PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A study protocol for a single-centre, prospective, non-blinded, randomised, 12-month, parallel-group superiority study to compare the efficacy of pharmacist intervention versus usual care for elderly patients hospitalised in orthopaedic wards
AUTHORS	Komagamine, Junpei; Sugawara, Kenichi; Kaminaga, Miho; Tatsumi, Shinpei

VERSION 1 – REVIEW

REVIEWER	Christine Eisenhower University of Rhode Island College of Pharmacy, U.S.A.
REVIEW RETURNED	17-Feb-2018

GENERAL COMMENTS	I agree that we need more literature describing the role of pharmacist-driven interventions to reduce re-admissions. My major study design concern relates to collection of data. Is it possible for the authors to collect data for the primary and secondary objectives via hospital electronic health record and by contacting primary care providers, instead of sending out a patient survey? This seems to be a more accurate method and the authors may not receive surveys back from some patients. Abstract, line 34: consider rewording to, "...at least one potentially inappropriate prescription, as identified by the 2015 STOPP criteria." Objectives: would further describe how you chose a readmission time frame of 1 year for the primary objective. What is the average 1 year readmission rate for patients aged 70 and older at your hospital? Literature search and review, line 131: did you exclude any studies from your literature search because they were not recent enough? What year was your cut-off? Eligibility criteria, line 162: please specify if medications needed to be maintenance (versus as needed) to count in the minimum number of five for inclusion. Exclusion criteria: consider excluding patients with limited life expectancy (i.e. less than one year) due to serious illness. Methods: will you consider medications that are discontinued after discharge? Sometimes, inpatient providers will defer those actions to the primary care provider. Pharmacist intervention group, lines 222-223: what did the medication use sessions entail? Were there any specific learning

	objectives? Intervention at admission, line 233: specify inpatient physician Usual care group, line 260: how will the authors determine/define apparent harmful effects of medications? Data collection: some patients may not complete the surveys if they find that they are confusing and/or have to mail it back. Outcomes: Primary outcome: if planned admissions are part of the exclusion criteria, should planned re-admissions also be excluded? Ethics and dissemination: is it appropriate to publish separate studies for the secondary outcomes? Will secondary objectives be powered to show statistical significance?

REVIEWER	Renaudin Pierre Hospital Pharmacist, University Hospital of Montpellier FRANCE
REVIEW RETURNED	18-Feb-2018

GENERAL COMMENTS	Thank you for giving me the opportunity to comment on this submission. INTRODUCTION : In your usual care group, medication reconciliation is included. However, in most of the studies that you quote in the introduction, the usual care group not included medication reconciliation, but only the prescription review. It would be wise to put it forward in the introduction to give more value to your intervention. INCLUSION CRITERIA : One of your inclusion criteria is “at least one potentially inappropriate prescription (as defined by the 2015 STOPP criteria [8]) upon admission”. However, in the pharmacist intervention, you say that the use of these STOPP criteria for the pharmacist intervention will not be mandatory. Can you clarify this part please. USUAL CARE GROUP : In the usual care group, is the patient excluded from the study when you tell the physician that there is an inappropriate medication in cases of apparent harmful effects of medications ? OUTCOMES : - The readmission at 6 and 24 months are secondary outcome. Thank to change in the primary outcome. - What the definition of readmission rate?

VERSION 1 – AUTHOR RESPONSE

Response to Reviewer #1
Comment: I agree that we need more literature describing the role of pharmacist-driven interventions to reduce re-admissions. My major study design concern relates to collection of data. Is it possible for the authors to collect data for the primary and secondary objectives via hospital electronic health record and by contacting primary care providers, instead of sending out a patient survey? This seems to be a more accurate method and the authors may not receive surveys back from some patients.

Response: Thank you for your comments. To collect data for the primary and secondary objectives, we sent out patient surveys rather than contacting primary care physicians because the primary care physicians of patients often change. However, as you noted, some patients may not return the questionnaire. Therefore, we will contact the participants by telephone if they do not respond to the survey or if the answers to the questionnaire are insufficient. We did not use the electronic medical records from our hospital because they lack information on admission to other hospitals. However, for accuracy, we will collect participant data from the electronic medical records at our hospital if participants are admitted or regularly visit our hospital during the study period. This information is included in the revised manuscript (Page 19, lines 287-292).

Comment: Abstract, line 34: consider rewording to, "...at least one potentially inappropriate prescription, as identified by the 2015 STOPP criteria."
Response: According to your suggestion, we modified this sentence in the revised manuscript (Page 3, lines 34-35).

Comment: Objectives: would further describe how you chose a readmission time frame of 1 year for the primary objective. What is the average 1-year readmission rate for patients aged 70 and older at your hospital?
Response: Thank you for your comments. Based on a past study (Arch Intern Med 2009;169:894-900), we selected a readmission time frame of one year for the primary objective. This information is included in the revised manuscript (Pages 8-9, lines 115-117). No data are available regarding the one-year readmission rate for patients aged 70 years and older at our hospital. However, the “unplanned” readmission rate of hip fracture patients aged 65 years or older with five or more medications at admission in our hospital was 19.5% during a mean 8.0-month follow-up period (BMC Geriatrics 2017;17:288).

Comment: Literature search and review, line 131: did you exclude any studies from your literature search because they were not recent enough? What year was your cut-off?
Response: Thank you for your comments. We searched without limits for the year when the articles were published. However, all the relevant randomised controlled trials were conducted after 1990. This information is included in the revised manuscript (Page 10, lines 133-134).

Comment: Eligibility criteria, line 162: please specify if medications needed to be maintenance (versus as needed) to count in the minimum number of five for inclusion.
Response: We apologize for this oversight. In this trial, as-needed medications will not be counted. This information is included in the revised manuscript (Page 12, lines 168-169).

Comment: Exclusion criteria: consider excluding patients with limited life expectancy (i.e., less than one year) due to serious illness.
Response: Thank you for your comment. In the early stage of this research, we thoroughly discussed whether patients with limited life expectancy should be excluded from the study. Polypharmacy and potentially inappropriate prescribing are also problems in a terminal care setting (Lancet Oncol 2015;16:e333-41). Furthermore, due to the lack of access to hospice care in Japan, we sometimes encounter patients with adverse drug events resulting in emergent hospital admission. Therefore, we believe pharmacist interventions for elderly patients with terminal illnesses may reduce the readmission rate. Therefore, we decided to include patients with a limited life expectancy in this study.

Comment: Methods: will you consider medications that are discontinued after discharge? Sometimes, inpatient providers will defer those actions to the primary care provider.
Response: Thank you for your comment. We will consider medications that are discontinued after discharge. If the physicians accept the advice from pharmacists but defer action to the primary care physicians, then the pharmacists will send the discharge summary including their advice to the

primary care physicians. This information is included in the revised manuscript (Page 16, lines 247-249).

Comment: Pharmacist intervention group, lines 222-223: what did the medication use sessions entail? Were there any specific learning objectives?
Response: Thank you for your comment. The aim of these training sessions was to standardise the intervention by the pharmacists as much as possible. For this purpose, we decided to refer to the 2015 STOPP/START criteria. Therefore, we conducted the training sessions based on the 2015 STOPP/START criteria. Nonetheless, these criteria do not cover medications that are not used in Europe but are used in Japan. Furthermore, some of these criteria have uncertain applicability to Japanese patients. For example, according to the 2015 START criteria, statin therapy is recommended for patients with a past history of cerebral vascular disease unless the patient's status is end-of-life or the patient is aged >85 years. However, the effectiveness of statin therapy for ischaemic stroke patients without dyslipidaemia has not been clearly demonstrated in Japan (EBioMedicine 2015;2(9):1071-8). Therefore, we decided that the use of these criteria for the pharmacist intervention is not mandatory. This information in included in the revised manuscript (Pages 15-16, lines 225-236).

Comment: Intervention at admission, line 233: specify inpatient physician
Response: Thank you for your comment. In our hospital, one of five orthopaedic physicians care for hospitalised orthopaedic patients. Therefore, pharmacists will perform the interventions through cooperation with these orthopaedic physicians. This information is included in the revised manuscript (Page 16, line 242).

Comment: Usual care group, line 260: how will the authors determine/define apparent harmful effects of medications?
Response: Thank you for your comment. Harmful effects of medications are defined as apparent when these effects are judged to be symptomatic by pharmacists. This information is included in the revised manuscript (Page////, Line////).

Comment: Data collection: some patients may not complete the surveys if they find that they are confusing and/or have to mail it back.
Response: Thank you for your comment. As we noted above, we will contact the participants by telephone if the participants do not respond to the survey or if their answers to the questionnaire are insufficient. This information is included in the revised manuscript (Page 18, lines 271-272).

Comment: Outcomes: Primary outcome: if planned admissions are part of the exclusion criteria, should planned re-admissions also be excluded?
Response: Thank you for your comment. In previous randomised controlled trials investigating the effectiveness of pharmacist interventions on readmission (Arch Intern Med 2009;169:894-900; JAMA Intern Med 2018;178:375-82), the targeted population was hospitalised patients with acute illnesses only, and the primary outcome was all readmissions (including planned admission). Therefore, planned admissions are included in the primary outcome of this study.

Comment: Ethics and dissemination: is it appropriate to publish separate studies for the secondary outcomes? Will secondary objectives be powered to show statistical significance?
Response: We apologize for this oversight. We will not publish separate studies for the secondary outcomes. We modified this section in the revised manuscript (Page 25, Line 399-400).

Response to Reviewer #2
Introduction

Comment: In your usual care group, medication reconciliation is included. However, in most of the studies that you quote in the introduction, the usual care group not included medication reconciliation, but only the prescription review. It would be wise to put it forward in the introduction to give more value to your intervention.
Response: Thank you for your comment. As you noted, in most of the studies that we cited in the Introduction, the usual care group did not include medication reconciliation but only a prescription review. Given the possible beneficial effect of medical reconciliation for hospitalised patients (BMJ Open 2016;6:e010003), its inclusion in the usual care group may mitigate the effectiveness of the pharmacist interventions in this study. This information is included in the Limitations in the revised manuscript (Page 27, lines 427-429).

Inclusion criteria
Comment: One of your inclusion criteria is “at least one potentially inappropriate prescription (as defined by the 2015 STOPP criteria [8]) upon admission”. However, in the pharmacist intervention, you say that the use of these STOPP criteria for the pharmacist intervention will not be mandatory. Can you clarify this part please.
Response: Thank you for your comment. In this study, the pharmacists will perform the interventions by following the 2015 STOPP/START criteria. However, these criteria do not cover medications that are not used in Europe but are used in Japan. Furthermore, some of these criteria have uncertain applicability to Japanese patients. For example, according to the 2015 START criteria, starting statin therapy is recommended for patients with a past history of cerebral vascular disease unless the patient’s status is end-of-life or the patient is aged >85 years. However, the effectiveness of statin therapy for ischaemic stroke patients without dyslipidaemia has not been clearly demonstrated in Japan (EBioMedicine 2015;2(9):1071-8). Therefore, we decided that the use of these criteria for the pharmacist intervention is not mandatory. This information is included in the revised manuscript (Pages 15-16, lines 230-236).

Usual care group
Comment: In the usual care group, is the patient excluded from the study when you tell the physician that there is an inappropriate medication in cases of apparent harmful effects of medications?
Response: Thank you for your comment. We believe the inclusion of these patients in the usual care group may underestimate the effect of the pharmacist interventions. However, this practice is part of the usual care of pharmacists at our hospital. Furthermore, we need to minimise the exclusion of patients after randomisation. Therefore, we will not exclude patients with apparent harmful effects from medications.

Outcomes
Comment: The readmission at 6 and 24 months are secondary outcome. Thank to change in the primary outcome. What the definition of readmission rate?
Response: Thank you for your comments. As you noted, the readmission rates at 6 and 24 months are secondary outcomes. Therefore, these outcomes have been moved to the Secondary outcomes in the revised manuscript (Pages 19-20, lines 295-305). The readmission rate is defined as the proportion of participants who are readmitted. Readmission will include both planned and unplanned admissions.

Formatting amendments
Comment: Required amendments will be listed here; please include these changes in your revised version:
1.Figure file format
Please provide another copy of your figures with better qualities and please ensure that Figures are of better quality or not pix-elated when zoom in. NOTE: They can be in TIFF or JPG format and make

sure that they have a resolution of at least 300 dpi. Figures in PDF, DOCUMENT, EXCEL and POWER POINT format are not acceptable.
Response: We re-uploaded our figure in TIFF format.

Comment: 2.Supplementary file format
Please re-upload your supplementary files in PDF format.
Response: We uploaded our supplementary file in PDF format.

VERSION 2 – REVIEW

REVIEWER	Centre Hospitalier Universitaire de Montpellier, Hôpital Lapeyronie, Pharmacie, Département de Pharmacie Clinique Dispensation et Economie de Santé, Montpellier, F-34000, France
REVIEW RETURNED	26-Mar-2018

GENERAL COMMENTS	Thank you for your response. I have one last comment regarding the definition of readmission. Can you please specify if it is: All-cause readmissions and/or emergency departments visits, i.e., the number of hospitalized patients regardless of the cause of hospitalization and the number of non-hospitalized patients who visited an emergency department. OR All-cause readmissions (the number of hospitalized patients regardless of the cause of hospitalization), Excludes patients presenting only in emergency departments and who are not hospitalized.

REVIEWER	Christine Eisenhower University of Rhode Island College of Pharmacy, U.S.A.
REVIEW RETURNED	04-Apr-2018

GENERAL COMMENTS	Thank you for thoroughly address my comments and questions. I believe your 2nd draft is more detailed and includes sufficient justification for your methods and interventions.

VERSION 2 – AUTHOR RESPONSE

Response to Reviewer #1(Christine Eisenhower)

Comment: Thank you for thoroughly address my comments and questions. I believe your 2nd draft is more detailed and includes sufficient justification for your methods and interventions.

Response: Thank you very much for your comment.

Response to Reviewer #2(Renaudin Pierre)

Comment: Can you please specify if it is:

All-cause readmissions and/or emergency departments visits, i.e., the number of hospitalized patients regardless of the cause of hospitalization and the number of non-hospitalized patients who visited an emergency department.

OR

All-cause readmissions (the number of hospitalized patients regardless of the cause of hospitalization), Excludes patients presenting only in emergency departments and who are not hospitalized.

Response: We apologize for the confusion. Readmission was defined as all-cause readmissions (the number of hospitalised patients regardless of the cause of hospitalisation). Patients who only visit the emergency department who are not hospitalised were not be counted. We modified the Methods section in the revised manuscript (Page 19, lines 295-298).