PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol of a randomized controlled trial on the efficacy of medication optimization in elderly inpatients: Medication optimization Protocol Efficacy for Geriatric inpatients (MPEG) trial
AUTHORS	Ie, Kenya; Hirose, Masanori; Sakai, Tsubasa; Motohashi, Iori; Aihara, Mari; Otsuki, Takuya; Tsuboya, Ayako; Matsumoto, Hiroshi; Hashi, Hikari; Inoue, Eisuke; Takahashi, Masaki; Komiya, Eiko; Itoh, Yuka; Tsuchida, Tomoya; Kurosu, Eri; Albert, Steven M.; Okuse, Chiaki; Matsuda, Takahide

VERSION 1 – REVIEW

REVIEWER	Jos Tournoy KULeuven, Belgium
REVIEW RETURNED	19-Jun-2020

GENERAL COMMENTS	This paper describes the protocol for an RCT on inpatient medication optimization. This research is relevant as the field is waiting evidence to be generated on the effect on clinical outcomes of this type op interventions. The protocol is well designed and clear, I only have a few suggestions: p5line 50: specify "any information" withing the interventions, could you clarify how the medication reconcilation process will be done p6 line 58: how will life expectancy be estimated p7line 35: how will unexpected outpatient clinic visit be determined line 37: how will rehospitalizations be measured, how will this be done if other hospitals are involved p8 line 10: it might be good to elaborate a little more on the Japanese LTC system eg how to interprete the levels p8 line 35: how will death be registered, national registry? p8 line 52 Falls or Injury due to falls? Falls registered only by recollection or als other methods? In general, the discussion is short also as there are no results to be discussed, but I would suggest to elaborate more on the strenghts and potential limitations of this particular study design

REVIEWER	Pier Mannuccio Mannucci University of Milan Italy
REVIEW RETURNED	19-Jun-2020

GENERAL COMMENTS	Well designed study, addressing an important item.

REVIEWER	Dr Nibu Parameswaran Nair

	University of Tasmania Australia
REVIEW RETURNED	04-Aug-2020

GENERAL COMMENTS	The MPEG trial protocol is well written and has followed the SPIRIT guidelines. However, the discussion section of the protocol is very short. Suggest expanding that section in a more detailed manner discussing the strength and limitations of this study. A single-center trial is a limitation. The chance of contamination is a limitation. Some other questions/comments are written below. 1) Page 7. The eligibility criteria for participants are: Predicted length of hospital stay after admission: 1 week or longer. Comment: How will you determine or judge the predicted length of hospital stay? 2) Page 7. Exclusion criteria include the following: life expectancy of less than 1 month. Comment: How will you determine or judge the life expectancy? 3) Page 7. In addition, monthly deprescribing-team meetings will be held for monitoring and quality control of intervention. Comment: Explain the process of monitoring and quality control of interventions. 4) Page 8. Does the harm outweigh the potential benefits? Study participants' symptoms and laboratory results will be reviewed to determine any adverse effect that outweighs the expected benefits of the prescribed drug. Comment: Explain with an example as shown in other questions. 5) Page 10. Any potential drug-related adverse events (AEs) will be recorded according to the Japanese version of CTCAE 4.0. Comment: How a potential drug-related adverse event is defined? How do you assess whether a drug is responsible for the adverse event? If a combination of drugs is involved, how will you determine the causality of each drug and the AE? 6) Page 12. The research assistant who performs the bimonthly telephone interview assessments will be blind to group allocation. Comment: How the blinding is ensured?

VERSION 1 – AUTHOR RESPONSE

[Reviewer 1]
Thank you for your time and effort in reviewing our manuscript. Your suggestions were very helpful and appreciated.

<Responses to the comments>
p5line 50: specify "any information"
Response: We have indicated the specific information collected on page 5, lines 25–26.

Could you clarify how the medication reconcilation process will be done
Response: The details of medication reconciliation have been included per your suggestion (page 5, lines 19–21).

p6 line 58: how will life expectancy be estimated
Response: Life expectancy will be estimated based on the clinical judgment of the participant's attending physician. We have added this explanation on page 5, line 11.

p7line 35: how will unexpected outpatient clinic visit be determined
line 37: how will rehospitalizations be measured, how will this be done if other hospitals are involved
Response: Unscheduled hospital visits and re-hospitalization will be determined based on follow-up telephone interviews performed by a trained research assistant. The details of collection of these data are described on page 11, lines 2–6.

p8 line 10: it might be good to elaborate a little more on the Japanese LTC system eg how to interprete the levels
Response: An explanation regarding the Japanese LTC system and its interpretation is included in the second subsection (Level of long-term care required) under "Secondary outcomes" (page 8, lines 8–13). We would appreciate recommendations for specific information to be added to this section.

p8 line 35: how will death be registered, national registry?
Response: Japan has a national deaths registration system. For the current study, however, patient death will be identified based on chart review and follow-up telephone interview.

p8 line 52 Falls or Injury due to falls? Falls registered only by recollection or als other methods?
Response: We appreciate your feedback. Falls, instead of injury due to falls, will be registered as a secondary endpoint. We have revised page 2, line 18 and page 9, line 3 accordingly.

In general, the discussion is short also as there are no results to be discussed, but I would suggest to elaborate more on the strenghts and potential limitations of this particular study design
Response: Thank you for your important suggestion. We agree that the discussion section should be enhanced, including the strengths and limitations of the study. We have revised the Discussion following your advice.

[Reviewer 2]
Thank you for your time and effort in reviewing our manuscript.

[Reviewer 3]
Thank you for your time and commitment to the review of our manuscript. We were particularly pleased to receive your specific guidance regarding the methods.

<Response to the questions>
However, the discussion section of the protocol is very short. Suggest expanding that section in a more detailed manner discussing the strength and limitations of this study. A single-center trial is a limitation. The chance of contamination is a limitation.
Response: Thank you for your important suggestion. We agree that the strengths and limitations of the study should be incorporated in the Discussion. We have revised the section accordingly.

1) Page 7. The eligibility criteria for participants are: Predicted length of hospital stay after admission: 1 week or longer.
Comment: How will you determine or judge the predicted length of hospital stay?
Response: The predicted length of hospital stay will be obtained from the treatment plan form on admission. We believe that the current description will not confuse readers. However, please let us know if you recommend including more detail on this criterion in the Methods and Analysis section.

2) Page 7. Exclusion criteria include the following: life expectancy of less than 1 month.
Comment: How will you determine or judge the life expectancy?
Response: The life expectancy will be estimated based on the clinical judgment of the participant's attending physician. We have added this explanation on page 5, line 11.

3) Page 7. In addition, monthly deprescribing-team meetings will be held for monitoring and quality control of intervention.
Comment: Explain the process of monitoring and quality control of interventions.

Response: The deprescribing team will review selected cases during the previous month to discuss the process of overall intervention for monitoring and quality control purposes. We have added this clarification on page 5, lines 27–28.

4) Page 8. Does the harm outweigh the potential benefits? Study participants' symptoms and laboratory results will be reviewed to determine any adverse effect that outweighs the expected benefits of the prescribed drug.
Comment: Explain with an example as shown in other questions.
Response: As recommended, we have added an example on page 6, lines 19–20.

5) Page 10. Any potential drug-related adverse events (AEs) will be recorded according to the Japanese version of CTCAE 4.0.
Comment: How a potential drug-related adverse event is defined? How do you assess whether a drug is responsible for the adverse event? If a combination of drugs is involved, how will you determine the causality of each drug and the AE?
Response: The potential drug-related adverse events will be determined based on consensus among the deprescribing team and attending physicians. We have clarified the same on page 8, lines 26–27.

6) Page 12. The research assistant who performs the bimonthly telephone interview assessments will be blind to group allocation.
Comment: How the blinding is ensured?
Response: Thank you for your question. Information regarding group allocation will be stored in a secure database (HOPE eACReSS) and reported to the staff member responsible for intervention. This information will not be included in the participant list that the research assistant uses for follow-up.