemination to trial participants.

Authorship for the primary and secondary results will be determined by all members of the Steering Committee. If the chief study investigator, participating physicians, and other members of the Steering Committee do not appear as co-author, they will be listed at the end of the article. Such authors may be listed as co-authors in some journals, but not in others.

After the publication of the main findings, we will register the anonymized data set in UMIN-Individual Case Data Repository (ICDR) (http://www.umin.ac.jp/icdr/index-j.html). Only researchers who are certified by the Steering Committee will be allowed access the data.

Discussion

KONOTORI is an EHR-nested, parallel-group, superiority randomized controlled trial examining the effectiveness of the reminder system for serum lithium level monitoring. This trial includes some prominent characteristics.

First, as mentioned previously, the trial program embedded with the EHR automatically prompts for screening, conduct random allocation, output reminders, and collect data without extra cost and time burden in everyday clinical practice. Embi et al. demonstrated a 10-fold increase in referral rate and the doubling of recruitment with an EHR-nested recruiting system.(14) Recently, several EHR-nested RCTs have been implemented for the assessment of the effectiveness of various interventions, such as alerts on kidney injury, warnings for harmful drug-drug interactions, laboratory test abnormalities, personalized antibiotics prescription feedback or dosing errors.(7, 9, 11) The REDUCE trial is ongoing to reduce unnecessary antibiotic prescriptions in general practitioners for respiratory tract infections with monthly feedback, educational and decision support tool and webinar using EHR.(8) Similarly, the Standard and New Antiepileptic Drugs II (SANAD II) trial is assessing the clinical and cost effectiveness of antiepileptic treatments for patients with newly diagnosed epilepsy.(10) However, the feasibility of EHR-nested RCT in Japan is unclear, because the aforementioned trials were conducted in Western countries, mostly in the US and UK. The KONOTORI trial will be the first EHR-nested RCT not conducted in a Western country.

Second, in our sample size calculation with an EHR based administrative database including Toyooka hospital, about 45% of patients had the blood lithium level of < 4.0 mEq/L or > 1.0 mEq/L. We assumed that the infrequent monitoring may partially have caused such deviation. Then, we expect that more frequent monitoring triggered by the reminders may be useful to keep blood lithium level within appropriate range and subsequent clinical outcomes. The two-step reminders (A&B) intends to remind not only the physicians but also the patient. The reminders may be through the increased frequency of the

reminder to the physician, the increased awareness on the part of the physicians, the increased recommendation from the physician to the patients based on such reminders, and/or through increased adherence on the part of the patients resulting from such interactions with the physician, that the primary outcome of the therapeutic serum concentration may be achieved. Then, it is not feasible masking the patient, because we remind not only the physician to increase the frequency but also the patient to improve adherence. If the automated reminder system is found to be effective for achieving the appropriate serum lithium level for patients taking lithium carbonate in this study, will be able to contribute directly to improvement in the quality of clinical practice, because its implementation does not require additional effort by clinicians. On the one hand, the trial was so designed to examine pragmatically the net effect of this procedure and not into the mechanisms by administering additional questionnaires to the physicians and the patients. This may be a weakness but also a strength in increasing the practicalness of the trial and also the generalizability of the final findings through facilitated recruitment.

Finally, both the EHR-nested RCT scheme and the EHR-nested automated reminder system may be applicable in medical specialties other than psychiatry. Overall, if the EHR-nested trial is successful, it can be expected to contribute to the so-called learning healthcare system, where every clinical encounter in routine care can provide an opportunity to expand the evidence base for future healthcare.(31)

Limitations

We acknowledge some difficulties in the trial. First, “alert fatigue” is possible; when treating physicians are exposed to too many clinical decision support alerts, they may stop responding to the alerts.(32) However, this risk will be relatively low in the present trial, because, in principle, the frequency of reminders is once every 6 months.

Second, because the study will be conducted in a single tertiary care center and randomization will be conducted for each patient rather than a clustered randomization, the number of blood tests and patient adherence may increase in the control group as well as in the intervention group through contamination among the participating physicians. Because the trial is conducted at a single facility, it is difficult to avoid such contamination; however, this is expected to result in an underestimation, rather than an overestimation, of the effectiveness of the EHR-reminder system. In future studies, the inclusion of multi-center and cluster randomization may be necessary to minimize this risk.

Third, a clinical endpoint such as exacerbation of mood disorders is more appropriate as the primary outcome than surrogate markers such as blood lithium level in a pragmatic trial. However, the expected number of a exacerbation is not large within the study period and therefore we do not have enough statistical power to detect the difference in a true endpoint in the trial. On the other hand, another objective of the trial is a proof-of-concept of an EHR-nested randomized control trial in Japanese circumstances. Surrogate outcome may be sufficient for the purpose. Then, we chose the blood lithium

level, instead of the number of blood tests, one of the secondary outcomes, because it was considered the most clinically relevant among surrogate outcomes.

Forth, the sample size with the drop-out of 10% and the effect size of 25% may be too optimistic. Some study reported higher drop-out rates in psychiatry trials of 25 to 60% than 7% in general.(33-35) However, these studies were largely different form our study because most studies in these reports were derived from acute phase trials with placebo-control or active comparator. Our study included patients after 6 months run-un period on the necessity of lithium continuation over 18 months. In addition, the study is a single-center study, and most moderate to severe patients are followed at Toyooka hospital because it is the only institution providing inpatient psychiatry care in the region. Furthermore, the estimated risk difference of 25% is also arbitrary, although the evidence of the reminders or alert systems of lithium monitoring is lacking.

Fifth, non-serious adverse events may be underreported because we monitor non-serious adverse events from the spontaneous reporting by each treating physician and the final blood test. However, the under-reporting is not likely for serious adverse events because researchers are obliged to report all the serious adverse events to the MHLW under the Ethical guidelines for medical and health research involving human subjects (2017 revision, Ministry of Education, Culture, Sports, Science and Technology, and MHLW).

Sixth, if the lithium level is not tested despite the reminder, it is undetectable which of the physician or the patient determined not to conduct the blood test.

After consideration of all these aspects, we hope that the KONOTORI trial and the EHR-nested RCTs will prove to be successful models for future clinicians, researchers, and decision-makers in the learning healthcare system.(31)

Trial status:

Participant recruitment was started in November 2018 and is ongoing at the time of submission of the protocol paper. We have recruited 101 patients since November 1, 2018 to September 11, 2019. We estimate that recruitment will be complete by March 31, 2020.

List Of Abbreviations:

KONOTORI: Kyoto tOyooka Nested cOntrolled Trial Of RemInders, RCT: Randomized control trial, EHR: electronic health record, UMIN: University Hospital Medical Information Network, PMDA: Pharmaceutical and Medical Devices, DSM: Diagnostic and Statistical Manual of Mental Disorders, PDC: Proportion of days covered, ICD: International Classification of Diseases, PRIME-MD: Primary Care Evaluation of Mental Disorders, MHLW: Ministry of Health, Labor and Welfare, ICDR: Individual Case Data Repository, SANAD II: Standard and New Antiepileptic Drugs II.

Declarations

Competing interest

TS received a stipend from Pfizer, Inc.

ST has received lecture fee from Boehringer Ingelheim, Astra-Zeneca, Taiho Pharmaceutical, Ono Pharmaceutical, and JMDC Inc. He received consultation fees from the Pharmaceuticals and Medical Devices Agency and DeNA Life Science and outsourcing fees from the Public Health Research Foundation. ST has received grants from the Japan Agency for Medical Research and Development, the Japanese Ministry of Health, Labour and Welfare, and the Japanese Ministry of Education, Culture, Sports, Science and Technology. He engaged in a research project of the Japan Agency for Medical Research and Development.

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Pharma Corporation, Novartis Pharma K.K., CMIC Co., Ltd., Amgen Astellas BioPharma K.K., Suntory Beverage & Food Ltd., and Medical Platform Co., Ltd.; and holds stocks in School Health Record Center Co., Ltd. and Real World Data, Co., Ltd. There are no patent products under development or marketed products to declare that are relevant to those companies.

TAF has received lecture fees from Janssen, Meiji, Mitsubishi-Tanabe, MSD,

and Pfizer. TAF has received research support from Mitsubishi-Tanabe and

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All other authors report that they have no relationships to disclose that are relevant to the contents of this paper.

Administrative information

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funders shall have any role in study design; collection, management, analysis, and interpretation of data; writing of the report; or the decision to submit the report for publication.

Authors' contributions

TS, MA, KK, and TAF conceived the study. TS, MA, HK, ST, KK, and TAF designed the study. ST is the trial statistician. TS, MA, and TAF wrote the first draft of the manuscript. All authors contributed to, critically reviewed, and approved the final version of the manuscript.

Steering Committee

The steering committee includes TS, MA, HK, TM and TAF. The steering committee's role and responsibilities are as follows: approval and amendment of the study protocol, statistical analysis plan and sub-study protocol; monitoring masked data; stopping trial intervention for participants and the trial; interpretation of the data; publication/dissemination of the study; authorship; data sharing agreement (if in place).

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Ethics approval and consent to participate

All researchers participating in the trial will abide by the Declaration of Helsinki and its amendments, as well as the Ethical guidelines for medical and health research involving human subjects (2017 revision, Ministry of Education, Culture, Sports, Science and Technology, and MHLW). The trial has been approved by the Ethics Committee of the Kyoto University Graduate School of Medicine (registration number: C1401) and the Institutional Review Boards of Toyooka Hospital (registration number: 180).

Availability of data and material

After the publication of the main findings, we will register the anonymized data set in UMIN-Individual Case Data Repository (ICDR) (http://www.umin.ac.jp/icdr/index-j.html). Only researchers who are certified by the Steering Committee will be allowed access the data.

Consent for publication

Not applicable.

References

1. Institute of Medicine. Large simple trials and knowledge generation in a learning health system: Workshop summary. Washington, DC: The National Academic Press; 2013.
2. Rothwell PM. External validity of randomised controlled trials: “To whom do the results of this trial apply?". Lancet. 2005;365:82-93.
3. Staa TP, Goldacre B, Gulliford M, Cassell J, Pirmohamed M, Taweel A, et al. Pragmatic randomised trials using routine electronic health records: putting them to the test. BMJ. 2012;344:e55.
4. Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutical trials. J Clin Epidemiol. 2009;62:499-505.
5. Seki T, Takeuchi M, Miki R, Kawakami K. Follow-up tests and outcomes for patients undergoing percutaneous coronary intervention: analysis of a Japanese administrative database. Heart Vessels. 2019;34:33-43.
6. Schneeweiss S, Avorn J. A review of uses of health care utilization databases for epidemiologic research on therapeutics. J Clin Epidemiol. 2005;58:323-37.
7. Wilson FP, Shashaty M, Testani J, Aqeel I, Borovskiy Y, Ellenberg SS, et al. Automated, electronic alerts for acute kidney injury: a single-blind, parallel-group, randomised controlled trial. Lancet. 2015;385:1966-74.
8. Juszczyk D, Charlton J, McDermott L, Soames J, Sultana K, Ashworth M, et al. Electronically delivered, multicomponent intervention to reduce unnecessary antibiotic prescribing for respiratory infections in primary care: a cluster randomised trial using electronic health records-REDUCE Trial study original protocol. BMJ Open. 2016;6:e010892.
9. Strom BL, Schinnar R, Aberra F, Bilker W, Hennessy S, Leonard CE, et al. Unintended effects of a computerized physician order entry nearly hard-stop alert to prevent a drug interaction: a randomized controlled trial. Arch Intern Med. 2010;170:1578-83.
10. Powell GA, Bonnett LJ, Tudur-Smith C, Hughes DA, Williamson PR, Marson AG. Using routinely recorded data in the UK to assess outcomes in a randomised controlled trial: The Trials of Access. Trials. 2017;18:389.
11. Hemkens LG, Saccilotto R, Reyes SL, Glinz D, Zumbrunn T, Grolimund O, et al. Personalized prescription feedback using routinely collected data to reduce antibiotic use in primary care: a randomized clinical trial. JAMA Intern Med. 2017;177:176-83.
12. Fiore LD, Lavori PW. Integrating randomized comparative effectiveness research with patient care. N Engl J Med. 2016;374:2152-8.

13. Mc Cord KA, Al-Shahi Salman R, Treweek S, Gardner H, Strech D, Whiteley W, et al. Routinely collected data for randomized trials: promises, barriers, and implications. Trials. 2018;19:29.
14. Embi PJ, Jain A, Clark J, Bizjack S, Hornung R, Harris CM. Effect of a clinical trial alert system on physician participation in trial recruitment. Arch Intern Med. 2005;165:2272-7.
15. Cornelius VR, McDermott L, Forster AS, Ashworth M, Wright AJ, Gulliford MC. Automated recruitment and randomisation for an efficient randomised controlled trial in primary care. Trials. 2018;19:341.
16. Mc Cord KA, Ewald H, Ladanie A, Briel M, Speich B, Bucher HC, et al. Current use and costs of electronic health records for clinical trial research: a descriptive study. CMAJ Open. 2019;7:E23-E32.
17. Geneva WHO. Global Health Estimates 2016: Disease burden by Cause, Age, Sex, by Country and by Region, 2000-2016. 2018. https://www.who.int/healthinfo/global_burden_disease/estimates/en/index1.html. Accessed 30 April 2019.
18. World Mental Health Japan Survey 2nd 2016 [Available from: http://wmhj2.jp/WMHJ2-2016R.pdf. Accessed 30 April 2019 (in Japanese)
19. Cipriani A, Smith K, Burgess S, Carney S, Goodwin G, Geddes J. Lithium versus antidepressants in the long-term treatment of unipolar affective disorder. Cochrane Database Syst Rev. 2006:Cd003492.
20. Miura T, Noma H, Furukawa TA, Mitsuyasu H, Tanaka S, Stockton S, et al. Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: a systematic review and network meta-analysis. Lancet Psychiatry. 2014;1:351-9.
21. Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Bond DJ, Frey BN, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. Bipolar Disord. 2018;20:97-170.
22. Kanba S, Kato T, Terao T, Yamada K. Guideline for treatment of bipolar disorder by the Japanese Society of Mood Disorders, 2012. Psychiatry Clin Neurosci. 2013;67:285-300.
23. Fountoulakis KN, Grunze H, Vieta E, Young A, Yatham L, Blier P, et al. The International College of Neuro-Psychopharmacology (CINP) Treatment Guidelines for Bipolar Disorder in Adults (CINP-BD-2017), part 3: The clinical guidelines. Int J Neuropsychopharmacol. 2017;20:180-95.
24. Marcus SC, Olfson M, Pincus HA, Zarin DA, Kupfer DJ. Therapeutic drug monitoring of mood stabilizers in Medicaid patients with bipolar disorder. Am J Psychiatry. 1999;156:1014-8.
25. Collins N, Barnes TR, Shingleton-Smith A, Gerrett D, Paton C. Standards of lithium monitoring in mental health Ttrusts in the UK. BMC Psychiatry. 2010;10:80.
26. Pharmaceuticals and Medical Devices Agency. Compliance with measurement of blood lithium level during treatment with lithium carbonate. 2012. http://www.pmda.go.jp/files/000153187.pdf. Accessed 30 April 2019.
27. Ooba N, Tsutsumi D, Kobayashi N, Hidaka S, Hayashi H, Obara T, et al. Prevalence of Therapeutic Drug Monitoring for Lithium and the Impact of Regulatory Warnings: Analysis Using Japanese Claims Database. Ther Drug Monit. 2018;40:252-6.

28. Choudhry NK, Shrank WH, Levin RL, Lee JL, Jan SA, Brookhart MA, et al. Measuring concurrent adherence to multiple related medications. Am J Manag Care. 2009;15:457-64.
29. Spitzer RL, Williams JB, Kroenke K, Linzer M, deGruy FV, 3rd, Hahn SR, et al. Utility of a new procedure for diagnosing mental disorders in primary care. The PRIME-MD 1000 study. JAMA. 1994;272:1749-56.
30. Wang D, Bakhai A. Clinical trial: A practical guide to design, analysis, and reporting. London: Remedica; 2006.
31. Greene SM, Reid RJ, Larson EB. Implementing the learning health system: from concept to action. Ann Intern Med. 2012;157:207-10.
32. Embi PJ, Leonard AC. Evaluating alert fatigue over time to EHR-based clinical trial alerts: findings from a randomized controlled study. J Am Med Inform Assoc. 2012;19:e145-8.
33. Kemmler G, Hummer M, Widschwendter C, Fleischhacker WW. Dropout rates in placebo-controlled and active-control clinical trials of antipsychotic drugs: a meta-analysis. JAMA Psychiatry. 2005;62:1305-12.
34. Leon AC, Mallinckrodt CH, Chuang-Stein C, Archibald DG, Archer GE, Chartier K. Attrition in randomized controlled clinical trials: methodological issues in psychopharmacology. Biol Psychiatry. 2006;59:1001-5.
35. Dumville JC, Torgerson DJ, Hewitt CE. Reporting attrition in randomised controlled trials. BMJ. 2006;332:969-71.

Table

Table 1. Algorithm of the reminders

Lithium monitoring after the last reminder (if applicable)		Yes			No		
Periods (months) [a]		<4	4 to 8	>8	<4	4 to 8	>8
Type of the previous reminder	No	No	Reminder A[b]	No	No	Reminder A[b]	No
	Reminder A[b]	No	Reminder A[b]	No	Reminder B[c]	Reminder B[c]	No
	Reminder B[c]	No	Reminder A[b]	No	No	Reminder A[b]	No

When the participant visits the outpatient clinic between 4 and 8 months after the last lithium monitoring, reminder B or the study registration, the reminder A will be sent to the treating physician. Else if the participant visits within 8 months after reminder A, the reminder B will be sent. Otherwise, no reminder is sent.

a. Periods are months after the informed consent, last reminder, or lithium monitoring

b. The text of reminder A is as follows: “Please notify the participant of the need for a blood test for serum lithium level at the next outpatient visit. If the next visit will be 8 months or further from the previous blood test, please notify the participant of the need to conduct a blood test today. The participant and the treating physician can decide whether to conduct the blood test.”

c. The text of reminder B is as follows: “Please notify the participant the need for a blood test for serum lithium level today. The participant and the treating physician can decide whether to conduct the blood test.”

Figures

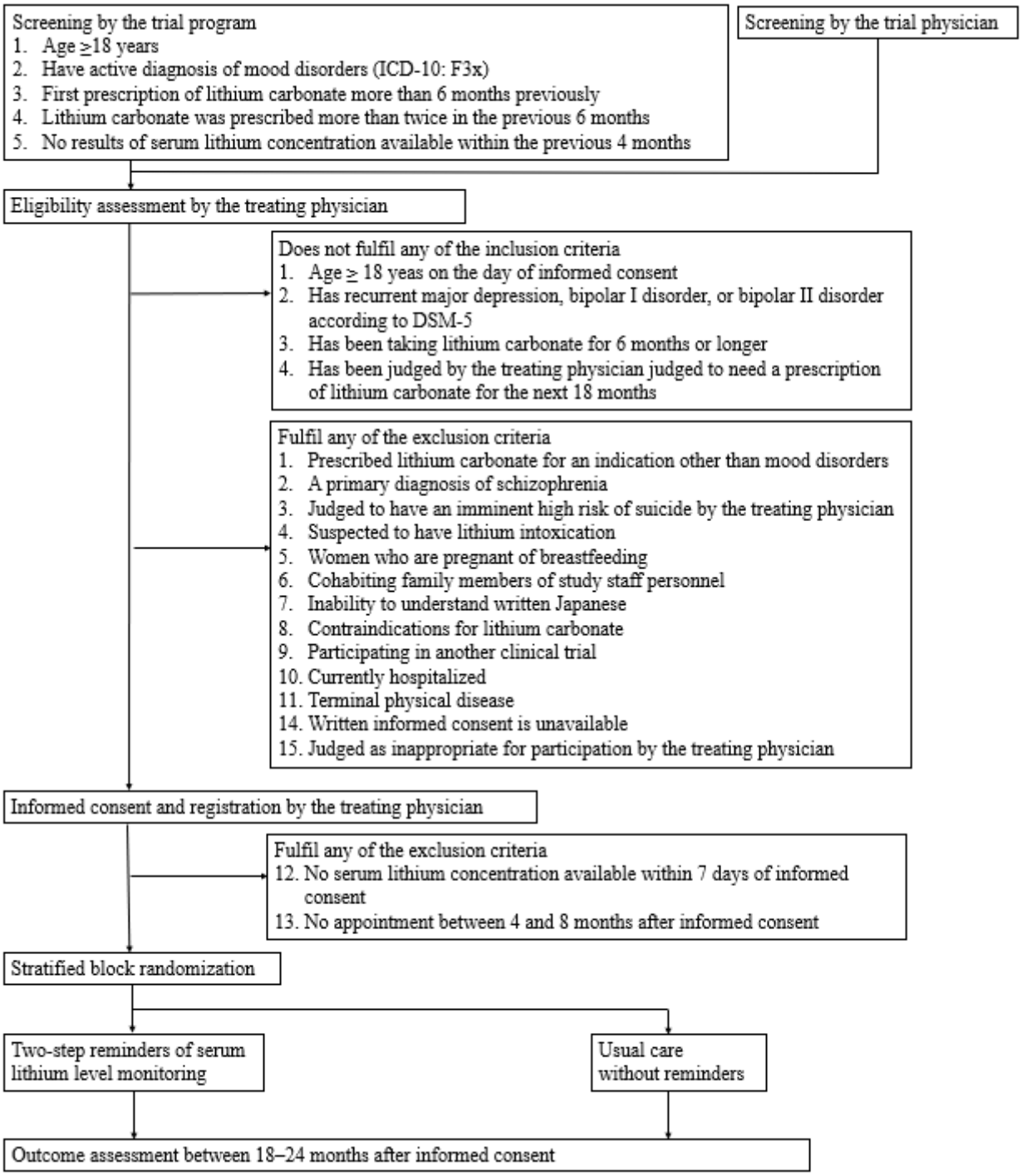

Figure 1

Flow diagram of the trial Exclusion criteria 12 and 13 are confirmed after informed consent, but before randomization. ICD: International classification of disease, DSM: Diagnostic and Statistical Manual of Mental Disorders.

	Study periods							
		Enrolment	Allocation	Post-allocation				Close-out
	Timepoints	T_{-1}	T_0	$T_{1\text{-}A}$	$T_{1\text{-}B}$	$T_{2\text{-}A}$	$T_{2\text{-}B}$	T_x [5]
Trial program	**Enrollment**							
	Screening	X						
	Randomization [1]		X					
	Intervention							
	Reminder A			X		X		
	Reminder B				X		X	
	Assessments							
	Baseline characteristics [2]	X						
Treating physician	**Enrollment**							
	PRIME-MD [3]	X						
	Eligibility assessment	X						
	Informed consent	X						
	Assessments							
	Lithium concentration [4]	X						X
	Liver function	X						X
	Kidney function	X						X
	Thyroid function							X

Figure 2

Schedule of the enrolment, intervention, and assessments 1. Stratified block randomization will be conducted if the candidate has a result for lithium blood concentration within 7 days of the informed consent and an appointment between 4 and 8 months after informed consent. 2. Basic information includes gender, age, and concomitant medication 3. The candidate will be classified as having major depression, bipolar I disorder, or bipolar II disorder 4. The serum lithium level will be classified into three groups (between 0.4 mEq/L and 1.0 mEq/L inclusive; <4.0 mEq/L; or >1.0 mEq/L). 5. The first scheduled

visit is between 18 and 24 months after informed consent. PRIME-MD: Primary Care Evaluation of Mental Disorders.

Supplementary Files

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- 20190926SPIRITchecklist.pdf