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: 30 Aug 2019

Reviewer: Benjamin Speich

Reviewer's report:

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

* 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".

* 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.

* 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).

* 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/).

* 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).

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

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

* 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")?
* Sample size (page 9; line 20): Please specify the test used.
* Intervention: Reword reminder B (also in Table 1).
* Intervention: Please add a short description of the control group (i.e. usual care).
* 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.
* "Screening of 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.
* 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?
* 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).
* 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).
* 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.

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