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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Author’s response to reviews:

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

We thank the Editor for the opportunity to resubmit 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-19-00486R1) to Trials. We also appreciate your and your reviewers’ time and effort, providing careful review and insightful suggestions. We have addressed the reviewers’ comments with point by point responses and revised the manuscript accordingly. Then, 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:

#1. The reminder intervention process is still not very clear, and you have not improved the chart (for example, using the superscript "b" as a footnote for reminder A, is mental gymnastics. Please consider using numbers instead).

We thank the reviewer for the constructive comments. We believe these comments were very helpful in improving the readability of our manuscript. As suggested, we changed the superscripts in figure 2 from alphabets to numbers. In addition, we reformatted the figure under the suggestion from reviewer #2.

#2. The text with the description of monitoring still needs some work. The wording has improved but I suggest these changes to make it clearer: "When the participant 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 again (thereafter or between 4-8 months, whichever wording you prefer here), reminder A will be sent another time.

As suggested, we changed the description in intervention (page 6, line 25 to page 7, line 4).

#3. I had not seen the part "Otherwise, no reminder is sent" previously. It is not clear when the reminder is not sent: Do all participants receive the monitoring upon registration to the study? It is possible that they register, no reminder is displayed, and then they never show up for follow-up? If so, only the lost to follow-up would be those without any reminders sent? Please clarify this in the methods section or where you see appropriate.

In order to clarify the situation, we changed the description as follows (page 7, lines 4-6): "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."

Reviewer #2:

#1. Table 1: Still difficult to read. Maybe adapt or drop entirely.

We thank the reviewer for additional insightful comments and believe these comments are quite helpful to improve our manuscript. We deleted the table because it was too difficult to simplify.

#2. The authors mention in the p-b-p response that they did a systematic literature search. This should be also clearly mentioned within the protocol.

We added some descriptions to the background (page 4, lines 16-17).
#3. Figure 2: Time points and abbreviations are still unclear.

As suggested, we reformatted the figure 2 and added two rows related to the time points within the study periods.

#4. Page 22; line 22: Replace "Recruitment will be finished on March 31, 2020" by "We estimate that recruitment will be complete by March 31, 2020"

We changed the sentence as suggested.