PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effect of medicines management versus standard care on readmissions in multimorbid patients: A randomized controlled trial
AUTHORS	Lea, Marianne; Mowe, Morten; Molden, Espen; Kvernrød, Kristin; Skovlund, Eva; Mathiesen, Liv

VERSION 1 – REVIEW

REVIEWER	Carlotta Lunghi Université du Québec à Rimouski, Canada
REVIEW RETURNED	31-Jul-2020

GENERAL COMMENTS	I thank the authors and the editor for the opportunity to comment on the manuscript “Effect of medicines management versus standard of care on readmissions in multimorbid patients: A randomized controlled trial.” I think the article is fascinating, well designed, and of good quality. I have only a few comments, especially on the statistical analyses, which may improve the manuscript. Abstract: • I suggest the authors give more details in the results section of the abstract since it seems contradictory to say that there was no significant effect on death within 12 months and a statistically significant overall survival. The author may explain better the difference between these two outcomes. Statistics: • I wonder why the authors did not perform a competing risk Cox analysis (Fine & Gray method), letting the primary outcome to be hospitalization and the competing risk of death. I think they should reperform this type of analysis, at least as sensitivity analysis (instead of merely censoring deaths). Patient and Public Involvement: • In this sentence, the authors used a past tense. Have study results not yet been presented to the patient representatives? Did the patient representatives were involved in the choice of methods? Results: • I suggest the authors report p-values in Table 2 to show how randomization worked. • They may also present p-values for Table 3 results. Discussion:

	• The number of patients in the study is presented as a strength of the study, but they may not have had sufficient power to detect a difference between groups, so I think it is not a real strength after all.

REVIEWER	Frank Moriarty Royal College of Surgeons in Ireland, Ireland
REVIEW RETURNED	10-Aug-2020

GENERAL COMMENTS	This paper reports an the evaluation of a medicines management intervention in people with multiple conditions in a randomised trial to evaluate the effect on readmissions and death. The manuscript is well written and reports on a well conducted study. The authors should be commended for their transparent reporting, by including the study protocol, amendments to this, statistical analysis plan, and details of changes made to procedures after the study commenced. I have some minor comments and requests for clarification. 1. Line 148 states that staff providing outcome data were not involved in data collection or preparation of data files. This is not entirely clear, particularly when the source of endpoint data is not mentioned until line 231. I assume the "staff" referred to here are those of the Norwegian Patient Registry and/or Cause of Death Registry? Perhaps this could be explicitly stated at line 148. 2. The protocol included in the appendices states that an intention-to-treat analysis will be conducted. This could be reported explicitly in the Methods for clarity. 3. The description of the intervention in a couple of places refers to it involving "medicines reconciliation at admission, medicines review repeatedly during the entire stay and medicines reconciliation and tailored information at discharge." The standard care group procedures "did not include either IMM or any other service from clinical pharmacists." (Line 206) However it appears medicines reconciliation at admission was conducted at baseline before randomisation for all participants. Is clinical pharmacist medicines reconciliation at admission part of standard of care in Norwegian hospitals typically? While it's clear that a different procedure for DRPs detected during baseline review for the control group, is the same true of discrepancies identified through medicines reconciliation? If not, reporting could be more clear in stating that the differences between what the intervention and control groups received was only the latter two parts of the IMM (i.e. reviews throughout stay and medicines reconciliation and information at discharge) 4. As per the protocol, the authors could perhaps add to the Methods that the inclusion criteria for four regular drugs is a count of those before medicines reconciliation. 5. The CONSORT checklist states NA for item 19, "All important harms of unintended effects in each group". Was there any mechanism within the study to capture adverse effects of the intervention or other safety incidents? If so, was there any governance arrangement e.g. safety monitoring committee to adjudicate on such events?

VERSION 1 – AUTHOR RESPONSE

Reviewer(s) Reports:
Reviewer: 1
Carlotta Lunghi
Université du Québec à Rimouski, Canada

I thank the authors and the editor for the opportunity to comment on the manuscript “Effect of medicines management versus standard of care on readmissions in multimorbid patients: A randomized controlled trial.” I think the article is fascinating, well designed, and of good quality. I have only a few comments, especially on the statistical analyses, which may improve the manuscript.

AR: Thank you for the positive comment on the study/manuscript.

Abstract:
• I suggest the authors give more details in the results section of the abstract since it seems contradictory to say that there was no significant effect on death within 12 months and a statistically significant overall survival. The author may explain better the difference between these two outcomes.

AR: We acknowledge the comment. The primary endpoint was difference in time to readmission or death within 12 months. Overall survival was a priori the clinically most important secondary endpoint, and was measured during 21-40 months follow-up. To better explain the difference between these two endpoints, we have rephrased the sentences in the revised results section in the abstract, see clean version of revised manuscript pages 2-3, lines 53-56.

Statistics:
• I wonder why the authors did not perform a competing risk Cox analysis (Fine & Gray method), letting the primary outcome to be hospitalization and the competing risk of death. I think they should reperform this type of analysis, at least as sensitivity analysis (instead of merely censoring deaths).

AR: Thank you for this valuable suggestion. We have performed the competing risk Cox analysis as suggested. Since this was not a pre-planned analysis, we have chosen to present it as a sensitivity analysis together with the sensitivity analysis censoring for deaths, see clean version of the manuscript page 16 lines 306-308. We have also included in the methods section that the Fine and Gray method has been used, emphasized that this was not a pre-planned analysis, and that we used STATA 16 in addition to SPSS, see clean version of revised manuscript page 13, lines 261-265.

Patient and Public Involvement:
• In this sentence, the authors used a past tense. Have study results not yet been presented to the patient representatives? Did the patient representatives were involved in the choice of methods?

AR: The user representatives were invited to comment on the study design, e.g. the choice of primary endpoint. We have clarified this in the Patient and Public Involvement section, see clean version of the manuscript page 13, lines 268-269. However, regarding the information about the study results, we have decided to await until the manuscript has been published. In the revised manuscript we have, to avoid confusion, deleted the sentence which described that study results will be presented for the patient representatives and that they will be involved in choosing the methods for and agreeing on plans for dissemination of study results, see clean version of revised manuscript, page 13, line 269.

Results:
• I suggest the authors report p-values in Table 2 to show how randomization worked.

• They may also present p-values for Table 3 results.

AR: We acknowledge the comment and understand the interest in seeing to which extent the randomization provided similar demographics in the two groups. However, as pointed out in the CONSORT guidelines as well as in several papers (e.g. de Boer et al. Int J Behav Nutr Phys Act 2015; 12: 4), testing for baseline imbalances in randomized controlled trials is discouraged, since such tests only assess the probability that observed baseline differences have occurred by chance. Thus, unless there are reasons to believe that the randomization was not conducted properly, statistical comparisons of the group demographics is not relevant. Accordingly, in line with the CONSORT guidelines, we prefer not to compare the groups by calculating and reporting p-values in Table 2. With regard to Table 3, presenting results from the secondary endpoint analyses, we are, however, happy to comply with the suggestion from the reviewer and have now included p-values, see clean version of revised manuscript, page 17, line 313.

Discussion:
• The number of patients in the study is presented as a strength of the study, but they may not have had sufficient power to detect a difference between groups, so I think it is not a real strength after all.

AR: Thank you for this comment. We agree and have removed the number of patients in the study as a study strength in the discussion, see clean version of revised manuscript page 21, line 397.

Reviewer: 2
Frank Moriarty
Royal College of Surgeons in Ireland, Ireland

This paper reports an the evaluation of a medicines management intervention in people with multiple conditions in a randomised trial to evaluate the effect on readmissions and death. The manuscript is well written and reports on a well conducted study. The authors should be commended for their transparent reporting, by including the study protocol, amendments to this, statistical analysis plan, and details of changes made to procedures after the study commenced.

AR: We appreciate the positive evaluation of our manuscript.

I have some minor comments and requests for clarification.

1. Line 148 states that staff providing outcome data were not involved in data collection or preparation of data files. This is not entirely clear, particularly when the source of endpoint data is not mentioned until line 231. I assume the "staff" referred to here are those of the Norwegian Patient Registry and/or Cause of Death Registry? Perhaps this could be explicitly stated at line 148.

AR: Thank you for the comment. The staff we are referring to are those from the Norwegian Patient Registry and the Cause of Death Registry. We have clarified this as suggested, see clean version of revised manuscript page 7, lines 150-151.

2. The protocol included in the appendices states that an intention-to-treat analysis will be conducted. This could be reported in the Methods for clarity.

AR: The analysis population was defined in the statistical analysis plan (SAP), which is shown in the S1 Appendix. According to the SAP, the primary efficacy analysis was a modified intention to treat excluding the patients who died during the hospital stay as they were never at risk for readmissions, and also the erroneously included patients (not fulfilling the inclusion criteria). We have clarified this in the method section, see clean version of revised manuscript page 12, line 243.

3. The description of the intervention in a couple of places refers to it involving "medicines reconciliation at admission, medicines review repeatedly during the entire stay and medicines reconciliation and tailored information at discharge." The standard care group procedures "did not include either IMM or any other service from clinical pharmacists." (Line 206) However it appears medicines reconciliation at admission was conducted at baseline before randomisation for all participants. Is clinical pharmacist medicines reconciliation at admission part of standard of care in Norwegian hospitals typically? While it's clear that a different procedure for DRPs detected during baseline review for the control group, is the same true of discrepancies identified through medicines reconciliation? If not, reporting could be more clear in stating that the differences between what the intervention and control groups received was only the latter two parts of the IMM (i.e. reviews throughout stay and medicines reconciliation and information at discharge)

AR: For all included patients, a baseline assessment was conducted, comprising medicines reconciliation and review and detecting medicines discrepancies and drug-related problems (DRPs). The purpose of this baseline assessment was to assess the prevalence of drug-related problems and drug-related hospitalizations (separate publication, Lea et al. PloS one. 2019;14(7):e0220071). Importantly though, the medicines discrepancies and DRPs revealed during these baseline assessments were, for the patients in the control group, not discussed in the multidisciplinary treatment team. Neither medicines reconciliation, nor medicine reviews or other clinical pharmacist services, are part of standard care in Norwegian hospitals. Hence the differences between the intervention and control groups were actually ‘treatment’ with the actions of the complete IMM model, i.e. medicines reconciliation at admission, medicines reviews during the entire hospital stay, and medicines reconciliation and tailored information at discharge. We have tried to improve the description of the baseline assessments underpinning that the medicines discrepancies and DRPs revealed here, were not discussed in the multidisciplinary treatment team, see clean version of revised manuscript page 8, lines 172-175. We have also tried to improve the description of standard care provided to the control group, see clean version of revised manuscript page 11, lines 208-211. Furthermore, the purpose of the baseline assessments, namely to assess the prevalence of DRPs and drug-related hospitalizations at admission is also described in the method section, including the reference to the separate publication, see clean version of revised manuscript page 8, lines 168-169.

4. As per the protocol, the authors could perhaps add to the Methods that the inclusion criteria for four regular drugs is a count of those before medicines reconciliation.

AR: The drugs were counted before medicines reconciliation according to the protocol. However, the original protocol also states that “if it is revealed during medicines reconciliation that a patient was using less than 4 regular drugs from less than 2 therapy classes before hospitalization, the patient will be excluded from the study”. We have included this information in the methods section of the manuscript, see clean version page 6, lines 131-133.

5. The CONSORT checklist states NA for item 19, "All important harms of unintended effects in each group". Was there any mechanism within the study to capture adverse effects of the intervention or other safety incidents? If so, was there any governance arrangement e.g. safety monitoring committee to adjudicate on such events?

AR: Thank you for the comment. It is agreed that the CONSORT statement on harms recommends safety data on harm if they have been collected. Our study did not include a system for adverse events reporting or a safety monitoring committee. Reporting on safety is captured with several of the endpoints, like readmission and survival, presented in figure 3a and 3b. Furthermore, assessing and solving adverse effects are part of the complex intervention, as described in the risk categories that

were systematically addressed for each drug in each patient during the medicines reviews (Table 1). And at last, there were no withdrawals due to adverse events, as reported in the CONSORT patient flow chart in figure 2. We have therefore completed item 19 on the revised CONSORT checklist, referring to figure 2 and figure 3a and 3b, as collected data on harm has been reported, see the new S2 Appendix.

VERSION 2 – REVIEW

REVIEWER	Carlotta Lunghi Université du Québec à Rimouski, Canada
REVIEW RETURNED	17-Nov-2020

GENERAL COMMENTS	The authors have already addressed my comments.

REVIEWER	Frank Moriarty Royal College of Surgeons in Ireland, Ireland
REVIEW RETURNED	09-Nov-2020

GENERAL COMMENTS	Thank you very much to the authors for their clear and detailed response to the comments from myself and the other reviewer. The authors transparent reporting of their study is to be commended, as well as their appropriate use of statistical tests as outlined in their response. My only further comment relating to the medicines reconciliation process for the control group. I am grateful for the clarifications already added to the manuscript that these were not discussed in the treatment team (Line 175). I am wondering whether any documentation of the discrepancies/DRPs was left in the patient's notes/record or whether these were only documented in the research database? The addition at Line 210 suggest the latter, however perhaps it could be stated explicitly at line 175 that these were neither discussed with the team, or documented in the patient record.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

Reviewer Name: Frank Moriarty

Institution and Country: Royal College of Surgeons in Ireland, Ireland

Comments to the Author

Thank you very much to the authors for their clear and detailed response to the comments from myself and the other reviewer. The authors transparent reporting of their study is to be commended, as well as their appropriate use of statistical tests as outlined in their response.

AR: Thank you for the positive comment on the reviewers response and the reporting of the study.

My only further comment relating to the medicines reconciliation process for the control group. I am grateful for the clarifications already added to the manuscript that these were not discussed in the treatment team (Line 175). I am wondering whether any documentation of the discrepancies/DRPs was left in the patient's notes/record or whether these were only documented in the research database? The addition at Line 210 suggest the latter, however perhaps it could be stated explicitly at line 175 that these were neither discussed with the team, or documented in the patient record.

AR: The medicines discrepancies and DRPs revealed for the patients were not included in the patient notes/record, but only documented in the research database. We have clarified this in the method section as suggested, see clean version of revised manuscript, page 8, lines 174-175.

Reviewer: 1

Reviewer Name: Carlotta Lunghi

Institution and Country: Université du Québec à Rimouski, Canada

Comments to the Author

The authors have already addressed my comments.