Author’s response to reviews

Title: 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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TRLS-D-19-00486
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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Trials

Dear Dr. Lars G. Hemkens, MD, PhD,

We thank the Editor for the opportunity to submit our revised manuscript, “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” (TRLS-D-19-00486) to Trials. We also appreciate your and your reviewers’ time and effort providing careful review and insightful suggestions. We believe that the manuscript has been substantially improved after incorporating the suggested changes.
Please find below the reviewer’s comments and our responses, including how and where the text was modified, and changes in the manuscript are highlighted in red. The revision has been reviewed by all coauthors, and each coauthor has approved the final revision.
We hope that our paper is now suitable for publication in Trials and look forward to hearing back from you in due course.

Sincerely yours,
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Response to Reviewers:
Reviewer #1
The authors describe the study design of a pragmatic RCT nested within the electronic health record (EHR) of a university hospital in Japan. The aim to assess the efficacy of a physician alert system embedded in the EHR to improve the Lithium hematic therapeutic range of in patients affected by mood disorders.
The trial design is novel and I appreciated reading your protocol manuscript.
I have 7 major revisions recommended:

We thank the reviewer for providing insightful comments that have helped us to significantly improve the manuscript.

Major points
#1. Please explain the context and settings of your trial in more detail. I could not understand in which department the trial would take place. Is it the entire hospital? Is it ER? Is it the psychiatric clinic? Based on a few statement made in the protocol, I assumed the clinicians receiving the interventions were primary care physicians or internists, but many of my following comments might not be pertinent depending on the actual setting of the trial (in particular, point 3).

We agree that the detail about the context and setting of the study was not fully described in the manuscript. The study is being conducted at the outpatient clinic of the psychiatry department in a tertiary care community hospital rather than a university hospital, and all physicians participating in the trial are not primary care physicians but psychiatrists. Patients with a moderate to severe mental disorder like bipolar are usually followed-up by psychiatrists rather than primary care physicians in Japan, probably due to the disease severity and the free access to health care. The trial program covers the entire EHR system in Toyooka Hospital but the reminder itself works only at the department of psychiatry. We clarified the description in study setting. (page 5, lines 9-13)

#2. I am worried of what the readers might think regarding the selection of the primary outcome. I recommend justifying the choice of outcome in the context of the intervention, and possibly clarify the link between the alert and the expected changes in blood lithium levels. There is an extra step between the intervention and the primary outcome that is not quite clear to
me. You aim to increase the lithium testing by the physician through an alert, which is expected to improve the appropriate hematic lithium levels. It may be that measuring the level more frequently does not have a direct impact on the biomarker itself. The dosage adjustment is not mentioned at all and you do not provide any guidance to the physicians regarding the therapy, but instead assume that the physician, which normally does not test (hence the need for this trial) would look for and assess the previous lithium level(s), and adjust the treatment to the therapeutic range. I think that considering the pragmatic aim of your trial, a more patient-centered outcome (such as your secondary outcomes) might have been more informative. Please justify the choice of your primary outcome (which fits an explanatory trial) in the context of the pragmatic trial (including consideration to the generalizability of your findings).

We thank the reviewer for the comment on the important point. First, we agree that a true endpoint such as exacerbation of mood disorders is more appropriate than surrogate markers such as blood lithium level, especially, in pragmatic trials. However, the expected number of exacerbations is not large within the study period and therefore we do not have enough statistical power to detect the difference in such true endpoints 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.

Second, as the reviewer pointed out, we do not have any predefined criteria for lithium dosage adjustment, because the dosage should be determined by not only the blood test but by the disease severity, the patient symptom, physician’s clinical experience and patient’s preference. On the other hand, 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.

Third, 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 announcement 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 in the trial, because we remind not only the physician to increase the frequency but also the patient to improve adherence.

We added the rationale of the reminders and outcomes in the Discussion section, (page 19, lines 22-page 20, line 9) and the reason for the outcome selection in the Limitation section. (page 21, lines 13-21)

#3. I did not fully understand how the recruitment of the participants works, and later how this leads to the inclusion in the trial. My understanding is that the EHR would flag patients with ICD codes that relate to mood disorders, so that the physician could consent the patient to the trial. Then you mention the use of the PRIME-MD to confirm the diagnosis. Do you expect a diagnosis that was already present in the EHR, hopefully supported by a psychiatric assessment,
to be overruled at the routine clinical encounter with a 10-item checklist? I suspect that this would introduce bias in the selection of your patients. Those that will have less symptoms (probably due to a better lithium level or other drug control, to name one of the many factors) will more likely not be identified by the PRIME-MD for support of the diagnosis. If this is not what you meant, please clarify this aspect in the text (in particular, who might have performed the diagnosis of the psychiatric disorder vs who may be the physician receiving the alert, such as psychiatrist vs PCP).

We thank the opportunity to clarify the important point about the screening using ICD-10 codes and eligibility check by psychiatrists.

First, as the reviewer suggested, we clarified the difference between the screening by the trial program and the inclusion by the treating physician. The trial program “automatically” screens from the EHR every morning, but the treating physician include patient “manually” from screened candidates. The treating physician checks the eligibility criteria and registers the participant through the EHR manually if applicable. (page 9, lines 6-7)

Second, a systematic review showed that the specificity and the positive predictive value of ICD codes for depression is substantially high (&gt;99% and 89%, respectively) than the sensitivity (28-35%) (1). On the other hand, diagnosis of mood disorder is mandatory for the reimbursement of lithium carbonate in Japan, although lithium is prescribed not only for mood disorders but as a mood stabilizer for other psychiatric disorders. Combination of the ICD-code of mood disorder and the prescription record of lithium carbonate may cause a false positive rather than false negative. We used the PRIME-MD by psychiatrists to exclude patients who prescribed lithium other than mood disorders and confirm the diagnosis rather than to overrule the previous diagnosis. We believe that the misclassification of eligible patient is unlikely after the combination of ICD-codes, lithium prescription and confirmation by psychiatrists.


As the reviewer pointed out, the risk of attrition in psychopharmacology trials varied from 20% to 65% were higher than our estimate of 10% in the sample size calculation.(2, 3) However, our study is completely different from such acute-phase trials with placebo-control or active comparator due to the following reasons: First, patients will be included in our study if they have been prescribed lithium carbonate for more than 6 months as a maintain therapy and expected to be necessary lithium continuation over 18 months, whereas previous studies included patients after 4 to 6 days run-in periods. Second, the study is a single-center study, and most patients with moderate to severe mental disorder are followed at Toyooka Hospital, because there is no other hospital providing inpatient psychiatry care in the region. Third, median dropout rates of RCTs in general are about 7% (IQR: 2 to 18) and similar to our estimates.(4) We added some description in Limitation (page 21, line 22-page 22, line 6) and references 33-35.
#5. Since the majority of your data will come from the EHR, it would be nice to have some validation or quality assurance of the data. How likely is it that the ICD code is correctly recorded when a diagnosis is present? How will you tell if the treating physician will have judged their need for a prescription at a minimum of 18 months (unless this is this only recorded in the RCT file)? How is the data collected from the EHR and connected to a separate trial document (any chance that error is introduced? If we don't see a lithium test result in the EHR, was it missing or was it not done? When this in not possible or available, please report it as such.

The treating physician enters the result of participant’s eligibility check through EHR including the need for a prescription at a minimum of 18 months and consent status. All diagnosis, orders, and test results are recorded in the EHR as well as eligibility and consent status except for the paper consent form. For example, we can distinguish whether blood test was not ordered, or the test was ordered but the result was not available. Please refer the second paragraph in Major points #2 about the validity of ICD codes.

#6. Please explain how adverse events will be monitored. In the section Harms, you say that during routine care, toxic lithium levels are tested. But the trials is done to increase testing of lithium levels since they are currently not performed at the standards required, so I'm not sure I understand how you will assess this. It is understandable not to measure the AE in the framework of the routine/pragmatic trial, but this statement might be misleading so please clarify.

We thank the reviewer for the insightful comment. As the reviewer pointed out, we cannot anticipate whether adverse events increase or decrease with more frequent monitoring. Underreporting of serious adverse events is unlikely because researchers are obliged to report all serious adverse events under the Ethical guidelines for medical and health research involving human subjects (2017 revision, Ministry of Education, Culture, Sports, Science and Technology, and Minister of Health, Labour and Welfare [MHLW]) in Japan. (5) On the other hand, non-serious adverse events may be underreported because we can monitor non-serious adverse events from the spontaneous reporting by each treating physician and the final blood test.(6) We added the description in Limitation. (page 22, lines 7-12)

#7. Masking - why are patients not masked? Since the lithium testing should be routine care, there was no need for them to know which arm they belonged to. The intervention is aimed at the physician, and I'm not too clear on why the testing is offered to the patient (would the treatment of lithium be continued without proper monitoring should the patient decline? I think that the testing is not optional here). I see the benefit of educating the patient to the need for lithium monitoring but this didn't seem like the proper context (at the end it might be difficult to differentiate on which of the two actually has an impact on testing frequency and lithium levels). Support your judgment of not blinding the participants, and of whether a reason for declining testing is recorded (at the end, the reader might want to know if the lithium testing was not done because the patient declined or because the physician's judgment). Please explain this better in the text, as a limitation if necessary.

We thank the chance to clarify the point. This is a pragmatic trial examining whether the reminder system embedded in the EHR increases the proportion of patients on lithium within
therapeutic ranges (and using the EHR system for the eligibility screening, enrollment, randomization and follow-up). As discussed in Major points #2, it is not feasible masking the patient in the trial, because we remind not only the physician to increase the frequency but also the patient to improve adherence.

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. On the one hand, 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. As a result, when 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. Such information should be recorded into the trial program in future studies as well as the recording of adverse effects.

We added a description in the Discussion section (page 20, lines 13-17).

Minor points
And the following minor revisions recommended as well:

#1. The 4th outcomes should be more specific already in the protocol (measures used to assess abnormalities in thyroid, renal and liver functions).

We added the cut-off value for thyroid-stimulating hormone (TSH) ≥ 1.0μIU/mL and estimated glomerular filtration rate (eGFR) < 60 mL/min per 1.73 m2 in Secondary outcomes. (page 8, lines 23-24)

#2. There is a mistake in the text of the intervention B (repeated words).

We changed reminder B to “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.” (page 7, lines 13-15 and Table 1)

#3. In the screening list, it is not clear why the patients must have received two prescriptions for lithium. Please clarify why this is necessary in the methods (if a patient has been on lithium for one year but under the same prescription, would he/she not be picked up by the screening?).

The algorithm that combined lithium prescription more than twice and the prescription period longer than 180 days ensure lithium continuation longer than 180 days, because the maximum prescription period is 90 days in Japan. Although there may be some false positive, the treating physician checks the eligibility manually. We have added the above description in Screening by the trial program. (page 9, lines 15-17)

#4. It is not clear how the study data is collected, at times it appears to be wholly EHR based, then in the Data collection and management sections a trial program/software is mentioned. Does the EHR data get extracted to a trial database? Is any data actively collected or checked manually?

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.

As suggested, we clarified the point in Data collection and management. (page 13, lines 2–5)

#5. It is amazing that you can "track" patients that refuse to be in the RCT but that give consent for their data to be collected. I urge you to highlight this more clearly in the methods since it is only understood later in the discussion. For example in the section Informed Consent.

We apologize that our explanation may have been confusing. At first, we considered that we would be able to check the similarity of patient characteristics and the generalizability of the study results retrospectively, by comparing our result with an EHR database. In fact, Toyooka Hospital is providing anonymized patient data to the RWD database, which is an EHR-based administrative database constructed by Real World Data. Co. Ltd. (Kyoto, Japan).

Anonymized patients’ routine clinical data is included in the database even if they refused to participate in the trial so long as they had not refused data provision to the RWD database. However, in the current study, which is the first EHR-based trial in Japan, we did not seek the informed consent to use such data when the participants declined the participation in the study. We therefore concluded that we could not confirm such generalizability in the current trial. Accordingly, we deleted the relevant paragraph in the Discussion section. (page 19)

#6. Please clarify if the statistical analysis plan, which you mentioned will be done at a later stage, will be determined a priori of the data being seen (code break) or after checking the data, since this can introduce bias.

We are planning to submit our statistical analysis plan before outcomes of the last participant are registered to the EHR. (7)

Accordingly, we changed the sentence in Statistical analysis as follows:

“The details of the statistical analysis will be decided within the statistical analysis protocol, 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.” (page 13, lines 19–22)

#7. In section "eligibility check" and "stopping assessment" please report that the exclusion of ineligible patients will be done after consent but before randomization (as I think you mentioned in the flowchart and elsewhere in the text).

I thank the opportunity to clarify the point. As the reviewer pointed out, our description in eligibility criteria, eligibility check and figure 1 were confusing. In figure 1, not only the criteria 12 & 13 but all the exclusion criteria seemed to be applied after the informed consent and before randomization. In reality, exclusion criteria except for 12 & 13 are applied before informed consent and only who met the criteria 12 & 13 will be excluded after informed consent and before the randomization. We revised the figure 1 along with the main text.

#8. Please clarify the data monitoring aspect. What are onsite visits? Of which department? What is assessed, and how is this in line with the pragmatic/real world data aspect of the RCT?
As the reviewer pointed out, the description of data monitoring was insufficient and confusing in our manuscript. 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 study logistics, like informed consent document. We changed the description in Data monitoring (page 14, lines 2-6)

#9. The chart with the study intervention is very confusing, please try to restructure in a more understandable way.

As the reviewer pointed out, our description of the reminder algorithm was very confusing. 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. We added the description in Interventions (page 6, line 23 - page 7, line 2) and the footnote in the Table 1.

#10. You mention that the randomization is done through the EHR, and then you mention a random sequence generated by an independent trial statistician. Please clarify this process.

As suggested, we have clarified the process of randomization in Allocation sequence generation and concealment. (page 11, lines 10-13)

#11. You do not specifically address allocation concealment, report it in more detail (how are the clinicians not aware of the allocation sequence. Is it all through the EHR?).

We added the following sentence in Allocation sequence generation and concealment. (page 11, lines 12-13)

"The allocation sequence is stored in the trial program and then concealed from researchers except for the statistician (ST)."

Please refer also the comment in Minor points #10.

#12. Please provide, in text or as an appendix, the actual ICD codes used to identify the patients through the EHR.

We added the ICD-10 code (F30.x, F31.x, F32.x, F33.x, F34.x, F38.x, and F39.x) (page 9, line 9-10)

#13. Line 21 (page 5), please delete the repeated word.

We deleted the repeated word as suggested. (page 5, line 24)

Reviewer #2:
Seki and colleagues are currently conducting the first EHR nested RCT in Japan. Their protocol is interesting and clearly written. Before publication I have a few points which should be considered.

We thank the reviewer for the time and effort for providing insightful comments that have helped us to significantly improve the manuscript.

#1 Intervention (Page 6): To me it is not entirely clear when reminder A or B is sent. Please also include some details about that within the text. Please label "Table" as "Table 1".

Please refer the comment at Reviewer #1 Minor comment #9.

#2 Primary outcome: I am wondering if this primary outcome might be biased. I could imagine that less patients in the intervention group miss the final blood test (e.g. because they have a better/closer connection to their physician and had already regular check-ups). As the primary endpoint regards missed final blood tests as not having achieved the primary endpoint (i.e. having a serum lithium concentration between 0.4 and 1.0 mEq/L after 18 months) this could influence the result. Maybe one could consider other strategies (e.g. imputating missing data). This is something which should be included at least in the discussion.

We thank the reviewer for this very important suggestion. We acknowledge that our results may be biased if the reason of missing data is not missing completely at random, missing data is more frequent in control group, and then our worst-case analysis may bias the result. We will add multiple imputation as a sensitivity analysis in the statistical analysis plan.

We added some description about the missing data and subsequent bias in Primary outcome (page 8, lines 9-12) and the sensitivity with a multiple imputation in Statistical analysis (page 13, lines 19-22).

#3 Sample size: The authors assume that 80% will achieve the primary outcome in the intervention vs. 55% in the control group. To me 80% seems very ambiguous (eventually over-ambiguous) especially when considering that missed final blood test will be counted as not achieving the primary endpoint. Also, according to the stopping rules, if the lithium treatment is stopped due to any reasons, the primary endpoint will be missed. Maybe this could be discussed (e.g. limitation).

We appreciate the opportunity to clarify the point. As the reviewer pointed out, our estimated effect size of 25% may be ambiguous. However, we had to estimate somehow although the evidence of reminder and alert systems for lithium monitoring is lacking.

In addition, because of very low adherence to serum lithium monitoring (at least once/year) of only 15% in Japan, we assumed that moderate proportion of patients will achieve the targeted serum lithium level due to the increased number of lithium monitoring. We added a sentence in the Limitation (page 22, lines 4–6).

#4 Background (page 3, lines 21-23): It is mentioned that most RCTs using EHRs are conducted in the US and UK. However, the reference listed here does not include any such
statement. Maybe consider other references here (e.g., https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6375253/).

We appreciate the reviewer for introducing an informative reference. As suggested, we added the references 16 in the Background section. (8) (page 3, line 23)

#5 Background: It is unclear if any other studies have already look at similar reminders for serum lithium level monitoring. Did the authors conduct a literature search? Please clarify (see also SPIRIT item 6a; https://www.bmj.com/content/bmj/346/bmj.e7586.full.pdf).

As suggested, we conducted additional literature search on PubMed with the following algorithms: (1) entry term “Lithium Carbonate[mh] AND bipolar disorder [mh]” and the filter of clinical trial; (2) entry term “Lithium Carbonate[mh] AND bipolar disorder [mh] AND (reminders [tiab] OR alert [tiab])” without any filters; (3) entry term “Lithium Carbonate[mh] AND bipolar disorder [mh] AND Medication Errors [mh]” without any filters; (4) entry term “Lithium Carbonate[mh] AND bipolar disorder [mh] AND Reminder Systems [mh]” without any filters. However, we could not find any relevant articles related to reminders or alerts and lithium carbonate.

#6 Trial design (page 5; lines 1-5): I would suggest adding the term "superiority" to the trial design.

We added the term “superiority” to the trial design (page 2, lines 9-11; page 5, lines 2-5; page 19, lines3-5).

#7 Page 5, line 21: Delete one of the two "judged" (the one after "physician")

See Reviewer#1 Minor Comment#13.

#8 Sample size (page 9, lines 18-19): It is not clear to me why 120 patients are included and not 110 considering a drop out rate of 10% ("As 49 participants are needed for each group, assuming a dropout rate of 10%, a total of 120 participants is required")?

We thank the reviewer for the careful review. After the re-calculation, the correct number in each group was 54 instead of 49. We corrected the number. (page 10, lines 17-21)

#9 Sample size (page 9; line 20): Please specify the test used.

As suggested, we corrected “two-sided hypothesis test” to “two-sided chi-square test” in Sample size calculation (page 10, lines 17-21).

#10 Intervention: Reword reminder B (also in Table 1).

Please see Reviewer#1 Minor Comment#2.

#11 Intervention: Please add a short description of the control group (i.e. usual care).
As suggested, we added the description of “Control” in page 7, lines 17-18.

#12 Participant timeline: The authors state that the participant timeline is shown in Figure 2. However, this is the example figure from the SPIRIT statement (https://www.bmj.com/content/bmj/346/bmj.e7586.full.pdf). The authors should create a specific timeline for their own trial, indicating the schedule of enrolment, interventions, and assessments.

We apologize that we falsely uploaded the example figure. We changed it to the correct one. (Figure 2)

#13 “Screening by the trial program”: To me it is not entirely clear what is meant here and how this is different to the inclusion/exclusion criteria. It would be great if the authors could explain this in a few sentences.

The trial program screens candidates “automatically” from all patients in the EHR every morning according to the information in the EHR. Treating physician confirm the inclusion/exclusion criteria “manually” from the candidates.

We have clarified the explanation in Screening by the trial program. (page 9, lines 6-7)

#14 Feasibility (page 9, lines 14-15): The authors refer to 1464 patients in a certain database. Are those patients that are currently treated (or at least live close) at the Toyooka hospital?

As asked by the reviewer, some of the 1464 patients were derived from Toyooka Hospital but others derived from other hospitals. We do not know how many patients were derived from Toyooka Hospital, because RWD database did not provide the number of patients in each hospital. We clarified the point in sample size calculation. (page 10, lines 9-16)

#15 Randomisation: Please give more information about the mentioned "trial program". Additionally, state who is conducting the randomisation (see SPIRIT items 16 a, b, and c).

Please refer Reviewer#1 Minor comment #10.

#16 Steering committee: A steering committee is mentioned several times. However, the composition of this committee is not described and the roles and responsibilities are not entirely clear (see SPIRIT item 5d)

As suggested, we added the description in the Steering committee. (page 24, lines 19-24)

#17 Trial status: As the trial is already recruiting since November 2018, it would be great if the authors would indicate how many patients are currently recruited and what they expect when the recruitment will be finished.

As suggested, we added the following sentences to the Trial status (page 22, lines 21-22): “We have recruited 101 patients since November 1, 2018 to September 11, 2019. Recruitment will be finished on March 31, 2020.”
Reference


