Reviewer’s report

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

Version: 0 Date: 26 Aug 2019

Reviewer: Kimberly McCord

Reviewer's report:

KONOTORI Review

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:

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 statements 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).

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).

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 treating physician 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).


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 is not possible or available, please report it as such.

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.

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.

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).

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

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?).
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? 
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. 
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. 
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). 
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? 
9. The chart with the study intervention is very confusing, please try to restructure in a more understandable way. 
10. You mention that the randomization is done through the EHR, and then you mention a random sequence generated by and independent trial statistician. Please clarify this process. 
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?). 
12. Please provide, in text or as an appendix, the actual ICD codes used to identify the patients through the EHR. 
13. Line 21 (page 5), please delete the repeated word. 

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