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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

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ABSTRACT

Introduction: Given that polypharmacy and potentially inappropriate prescribing are common in elderly orthopaedic patients, pharmacist interventions to improve medication practices among this population are important. However, past studies have reported mixed results regarding the effectiveness of pharmacist-led interventions in inpatient elderly care. Furthermore, few randomised controlled trials have evaluated patient-relevant outcomes as a primary endpoint. Therefore, we will evaluate whether a pharmacist-led intervention could reduce readmission of hospitalised elderly orthopaedic patients with polypharmacy or potentially inappropriate prescribing.

Methods and analysis: This is an ongoing single-centre, prospective, non-blinded, randomised controlled trial designed to evaluate the superiority of a pharmacist-led intervention for hospitalised elderly patients compared with usual care. The trial will include newly admitted orthopaedic patients 70 years of age and older with polypharmacy or at least one potentially inappropriate prescription. Usual care includes medication reconciliation, patient education, and monitoring, as well as providing information about discharge medications. Pharmacist interventions, in addition to usual care, include advising the patient's physician to stop unnecessary or inappropriate medications and start necessary medications. The primary outcome is the one-year

readmission rate. Secondary outcomes are the proportion of patients who undergo emergency department visits and the occurrences of all-cause death, a new fracture, myocardial infarction, and ischaemic stroke. The study started in November 2017, and up to approximately 220 patients will be enrolled.

Ethics and dissemination: The protocol was approved by the Medical Ethics Committee of the National Hospital Organization Tochigi Medical Center (No. 29-22). The trial was registered at the UMIN clinical registry. The results of the primary trials and each of the secondary outcomes will be submitted for publication in a peer-reviewed journal.

Trial registration number: UMIN000029404 (registered October 3, 2017).

Key words: Emergency, Orthopaedic ward, Pharmacist intervention, Polypharmacy, Potentially inappropriate prescribing

Strengths and limitations of this study

- This randomised controlled trial will evaluate the effectiveness of pharmacist interventions for hospitalised orthopaedic elderly patients, using patient-relevant outcomes as the primary outcomes.

- This is a single-centre study with a small sample size and short-term follow-up.
- Orthopaedic patients who are admitted electively or discharged within less than seven days after admission will be excluded.
- Orthopaedic patients who are prescribed fewer than five medications and are taking no potentially inappropriate medications at admission will be excluded.

INTRODUCTION

In recent decades, as the population has aged, polypharmacy and multi-morbidities have become more complicated problems among elderly patients.[1-3] Polypharmacy in elderly patients is associated with inappropriate prescribing[4] and adverse events, such as adverse drug events and death.[5] Because adverse drug events are a primary cause of preventable hospital admissions among elderly patients,[6] strategies to prevent drug-related events has been proposed in recent decades.[7-9] These strategies include deprescribing for polypharmacy[9] and reducing potentially inappropriate prescribing and potential prescription omissions.[7,8]

Polypharmacy and potentially inappropriate prescribing among elderly patients are particularly common in acute care settings compared with primary care settings.[10-12] Therefore, it is important to improve the appropriateness of medications used during hospitalisation. In fact, the American College of Emergency Physicians Geriatric Emergency Department Guidelines recommend a multidisciplinary team intervention for all elderly patients who present to the emergency department and are prescribed more than five medications or at least one potentially inappropriate medication, regardless of the presenting complaint.[13] Given that physicians are often unaware of adverse drug events,[14,15] the role of hospital pharmacists in improving

polypharmacy and potentially inappropriate prescribing in hospitalised elderly patients is important. Nonetheless, past studies have reported mixed results regarding the effectiveness of a pharmacist-led intervention in improving the appropriateness of medications in inpatient elderly care. Although pharmacist intervention can improve the appropriateness of medications in hospitalised elderly patients,[16] the conclusions of past systematic reviews and meta-analyses have been inconsistent regarding whether patient-relevant outcomes, such as mortality and readmission, were improved by these interventions.[17-20] One recent meta-analysis that included seven randomised controlled trials that evaluated the effectiveness of a pharmacist-led intervention in inpatient elderly care also reported little impact of pharmacist interventions on readmission rates.[21] However, most trials included in this meta-analysis were considered to have a high risk of bias. Furthermore, only two of the seven randomised controlled trials included in the meta-analysis evaluated patient-relevant outcomes as primary endpoints.[22,23] In one of those two trials, a comprehensive pharmacist intervention for hospitalised elderly patients with polypharmacy led to a significant reduction in hospital visits.[23] Therefore, it is still too early to conclude that pharmacist-led interventions for hospitalised elderly patients do not improve patient-relevant outcomes. Furthermore, most studies have targeted internal medicine

patients, while few studies have ever investigated the effectiveness of pharmacist interventions for elderly patients hospitalised in an orthopaedic ward.[21] The prevalence of polypharmacy and potentially inappropriate prescribing are particularly high in elderly orthopaedic patients, and these practices often continue after recovery from a fracture.[24,25] Furthermore, polypharmacy is associated with an increased risk of fall and fracture.[5,26] Therefore, pharmacist interventions for improving the appropriateness of medications in hospitalised elderly orthopaedic patients may be associated with better patient outcomes compared with other settings. Thus, we will conduct a randomised controlled trial to evaluate whether a pharmacist-led intervention reduces readmission in hospitalised elderly orthopaedic patients with polypharmacy or potentially inappropriate prescribing.

Objectives

Primary objective

Our primary objective is to determine whether pharmacist intervention for elderly orthopaedic patients with polypharmacy or potentially inappropriate prescribing at admission reduces one-year readmission rates compared with usual care.

Secondary objectives

The key secondary objectives are to determine whether pharmacist intervention for elderly orthopaedic patients with polypharmacy or potentially inappropriate prescribing at admission reduces patient-relevant outcomes, such as all-cause death, myocardial infarction, ischaemic stroke, and any fractures, compared with usual care. Other secondary objectives are to determine whether pharmacist intervention for elderly orthopaedic patients with polypharmacy or potentially inappropriate prescribing at admission reduces the total number of medications, potentially inappropriate prescribing, and potential prescription omissions.

Literature search and review

We performed a literature search and review of pharmacist interventions in elderly hospitalised orthopaedic patients. We used the terms “pharmacist”, “polypharmacy”, “medication review”, and “inappropriate prescribing” alone and in combination to search the PubMed and Google Scholar databases through 5 August 2017. We restricted our review to full-text articles published in English or Japanese. We also identified

references from the relevant articles. We primarily selected randomised controlled trials, systematic reviews, and meta-analyses. We found a recent systematic review regarding the effectiveness of pharmacist-led intervention on patient outcomes in elderly hospitalised patients.[21] Based on this systematic review, we designed this trial.

METHODS AND ANALYSIS

Trial design

This study is a single-centre, prospective, non-blinded, randomised, controlled, superiority trial with two parallel groups. All participants who provide consent for participation and fulfil the inclusion criteria will be randomly assigned to the pharmacist intervention group or the usual care group with a 1:1 allocation. The study was approved by the Medical Ethics Committee of the National Hospital Organization Tochigi Medical Center (No. 29-22) and will be conducted in accordance with the Declaration of Helsinki. Standard Protocol Items: The Recommendations for Interventional Trials (SPIRIT checklist)[27] was followed in designing the study protocol (supplementary appendix). Figure 1 summarises the design of the trial, and each of the trial aspects is described in detail below.

Study setting

This study will be conducted in the orthopaedic ward at the National Hospital Organization Tochigi Medical Center. Our hospital is a 350-bed acute care community hospital and is one of five main hospitals that serve approximately 0.5 million individuals in Utsunomiya in the Tochigi prefecture in Japan.

Eligibility criteria

Eligible patients are those who meet all of the following inclusion criteria and who do not have any listed exclusion criteria. Based on the American College of Emergency Physicians Geriatric Emergency Department Guidelines[11], the number of medications taken or the presence of potentially inappropriate prescribing at admission will be used as the inclusion criteria. However, the minimum number of medications for inclusion will be five, based on a past study showing that taking five or more medications was a useful parameter for estimating medication-related adverse effects related to frailty, disability, and mortality among men aged 70 years and older.[28]

Inclusion criteria

1. Age 70 years and older

2. Polypharmacy (defined as 5 or more medications) or at least one potentially inappropriate prescription (as defined by the 2015 STOPP criteria[8]) upon admission

Exclusion criteria

1. Elective admission
2. Inability to contact patient within 72 hours after their admission
3. Expected hospital stay duration of < one week

Study duration, enrolment and number of sites

The study will be conducted at a single hospital in Japan. The planned sample size is approximately 220 patients. This study began after November 2017. The planned follow-up duration for each patient will be two years after the randomisation. Our investigation period is projected to be three years. However, unless we can recruit the planned number of patients within three years after beginning this study, we will extend the investigation duration to achieve the planned number of patients.

Screening and registration

All elderly patients who are hospitalised in an orthopaedic ward in our hospital will be screened for eligibility for the trial by one of three pharmacists (KS, ST, MK) every weekday morning. Patients who are hospitalised on weekends will be screened on the following Monday morning. If the screened patients are not eligible, we will document the reason for ineligibility for the trial and the number of ineligible patients. All patients who fulfil the inclusion criteria and have no exclusion criteria will be registered by one of three pharmacists (KS, ST, MK) in the central data centre at the National Hospital Organization Tochigi Medical Center. Unless written informed consent is provided by the patients, we will document the reasons why the patients did not provide consent to participate in the trial and document the number of patients who declined to participate in the trial.

Randomisation and allocation concealment

All patients who provide consent for participation and who fulfil the inclusion criteria will be randomised. Randomisation will be requested by one of three pharmacists (KS, ST, MK) to the independent randomisation centre at the National Hospital Organization Tochigi Medical Center via webmail. Participants will be randomly assigned to either

the pharmacist intervention group or the usual care group. Randomisation will be performed as block randomisation with a 1:1 allocation. The computer-generated random allocation sequence will be provided by an independent staff pharmacist who is not involved in the treatment of patients or with the assessment of patient outcomes. The randomisation will not be stratified. The block sizes will be concealed until the primary outcome is analysed. Throughout the study, the randomisation list will also be concealed until the end of the study.

Blinding

Due to the nature of the intervention, neither the participants nor the clinical pharmacists can be blinded to the allocation. Patients will be informed of the group to which they have been randomly allocated. Assessments regarding the outcomes will be conducted by an assessor who knows the treatment allocation. The analysis regarding the primary outcome will be conducted by independent investigators who are blinded to the treatment allocation and are not involved in the assessment of patient outcomes.

Pharmacist intervention group

Before starting the study, three study pharmacists (KS, ST, MK) were trained during a three-month period from May 2017 to July 2017. Approximately 16 sessions (one hour per session) on medication use in elderly patients based on the 2015 STOPP/START criteria[8] were provided by one internal medicine physician (JK). Therefore, these pharmacists are aware of the 2015 STOPP/START criteria, however, the use of these criteria for the pharmacist intervention will not be mandatory. One of these trained pharmacists (KS, ST, MK) will treat the participants from admission to discharge at the following three stages.

Intervention at admission

A comprehensive list of current medications will be compiled within 72 hours after admission. A drug review will be performed, and advice about the following factors will be given to the patient's physician: (1) deprescribing inappropriate or unnecessary medications, (2) starting effective or necessary medications, and (3) modifying medication dosages. However, the final decision to adhere to the advice provided by pharmacists will be made by the physician in charge. Pharmacists will document whether the physicians follow their advice.

Intervention during hospitalisation

During the hospital stay, patients will be educated about the harms and benefits of their medications. Pharmacists will also provide information about the rationale for medication use and therapeutic goals. Patients will be monitored after starting or stopping medications.

Intervention at discharge

Information about discharge medications (e.g., rationale for changes and monitoring needs for newly started or stopped medications) will be summarised in a written document by the pharmacists. Patients will receive discharge counselling with this summary. The summary will also be sent to the primary care physicians and community pharmacists.

Usual care group

Usual care typically includes the same elements as those received by the intervention group but is less extensive. In the usual care group, a comprehensive list of current medications will be compiled by the pharmacists (KS, ST, MK) within 72 hours after admission. Patients will be monitored and educated about newly started medications by their physician and will receive discharge counselling. However, unlike in the intervention group, advice from pharmacists about deprescribing and starting medications will not be provided to the patient's physician, except for in cases of apparent harmful effects of medications. Furthermore, pharmacists will neither prepare the summary about discharge medications nor send it to the primary care physicians and community pharmacists. However, at the discretion of the pharmacist providing advice about medications for the physicians, the summary about discharge medications will be prepared. These procedures are the standard practice for pharmacists in most Japanese hospitals.[29]

Data collection

One of the pharmacists (ST, KS, MK) will collect the demographic and baseline medical information from the patients and/or their caregivers at admission and

summarise this information on a patient registration form. Participants will be followed and assessed for two years after study entry (Table 1). One of the pharmacists (ST, KS, MK) will assess outcomes at discharge. We will survey the participants or their caregivers regarding information about primary and secondary outcomes by sending letters at 6 months, 12 months, and 24 months after randomisation. If the participants do not respond to the survey, we will try to contact them or their caregivers by telephone to minimise the effect of missing data on study outcomes.

Outcomes

Primary outcome

The primary outcome is the readmission rate within one year after randomisation. Readmission includes both planned and unplanned admissions. We will evaluate the difference between the two treatment groups in the proportion of participants who are readmitted within one year after randomisation. We will also evaluate the differences in readmission rates between the groups at 6 and 24 months.

Secondary outcomes

The secondary outcomes are provided below. These outcomes will be evaluated at discharge and at 6 months, 12 months and 24 months after randomisation. We will evaluate the differences between the two treatment groups regarding these outcomes at discharge, 6 months, 12 months and 24 months.

- Any-cause death
- Total number of medications
- Potentially inappropriate prescribing based on the 2015 STOPP criteria[8]
- Potential prescribing omission based on the 2015 START criteria[8]
- Any fractures
- Ischaemic stroke
- Myocardial infarction
- Emergency department visits

Statistical analysis

Sample size calculation

We estimated that a sample of 200 patients would provide the study with a power of at least 80% to show a relative risk reduction of 33% for the primary outcome in the intervention group compared with the usual care group (at a two-sided alpha level of 0.05), assuming that the proportion of patients who are readmitted within one year is 60% in the usual care group (based on a previous study[23]). Assuming that the dropout rate is 10%, we would need to enrol approximately 220 patients.

Statistical analysis

The baseline characteristics of the study population will be summarised using descriptive statistics. The intervention group will be compared against the usual group for all primary and secondary outcomes (Table 2). We will use a chi-squared test for binary outcomes and Student's t-test for continuous outcomes. We will calculate the relative risk and number needed to treat with corresponding 95% confidence intervals to compare dichotomous variables, and the difference in the means will be used for an additional analysis of continuous variables. For all tests, we will use 2-sided p-values with an alpha < 0.05 for the level of significance.

Analyses for all outcomes will include all patients who have undergone randomisation and have provided valid informed consent (intention-to-treat population). Regarding the procedure for missing data, we will exclude the data from participants who are lost to follow-up or whose outcomes are missing. These analyses will be performed using IBM SPSS Statistics Base version 21.0 (IBM Corporation, Nihonbashi, Tokyo, Japan) or Excel statistical software package version 2.11 (Bellcurve for Excel; Social Survey Research Information Co., Ltd., Tokyo, Japan). All analyses will be conducted by investigators who are blinded to the study group allocations.

Data management

The trial data about study participants will be transmitted to and stored in the research database at National Hospital Organization Tochigi Medical Center. This will not include the participants' identifying information. Rather, individual participants and research data will be identified by a unique study identification number. At the end of the study, the data will be locked. Data will be stored for at least five years after study completion. Access to stored data will be limited to investigators. Data will be stored using codes assigned by the investigators. Data will be kept on password-protected computers.

Monitoring

Data monitoring

The risk associated with participation in this study is low, because our aim is to improve the quality of medications in patients. According to the Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects (as of March 2015), our intervention corresponds with a non-invasive procedure. Therefore, we will not need a data monitoring committee. However, an independent staff pharmacist who is not involved with the trial intervention will monitor the data periodically to ensure safety.

Adverse events

In our study, an adverse event will be defined as any undesirable medical occurrence in a participant without regard to the possibility of a causal relationship. Data on adverse events will be collected after the participants have provided consent and enrolled in the study. If a participant experiences an adverse event after the informed consent document is signed and the participant has not yet started to receive the study intervention, the event will be reported as not being related to the study intervention. All adverse events

that occur after entry into the study and for two years after randomisation will be recorded. A serious adverse event for this study is any undesirable medical occurrence that is believed by the investigators to be causally related to the study intervention and results in any of the following: a life-threatening condition (that is, immediate risk of death) or severe or permanent disability.

Auditing

According to the Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects (as of March 2015), our intervention corresponds with a non-invasive procedure. Furthermore, past studies investigating the effectiveness of a pharmacist intervention have reported few adverse events.[16-23] Therefore, we will not need auditing.

Ethics and dissemination

This study protocol was approved by the Medical Ethics Committee of the National Hospital Organization Tochigi Medical Center (Tochigi, Japan). They judged the study design, ethics, and safety. Substantial amendments of the study protocol must be

approved by the Medical Ethics Committee of the National Hospital Organization Tochigi Medical Center. The trial was registered at the UMIN clinical registry on October 3, 2017. We will obtain informed consent from the trial participants or their authorised surrogates according to the Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects (as of March 2015). One of three pharmacists (ST, KS, MK) will introduce the trial to patients and discuss the trial with all patients using the information sheets about the nature, purpose, and possible risks and benefits of the trial, which was approved by the Medical Ethics Committee of the National Hospital Organization Tochigi Medical Center. Then, the pharmacists will obtain written informed consent from patients willing to participate in the trial. To assure confidentiality, trial participants will be allocated a unique trial identification number throughout the trial.

A manuscript with the results of the primary study will be published in a peer-reviewed journal. Separate manuscripts will be written on each of the secondary aims, and these manuscripts will also be submitted for publication in peer-reviewed journals.

DISCUSSION

Given that polypharmacy and potentially inappropriate prescribing among elderly patients is common in acute care settings,[10] it is important to improve the appropriateness of medications during hospitalisation. Therefore, the role of hospital pharmacists in improving polypharmacy and potentially inappropriate prescribing in hospitalised elderly patients is important. Nonetheless, there are conflicting results regarding the effectiveness with which pharmacist interventions in elderly inpatient care can improve polypharmacy and potentially inappropriate prescribing to affect patient-relevant outcomes.[17-21] Given that few past randomised controlled trials have evaluated a patient-relevant outcome as a primary endpoint,[22,23] it is important to conduct a randomised controlled trial to evaluate whether a pharmacist-led intervention improves patient-relevant outcomes, such as readmission and death, in hospitalised elderly orthopaedic patients with polypharmacy or potentially inappropriate prescribing.

There are several limitations to this study. First, the non-blinded study design may overestimate the effectiveness of pharmacist intervention.[30] However, due to the nature of the intervention, it is difficult for both participants and clinical pharmacists to be blinded to the allocation. Second, this study is a single-centre trial. Although most past randomised controlled trials were also a single-centre trials,[21,23,31-34] the external validity of this study is limited. Therefore, an additional randomised controlled

trial may be needed. Third, we will exclude elderly orthopaedic patients who are admitted electively or who are taking less than five prescribed medications or have no potentially inappropriate prescriptions. Furthermore, elderly patients admitted to other specialty wards, such as internal medicine or general surgery, will also be excluded. Therefore, it is unclear whether the findings of this trial will be applicable to elderly patients who are admitted electively or to other wards besides the orthopaedic ward. Finally, we will not assess the cost-effectiveness of the intervention.

Although these limitations are important, this study is one of a few randomised controlled trials to investigate the effectiveness of a pharmacist-led intervention and use a patient-relevant outcome as the primary outcome for hospitalised elderly patients. Given that the burdens of polypharmacy and multi-morbidities among elderly patients have increased in recent years, this trial will provide important information on improving the acute care of elderly patients with polypharmacy or potentially inappropriate prescribing.

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Contributors: KS and JK conceived the project. JK performed the literature search and review. KS, JK, ST, and MK designed the study. KS and JK wrote the draft of the protocol for the study. All authors contributed equally to writing the original protocol for this study. KS is the chief investigator of this study. JK wrote the draft of this manuscript. All authors provided final approval for submission of this manuscript for publication consideration.

Competing interests: All authors have completed the ICMJE unified disclosure from competing interest form at www.icmje.org/coi_disclosure.pdf (available upon request from the corresponding author). All authors declare that they have no conflicts of interest.

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Ethical approval: This study was approved by the Medical Ethics Committee of the National Hospital Organization Tochigi Medical Center (No. 29-22).

REFERENCES

1 Wolff JL, Starfield B, Anderson G. Prevalence, expenditures, and complications of multiple chronic conditions in the elderly. *Arch Intern Med* 2002;162:2269-76. doi:10.1001/archinte.162.20.2269.

2 Kaufman DW, Kelly JP, Rosenberg L et al. Recent patterns of medication use in the ambulatory adult population of the United States: The Slone survey. *JAMA* 2002;287:337-44. doi:10.1001/jama.287.3.337.

3 Boyd CM, Dare J, Boult C, et al. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases. *JAMA* 2005;294:716-24. doi:10.1001/jama.294.6.716.

4 Steinman MA, Landefeld CS, Rosenthal GE, et al. Polypharmacy and prescribing quality in older people. *J Am Geriatr Soc* 2006;54:1516-23. doi:10.1111/j.1532-5415.2006.00889.x.

5 Fried TR, O'Leary J, Towle V, et al. Health outcomes associated with polypharmacy in community-dwelling older adults: a systematic review. *J Am Geriatr Soc* 2014;62:2261-72. doi:10.1111/jgs.13153.

6 Beijer HJ, de Blaey CJ. Hospitalisations caused by adverse drug reactions (ADR): a meta-analysis of observational studies. *Pharm World Sci* 2002;24:46-54. doi:10.1023/A:1015570104121.

7 The American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 updated Beers Criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc* 2015;63:2227-46. doi:10.1111/jgs.13702.

8 O'Mahony D, O'Sullivan D, Byrne S, et al. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. *Age Ageing* 2015;44:213-8. doi:10.1093/ageing/aful145.

9 Scott IA, Hilmer SN, Reeve E, et al. Reducing inappropriate polypharmacy: the process of deprescribing. *JAMA Intern Med* 2015;175(5):827-34. doi:10.1001/jamainternmed.2015.0324.

10 Gallagher P, Lang PO, Cherubini A, et al. Prevalence of potentially inappropriate prescribing in an acutely ill population of older patients admitted to six European hospitals. *Eur J Clin Pharmacol* 2011;67:1175-88. doi:10.1007/s00228-011-1061-0.

11 Tommelein E, Mehuys E, Petrovic M, et al. Potentially inappropriate prescribing in community-dwelling older people across Europe: a systematic literature review. *Eur J Clin Pharmacol* 2015;71(12):1415-27. doi:10.1007/s00228-015-1954-4.

12 Opondo D, Eslami S, Visscher S, et al. Inappropriateness of medication prescriptions to elderly patients in the primary care setting: a systematic review. *PLoS ONE* 2012;7(8):e43617. doi:10.1371/journal.pone.0043617.

13 The American College of Emergency Physicians, the American Geriatrics Society, Emergency Nurses Association and the Society for Academic Emergency Medicine. Geriatric emergency department guidelines. *Ann Emerg Med* 2014;63:e7-e25. doi: 10.1016/j.annemergmed.2014.02.008.

14 Hohl CM, Zed PJ, Brubacher JR, et al. Do emergency physicians attribute drug-related emergency department visits to medication-related problems? *Ann Emerg Med* 2010;55:493-502. doi:10.1016/j.annemergmed.2009.10.008.

15 Gandhi TK, Weingart SN, Borus J, et al. Adverse drug events in ambulatory care. *New Engl J Med* 2003;348:1556-64. doi:10.1056/NEJMsa020703

16 Walsh KA, O'Riordan D, Kearney PM, et al. Improving the appropriateness of prescribing in older patients: a systematic review and meta-analysis of pharmacists'

interventions in secondary care. *Age Ageing* 2016;45:201-9. doi:10.1093/ageing/afv190.

17 Kaboli PJ, Hoth AB, McClimon BJ, et al. Clinical pharmacists and inpatient medical care: a systematic review. *Arch Intern Med* 2006;166:955-64. doi:10.1001/archinte.166.9.955.

18 Holland R, Desborough J, Goodyer L, et al. Does pharmacist-led medication review help to reduce hospital admissions and deaths in older people? A systematic review and meta-analysis. *Br J Clin Pharmacol* 2007;65(3):303-16. doi:10.111/j.1365-2125.2007.03071.x.

19 Koshman SL, CHarrois TL, Simpson SH, et al. Pharmacist care of patients with heart failure: a systematic review of randomized trials. *Arch Intern Med* 2008;168(7):687-94. doi:10.1001/archinte.168.7.687.

20 Renaudin P, Boyer L, Esteve MA, et al. Do pharmacist-led medication reviews in hospitals help reduce hospital readmissions? A systematic review and meta-analysis. *Br J Clin Pharm* 2016;82:1660-73. doi:10.111/bcp.13085.

21 Thomas R, Huntley AL, Mann M, et al. Pharmacist-led interventions to reduce unplanned admissions for older people: a systematic review and meta-analysis of randamised controlled trials. *Age Ageing* 2014;43:174-87.

doi:10.1093/ageing/aft169.

22 Nazareth I, Burton A, Shulman S, et al. A pharmacy discharge plan for hospitalized elderly patients: a randomized controlled trial. *Age Ageing* 2001;30:33-40. doi:10.1093/ageing/30.1.33.

23 Gillespie U, Alassaad A, Henrohn D, et al. A comprehensive pharmacist intervention to reduce morbidity in patients 80 years or older: a randomized controlled trial. *Arch Intern Med* 2009;169(9):894-900. doi:10.1001/archinternmed.2009.71.

24 McMahon CG, Cahir CA, Kenny RA, et al. Inappropriate prescribing in older fallers presenting to an Irish emergency department. *Age Ageing* 2014;43:44-50. doi:10.1093/ageing/aft114.

25 Kragh A, Elmståhl S, Atroshi I. Older adults' medication use 6 months before and after hip fracture: A population-based cohort study. *J Am Geriatr Soc* 2011;59:863-8. doi:10.1111/j.1532-5415.2011.03372.x.

26 Lai SW, Liao KF, Liao CC, et al. Polypharmacy correlates with increased risk for hip fracture in the elderly. A population-based study. *Medicine* 2010;89:295-9. doi:10.1097/MD.0b013e3181fl5efc.

27 Chan AW, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586. doi:10.1136/bmj.e7586.

28 Gnjidic D, Hilmer SN, Blyth FM, et al. Polypharmacy cutoff and outcomes: five or more medicines were used to identify community-dwelling older men at risk of different adverse outcomes. *J Clin Epidemiol* 2012;65:989-95. doi:10.1016/j.jclinepi.2012.02.018.

29 Nakagawa S, Kume N. Pharmacy practice in Japan. *Can J Hosp Pharm* 2017;70(3):232-42. doi:10.4212/cjhp.v70i3.1663.

30 Wood L, Egger M, Gluud LL, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *BMJ* 2008;336(7644):601-5. doi:10.1136/bmj.39465.451748.AD.

31 Lisby M, Thomsen A, Nielsen LP, et al. The effect of systematic review in elderly patients admitted to an acute ward of internal medicine. *Basic Clin Pharmacol Toxicol* 2010;106(5):422-7. doi:10.1111/j.1742-7843.2009.00511.x.

32 McMullin ST, Hennenfent JA, Ritchie DJ, et al. A prospective, randomized trial to assess the cost impact of pharmacist-initiated interventions. *Arch Intern Med* 1999;159(19):2306-9. doi:10.1001/archinte.159.19.2306.

33 Spinewine A, Swine C, Dhillon S, et al. Effect of a collaborative approach on the quality of prescribing for geriatric inpatients: a randomized, controlled trial. *J Am Geriatr Soc* 2007;55(5):658-65. doi:10.1111/j.1532-5415.2007.01132.x.

34 Lipton HL, Bird JA. The impact of clinical pharmacists' consultations on geriatric patients' compliance and medical care use: a randomized controlled trial. *Gerontologist* 1994;34(3):307-15. doi:10.1093/geront/34.3.307.

551 **Table 1.** Time schedule of participant enrolment, interventions, and assessments.

	STUDY PERIOD					
	Enrolment	**Allocation**	**Post-allocation**			
TIMEPOINT*	$-t_1$	**0**	t_1	t_2	t_3	t_4
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Allocation		X				
INTERVENTIONS:						
Pharmacist intervention		⟺	⟺			
Usual care (control)		⟺	⟺			
ASSESSMENTS:						
Number of medications	X		X	X	X	X
Number of PIP†	X		X	X	X	X
Number of PPO†	X		X	X	X	X
Adverse drug events			X			
Discharge destination			X			
Duration of hospital stay			X			
All-cause death			X	X	X	X
Readmission				X	X	X
ED visit				X	X	X

Myocardial infarction			X	X	X	X
Ischaemic stroke			X	X	X	X
Fracture			X	X	X	X

*t_1, within 72 hours after admission; t_1, at discharge; t_2, six months after randomisation; t_3, 12 months after randomisation; t_4, 24 months after randomisation.

†PIP and PPO are defined based on the 2015 STOPP/START Criteria.

ED, emergency department; PIP, potentially inappropriate prescribing; PPO, potential prescribing omission.

558 **Table 2.** Variables, measures, and analysis methods.

Variable/outcome	Hypothesis	Measured outcomes	Methods of analysis
Primary			
Readmission* at 12 months	Improvement occurred	Readmission rate % [binary]	Chi-squared test
Secondary			
Number of medications at discharge, at 6, 12, and 24 months	Decline occurred	Total number of medications [continuous]	T-test
PIP† at discharge, at 6, 12, and 24 months	Decline occurred	Total number of PIP [continuous]	T-test
	Improvement occurred	Proportion of patients who take any PIP % [binary]	Chi-squared test
PPO† at discharge, at 6, 12, and 24 months	Decline occurred	Total number of PPO [continuous]	T-test
	Improvement occurred	Proportion of patients who take any PPO % [binary]	Chi-squared test
Readmission* at 6 and 24 months	Improvement occurred	Readmission rate % [binary]	Chi-squared test
ED visit at 6, 12, and 24 months	Improvement occurred	Proportion of patients who visit ED % [binary]	Chi-squared test
All-cause death at 6, 12, and 24 months	Improvement occurred	All-cause mortality % [binary]	Chi-squared test
Acute myocardial infarction at 6, 12, and 24 months	Improvement occurred	Proportion of patients whom acute myocardial infarction occurred % [binary]	Chi-squared test
Acute ischaemic stroke at 6, 12, and 24 months	Improvement occurred	Proportion of patients whom acute ischemic stroke occurred % [binary]	Chi-squared test
Any fractures at 6, 12, and 24 months	Improvement occurred	Proportion of patients whom any fractures occurred % [binary]	Chi-squared test

559 *Includes both planned and unplanned hospitalization.

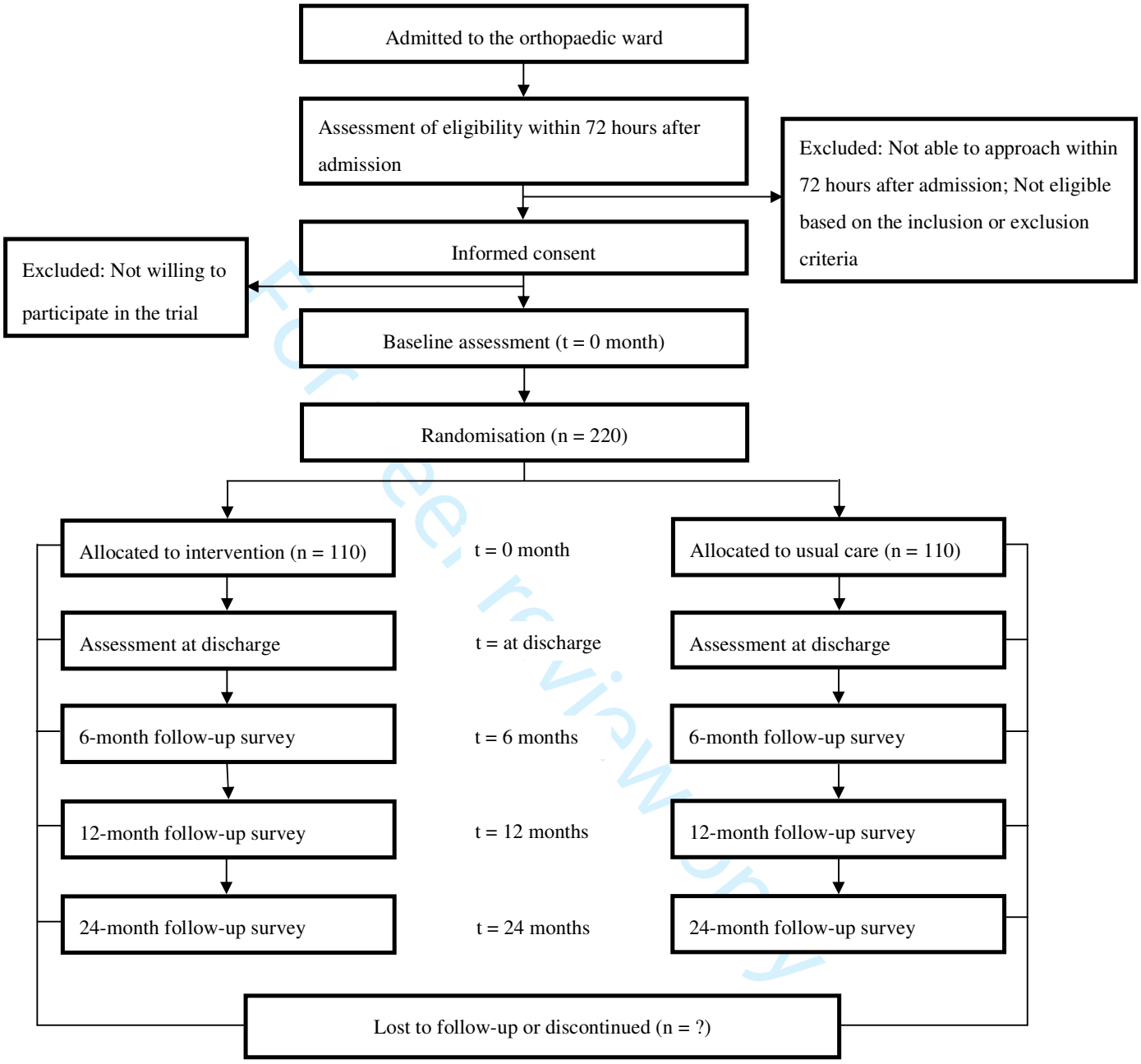
560 †PIP and PPO are defined based on the 2015 STOPP/START Criteria.

561 ED, emergency department; PIP, potentially inappropriate prescribing; PPO, potential

562 prescribing omission.

Figure 1. Flow diagram of the participant.

564



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page Number on which item is reported
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	4
Protocol version	3	Date and version identifier	NA
Funding	4	Sources and types of financial, material, and other support	27
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	27
	5b	Name and contact information for the trial sponsor	NA
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	NA
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6-9
	6b	Explanation for choice of comparators	17
Objectives	7	Specific objectives or hypotheses	8-9
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	10
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	11
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	11-12
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	14-16
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	17
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	16-17
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	18-19

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	17-18, Figure 1, Table 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12, 20
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	12-13
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	13-14
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	13-14
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	13-14
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	14
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	17-18
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	18
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	21
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	20-21, Table 2
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	20-21, Table 2
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	21
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	22
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	22-23
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	23
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	23
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	23-24
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	24
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	24
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	27
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	21
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	24

	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

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

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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

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ABSTRACT

Introduction: Given that polypharmacy and potentially inappropriate prescribing are common in elderly orthopaedic patients, pharmacist interventions to improve medication practices among this population are important. However, past studies have reported mixed results regarding the effectiveness of pharmacist-led interventions in inpatient elderly care. Furthermore, few randomised controlled trials have evaluated patient-relevant outcomes as a primary endpoint. Therefore, we will evaluate whether a pharmacist-led intervention could reduce readmission of hospitalised elderly orthopaedic patients with polypharmacy or potentially inappropriate prescribing.

Methods and analysis: This is an ongoing single-centre, prospective, non-blinded, randomised controlled trial designed to evaluate the superiority of a pharmacist-led intervention for hospitalised elderly patients compared with usual care. The trial will include newly admitted orthopaedic patients 70 years of age and older with polypharmacy or at least one potentially inappropriate prescription, as identified by the 2015 STOPP criteria. Usual care includes medication reconciliation, patient education, and monitoring, as well as providing information about discharge medications. Pharmacist interventions, in addition to usual care, include advising the patient's physician to stop unnecessary or inappropriate medications and start necessary

medications. The primary outcome is the one-year readmission rate. Secondary outcomes are the proportion of patients who undergo emergency department visits and the occurrences of all-cause death, a new fracture, myocardial infarction, and ischaemic stroke. The study started in November 2017, and up to approximately 220 patients will be enrolled.

Ethics and dissemination: The protocol was approved by the Medical Ethics Committee of the National Hospital Organization Tochigi Medical Center (No. 29-22). The trial was registered at the UMIN clinical registry. The results of this trial will be submitted for publication in a peer-reviewed journal.

Trial registration number: UMIN000029404 (registered October 3, 2017).

Key words: Emergency, Orthopaedic ward, Pharmacist intervention, Polypharmacy, Potentially inappropriate prescribing

Strengths and limitations of this study

- This randomised controlled trial will evaluate the effectiveness of pharmacist interventions for hospitalised orthopaedic elderly patients, using patient-relevant outcomes as the primary outcomes.

- This is a single-centre study with a small sample size and short-term follow-up.
- Orthopaedic patients who are admitted electively or discharged within less than seven days after admission will be excluded.
- Orthopaedic patients who are prescribed fewer than five medications and are taking no potentially inappropriate medications at admission will be excluded.

INTRODUCTION

In recent decades, as the population has aged, polypharmacy and multi-morbidities have become more complicated problems among elderly patients.[1-3] Polypharmacy in elderly patients is associated with inappropriate prescribing[4] and adverse events, such as adverse drug events and death.[5] Because adverse drug events are a primary cause of preventable hospital admissions among elderly patients,[6] strategies to prevent drug-related events has been proposed in recent decades.[7-9] These strategies include deprescribing for polypharmacy[9] and reducing potentially inappropriate prescribing and potential prescription omissions.[7,8]

Polypharmacy and potentially inappropriate prescribing among elderly patients are particularly common in acute care settings compared with primary care settings.[10-12] Therefore, it is important to improve the appropriateness of medications used during hospitalisation. In fact, the American College of Emergency Physicians Geriatric Emergency Department Guidelines recommend a multidisciplinary team intervention for all elderly patients who present to the emergency department and are prescribed more than five medications or at least one potentially inappropriate medication, regardless of the presenting complaint.[13] Given that physicians are often unaware of adverse drug events,[14,15] the role of hospital pharmacists in improving

polypharmacy and potentially inappropriate prescribing in hospitalised elderly patients is important. Nonetheless, past studies have reported mixed results regarding the effectiveness of a pharmacist-led intervention in improving the appropriateness of medications in inpatient elderly care. Although pharmacist intervention can improve the appropriateness of medications in hospitalised elderly patients,[16] the conclusions of past systematic reviews and meta-analyses have been inconsistent regarding whether patient-relevant outcomes, such as mortality and readmission, were improved by these interventions.[17-20] One recent meta-analysis that included seven randomised controlled trials that evaluated the effectiveness of a pharmacist-led intervention in inpatient elderly care also reported little impact of pharmacist interventions on readmission rates.[21] However, most trials included in this meta-analysis were considered to have a high risk of bias. Furthermore, only two of the seven randomised controlled trials included in the meta-analysis evaluated patient-relevant outcomes as primary endpoints.[22,23] In one of those two trials, a comprehensive pharmacist intervention for hospitalised elderly patients with polypharmacy led to a significant reduction in hospital visits.[23] Therefore, it is still too early to conclude that pharmacist-led interventions for hospitalised elderly patients do not improve patient-relevant outcomes. Furthermore, most studies have targeted internal medicine

patients, while few studies have ever investigated the effectiveness of pharmacist interventions for elderly patients hospitalised in an orthopaedic ward.[21] The prevalence of polypharmacy and potentially inappropriate prescribing are particularly high in elderly orthopaedic patients, and these practices often continue after recovery from a fracture.[24,25] Furthermore, polypharmacy is associated with an increased risk of fall and fracture.[5,26] Therefore, pharmacist interventions for improving the appropriateness of medications in hospitalised elderly orthopaedic patients may be associated with better patient outcomes compared with other settings. Thus, we will conduct a randomised controlled trial to evaluate whether a pharmacist-led intervention reduces readmission in hospitalised elderly orthopaedic patients with polypharmacy or potentially inappropriate prescribing.

Objectives

Primary objective

Our primary objective is to determine whether pharmacist intervention for elderly orthopaedic patients with polypharmacy or potentially inappropriate prescribing at admission reduces one-year readmission rates compared with usual care. Based on a

past study,[23] we selected a readmission time frame of one year for the primary objective.

Secondary objectives

The key secondary objectives are to determine whether pharmacist intervention for elderly orthopaedic patients with polypharmacy or potentially inappropriate prescribing at admission reduces patient-relevant outcomes, such as all-cause death, myocardial infarction, ischaemic stroke, and any fractures, compared with usual care. Other secondary objectives are to determine whether pharmacist intervention for elderly orthopaedic patients with polypharmacy or potentially inappropriate prescribing at admission reduces the total number of medications, potentially inappropriate prescribing, and potential prescription omissions.

Literature search and review

We performed a literature search and review of pharmacist interventions in elderly hospitalised orthopaedic patients. We used the terms “pharmacist”, “polypharmacy”,

"medication review", and "inappropriate prescribing" alone and in combination to search the PubMed and Google Scholar databases until 5 August 2017 without limits for the year when the articles were published. We restricted our review to full-text articles published in English or Japanese. We also identified references from the relevant articles. We primarily selected randomised controlled trials, systematic reviews, and meta-analyses. We found a recent systematic review regarding the effectiveness of pharmacist-led intervention on patient outcomes in elderly hospitalised patients.[21] Based on this systematic review, we designed this trial.

METHODS AND ANALYSIS

Trial design

This study is a single-centre, prospective, non-blinded, randomised, controlled, superiority trial with two parallel groups. All participants who provide consent for participation and fulfil the inclusion criteria will be randomly assigned to the pharmacist intervention group or the usual care group with a 1:1 allocation. The study was approved by the Medical Ethics Committee of the National Hospital Organization Tochigi Medical Center (No. 29-22) and will be conducted in accordance with the Declaration of Helsinki. Standard Protocol Items: The Recommendations for

Interventional Trials (SPIRIT checklist)[27] was followed in designing the study protocol (supplementary appendix). Figure 1 summarises the design of the trial, and each of the trial aspects is described in detail below.

Study setting

This study will be conducted in the orthopaedic ward at the National Hospital Organization Tochigi Medical Center. Our hospital is a 350-bed acute care community hospital and is one of five main hospitals that serve approximately 0.5 million individuals in Utsunomiya in the Tochigi prefecture in Japan.

Eligibility criteria

Eligible patients are those who meet all the following inclusion criteria and who do not have any listed exclusion criteria. Based on the American College of Emergency Physicians Geriatric Emergency Department Guidelines,[11] the number of medications taken or the presence of potentially inappropriate prescribing at admission will be used as the inclusion criteria. However, the minimum number of medications for inclusion will be five, based on a past study showing that taking five or more medications was a

useful parameter for estimating medication-related adverse effects related to frailty, disability, and mortality among men aged 70 years and older.[28] As-needed medications will be not be counted.

Inclusion criteria

1. Age 70 years and older
2. Polypharmacy (defined as 5 or more medications) or at least one potentially inappropriate prescription (as defined by the 2015 STOPP criteria[8]) upon admission

Exclusion criteria

1. Elective admission
2. Inability to contact patient within 72 hours after their admission
3. Expected hospital stay duration of < one week

Study duration, enrolment and number of sites

The study will be conducted at a single hospital in Japan. The planned sample size is approximately 220 patients. This study began after November 2017. The planned

follow-up duration for each patient will be two years after the randomisation. Our investigation period is projected to be three years. However, unless we can recruit the planned number of patients within three years after beginning this study, we will extend the investigation duration to achieve the planned number of patients.

Screening and registration

All elderly patients who are hospitalised in an orthopaedic ward in our hospital will be screened for eligibility for the trial by one of three pharmacists (KS, ST, or MK) every weekday morning. Patients who are hospitalised on weekends will be screened on the following Monday morning. If the screened patients are not eligible, we will document the reason for ineligibility for the trial and the number of ineligible patients. All patients who fulfil the inclusion criteria and have no exclusion criteria will be registered by one of three pharmacists in the central data centre at the National Hospital Organization Tochigi Medical Center. Unless written informed consent is provided by the patients, we will document the reasons why the patients did not provide consent to participate in the trial and document the number of patients who declined to participate in the trial.

Randomisation and allocation concealment

All patients who provide consent for participation and who fulfil the inclusion criteria will be randomised. Randomisation will be requested by one of three pharmacists (KS, ST, or MK) to the independent randomisation centre at the National Hospital Organization Tochigi Medical Center via webmail. Participants will be randomly assigned to either the pharmacist intervention group or the usual care group. Randomisation will be performed as block randomisation with a 1:1 allocation. The computer-generated random allocation sequence will be provided by an independent staff pharmacist who is not involved in the treatment of patients or with the assessment of patient outcomes. The randomisation will not be stratified. The block sizes will be concealed until the primary outcome is analysed. Throughout the study, the randomisation list will also be concealed until the end of the study.

Blinding

Due to the nature of the intervention, neither the participants nor the clinical pharmacists can be blinded to the allocation. Patients will be informed of the group to which they have been randomly allocated. Assessments regarding the outcomes will be

conducted by an assessor who knows the treatment allocation. The analysis regarding the primary outcome will be conducted by independent investigators who are blinded to the treatment allocation and are not involved in the assessment of patient outcomes.

Pharmacist intervention group

Before starting the study, three study pharmacists (KS, ST, and MK) were trained during a three-month period from May 2017 to July 2017. To standardise the intervention by these pharmacists, approximately 16 sessions (one hour per session) regarding medication use in elderly patients based on the 2015 STOPP/START criteria[8] were provided by one internal medicine physician (JK). Therefore, these pharmacists will perform the interventions by following the 2015 STOPP/START criteria. However, the use of these criteria for the pharmacist intervention will not be mandatory because some 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.[29] One of these trained pharmacists (KS, ST, or MK) will treat the participants from admission to discharge at the following three stages.

Intervention at admission

A comprehensive list of current medications will be compiled within 72 hours after admission. A drug review will be performed, and advice regarding the following factors will be provided to one of five orthopaedic physicians who care for patients: (1) deprescribing inappropriate or unnecessary medications, (2) starting effective or necessary medications, and (3) modifying medication dosages. However, the final decision to adhere to the advice provided by pharmacists will be determined by the orthopaedic physician in charge. Pharmacists will document whether the orthopaedic physicians follow their advice. If the orthopaedic physicians accept the advice but defer action to the primary care physicians, pharmacists will send the discharge summary including their advice to the primary care physicians.

Intervention during hospitalisation

During the hospital stay, patients will be educated about the harms and benefits of their medications. Pharmacists will also provide information about the rationale for medication use and therapeutic goals. Patients will be monitored after starting or stopping medications.

Intervention at discharge

Information about discharge medications (e.g., rationale for changes and monitoring needs for newly started or stopped medications) will be summarised in a written document by the pharmacists. Patients will receive discharge counselling with this summary. The summary will also be sent to the primary care physicians and community pharmacists.

Usual care group

Usual care typically includes the same elements as those received by the intervention group but is less extensive. In the usual care group, a comprehensive list of current medications will be compiled by the pharmacists (KS, ST, or MK) within 72 hours after

admission. Patients will be monitored and educated about newly started medications by their physician and will receive discharge counselling. However, unlike in the intervention group, advice from pharmacists about deprescribing and starting medications will not be provided to the patient's physician, except in cases of apparent harmful effects of medications that are judged to be symptomatic by pharmacists. Furthermore, pharmacists will neither prepare the summary about discharge medications nor send it to the primary care physicians and community pharmacists. However, at the discretion of the pharmacist providing advice about medications for the physicians, the summary about discharge medications will be prepared. These procedures are the standard practice for pharmacists in most Japanese hospitals.[30]

Data collection

One of the pharmacists (ST, KS, or MK) will collect the demographic and baseline medical information from the patients and/or their caregivers at admission and summarise this information on a patient registration form. Participants will be followed and assessed for two years after study entry (Table 1). One of the pharmacists (ST, KS, or MK) will assess outcomes at discharge. We will survey the participants or their

caregivers regarding information about primary and secondary outcomes by sending letters at 6 months, 12 months, and 24 months after randomisation. If the participants do not respond to the survey appropriately, we will contact them or their caregivers by telephone to minimise the effect of missing data on study outcomes. Furthermore, to collect more accurate data, we will also use data from electronic medical records of our hospital if the participants are admitted or visit our hospital regularly during the study period.

Outcomes

Primary outcome

The primary outcome is the readmission rate within one year after randomisation. The readmission rate is defined as the proportion of participants who are readmitted. Readmission includes both planned and unplanned admissions. We will evaluate the difference in the readmission rate within one year after randomisation between the two treatment groups.

Secondary outcomes

The secondary outcomes are readmission rates within 6 and 24 months after randomisation. We will evaluate the differences in the readmission rates at 6 and 24 months between the two treatment groups. The other secondary outcomes are provided below. These outcomes will be evaluated at discharge and at 6 months, 12 months and 24 months after randomisation. We will evaluate the differences between the two treatment groups regarding these outcomes at discharge, 6 months, 12 months and 24 months.

- Any-cause death
- Total number of medications
- Potentially inappropriate prescribing based on the 2015 STOPP criteria[8]
- Potential prescribing omission based on the 2015 START criteria[8]
- Any fractures
- Ischaemic stroke
- Myocardial infarction
- Emergency department visits

Statistical analysis

Sample size calculation

We estimated that a sample of 200 patients would provide the study with a power of at least 80% to show a relative risk reduction of 33% for the primary outcome in the intervention group compared with the usual care group (at a two-sided alpha level of 0.05), assuming that the proportion of patients who are readmitted within one year is 60% in the usual care group (based on a previous study[23]). Assuming that the dropout rate is 10%, we would need to enrol approximately 220 patients.

Statistical analysis

The baseline characteristics of the study population will be summarised using descriptive statistics. The intervention group will be compared against the usual group for all primary and secondary outcomes (Table 2). We will use a chi-squared test for binary outcomes and Student's t-test for continuous outcomes. We will calculate the relative risk and number needed to treat with corresponding 95% confidence intervals to compare dichotomous variables, and the difference in the means will be used for an

additional analysis of continuous variables. For all tests, we will use 2-sided p-values with an alpha < 0.05 for the level of significance.

Analyses for all outcomes will include all patients who have undergone randomisation and have provided valid informed consent (intention-to-treat population). Regarding the procedure for missing data, we will exclude the data from participants who are lost to follow-up or whose outcomes are missing. These analyses will be performed using IBM SPSS Statistics Base version 21.0 (IBM Corporation, Nihonbashi, Tokyo, Japan) or Excel statistical software package version 2.11 (Bellcurve for Excel; Social Survey Research Information Co., Ltd., Tokyo, Japan). All analyses will be conducted by investigators who are blinded to the study group allocations.

Data management

The trial data of the study participants will be transmitted to and stored in the research database at National Hospital Organization Tochigi Medical Center. This data will not include the participants' identifying information. Instead, individual participants and research data will be identified by unique study identification numbers. At the end of the study, the data will be locked. The data will be stored for at least five years after study completion. Access to the stored data will be limited to investigators. The data

will be stored using codes assigned by the investigators and kept on password-protected computers.

Monitoring

Data monitoring

The risk associated with participation in this study is low, because our aim is to improve the quality of medications in patients. According to the Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects (as of March 2015), our intervention corresponds with a non-invasive procedure. Therefore, we will not need a data monitoring committee. However, an independent staff pharmacist who is not involved with the trial intervention will monitor the data periodically to ensure safety.

Adverse events

In our study, an adverse event will be defined as any undesirable medical occurrence in a participant without regard to the possibility of a causal relationship. Data on adverse events will be collected after the participants have provided consent and enrolled in the study. If a participant experiences an adverse event after the informed consent document

is signed and the participant has not yet started to receive the study intervention, the event will be reported as not being related to the study intervention. All adverse events that occur after entry into the study and for two years after randomisation will be recorded. A serious adverse event for this study is any undesirable medical occurrence that is believed by the investigators to be causally related to the study intervention and results in any of the following: a life-threatening condition (that is, immediate risk of death) or severe or permanent disability.

Auditing

According to the Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects (as of March 2015), our intervention corresponds with a non-invasive procedure. Furthermore, past studies investigating the effectiveness of a pharmacist intervention have reported few adverse events.[16-23] Therefore, we will not need auditing.

Ethics and dissemination

This study protocol was approved by the Medical Ethics Committee of the National Hospital Organization Tochigi Medical Center (Tochigi, Japan). They judged the study design, ethics, and safety. Substantial amendments to the study protocol must be approved by the Medical Ethics Committee of the National Hospital Organization Tochigi Medical Center. The trial was registered at the UMIN clinical registry on October 3, 2017. We will obtain informed consent from the trial participants or their authorised surrogates according to the Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects (as of March 2015). One of three pharmacists (ST, KS, or MK) will introduce the trial to patients and discuss the trial with all patients using the information sheets about the nature, purpose, and possible risks and benefits of the trial, which was approved by the Medical Ethics Committee of the National Hospital Organization Tochigi Medical Center. Then, the pharmacists will obtain written informed consent from patients willing to participate in the trial. To assure confidentiality, trial participants will be allocated a unique trial identification number throughout the trial. A manuscript with the results of this study will be published in a peer-reviewed journal.

Patient involvement

No patients were involved in determining the research question or outcome measures nor were they involved in developing plans to design or implement the study. No patients were involved in evaluating the burden of the intervention. There are no plans to disseminate the results of this research to study participants or the relevant patient community.

DISCUSSION

Given that polypharmacy and potentially inappropriate prescribing among elderly patients is common in acute care settings,[10] it is important to improve the appropriateness of medications during hospitalisation. Therefore, the role of hospital pharmacists in improving polypharmacy and potentially inappropriate prescribing in hospitalised elderly patients is important. Nonetheless, there are conflicting results regarding the effectiveness with which pharmacist interventions in elderly inpatient care can improve polypharmacy and potentially inappropriate prescribing to affect patient-relevant outcomes.[17-21] Given that few past randomised controlled trials have evaluated a patient-relevant outcome as a primary endpoint,[22,23] it is important to conduct a randomised controlled trial to evaluate whether a pharmacist-led intervention

improves patient-relevant outcomes, such as readmission and death, in hospitalised elderly orthopaedic patients with polypharmacy or potentially inappropriate prescribing.

There are several limitations to this study. First, the non-blinded study design may overestimate the effectiveness of pharmacist intervention.[31] However, due to the nature of the intervention, it is difficult for both participants and clinical pharmacists to be blinded to the allocation. Second, this study is a single-centre trial. Although most past randomised controlled trials were also single-centre trials,[21,23,32-35] the external validity of this study is limited. Therefore, an additional randomised controlled trial may be needed. Third, we will exclude elderly orthopaedic patients who are admitted electively or who are taking less than five prescribed medications or have no potentially inappropriate prescriptions. Furthermore, elderly patients admitted to other specialty wards, such as internal medicine or general surgery, will also be excluded. Therefore, it is unclear whether the findings of this trial will be applicable to elderly patients who are admitted electively or to other wards besides the orthopaedic ward. Fourth, medication reconciliation is included in the usual care group in this study. The possible beneficial effect of medical reconciliation for hospitalised patients[36] may mitigate the effectiveness of the pharmacist intervention in this study. Finally, we will not assess the cost-effectiveness of the intervention.

Although these limitations are important, this study is one of a few randomised controlled trials to investigate the effectiveness of a pharmacist-led intervention and use a patient-relevant outcome as the primary outcome for hospitalised elderly patients. Given that the burdens of polypharmacy and multi-morbidities among elderly patients have increased in recent years, this trial will provide important information on improving the acute care of elderly patients with polypharmacy or potentially inappropriate prescribing.

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Contributors: KS and JK conceived the project. JK performed the literature search and review. KS, JK, ST, and MK designed the study. KS and JK wrote the draft of the protocol for the study. All authors contributed equally to writing the original protocol for this study. KS is the chief investigator of this study. JK wrote the draft of this manuscript. All authors provided final approval for submission of this manuscript for publication consideration.

Competing interests: All authors have completed the ICMJE unified disclosure from competing interest form at www.icmje.org/coi_disclosure.pdf (available upon request from the corresponding author). All authors declare that they have no conflicts of interest.

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Ethical approval: This study was approved by the Medical Ethics Committee of the National Hospital Organization Tochigi Medical Center (No. 29-22).

REFERENCES

1 Wolff JL, Starfield B, Anderson G. Prevalence, expenditures, and complications of multiple chronic conditions in the elderly. *Arch Intern Med* 2002;162:2269-76. doi:10.1001/archinte.162.20.2269.

2 Kaufman DW, Kelly JP, Rosenberg L et al. Recent patterns of medication use in the ambulatory adult population of the United States: The Slone survey. *JAMA*

2002;287:337-44. doi:10.1001/jama.287.3.337.

3 Boyd CM, Dare J, Boult C, et al. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases. *JAMA* 2005;294:716-24. doi:10.1001/jama.294.6.716.

4 Steinman MA, Landefeld CS, Rosenthal GE, et al. Polypharmacy and prescribing quality in older people. *J Am Geriatr Soc* 2006;54:1516-23. doi:10.1111/j.1532-5415.2006.00889.x.

5 Fried TR, O'Leary J, Towle V, et al. Health outcomes associated with polypharmacy in community-dwelling older adults: a systematic review. *J Am Geriatr Soc* 2014;62:2261-72. doi:10.1111/jgs.13153.

6 Beijer HJ, de Blaey CJ. Hospitalisations caused by adverse drug reactions (ADR): a meta-analysis of observational studies. *Pharm World Sci* 2002;24:46-54. doi:10.1023/A:1015570104121.

7 The American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 updated Beers Criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc* 2015;63:2227-46. doi:10.1111/jgs.13702.

8 O'Mahony D, O'Sullivan D, Byrne S, et al. STOPP/START criteria for potentially

inappropriate prescribing in older people: version 2. *Age Ageing* 2015;44:213-8. doi:10.1093/ageing/aful145.

9 Scott IA, Hilmer SN, Reeve E, et al. Reducing inappropriate polypharmacy: the process of deprescribing. *JAMA Intern Med* 2015;175(5):827-34. doi:10.1001/jamainternmed.2015.0324.

10 Gallagher P, Lang PO, Cherubini A, et al. Prevalence of potentially inappropriate prescribing in an acutely ill population of older patients admitted to six European hospitals. *Eur J Clin Pharmacol* 2011;67:1175-88. doi:10.1007/s00228-011-1061-0.

11 Tommelein E, Mehuys E, Petrovic M, et al. Potentially inappropriate prescribing in community-dwelling older people across Europe: a systematic literature review. *Eur J Clin Pharmacol* 2015;71(12):1415-27. doi:10.1007/s00228-015-1954-4.

12 Opondo D, Eslami S, Visscher S, et al. Inappropriateness of medication prescriptions to elderly patients in the primary care setting: a systematic review. *PLoS ONE* 2012;7(8):e43617. doi:10.1371/journal.pone.0043617.

13 The American College of Emergency Physicians, the American Geriatrics Society, Emergency Nurses Association and the Society for Academic Emergency Medicine. Geriatric emergency department guidelines. *Ann Emerg Med* 2014;63:e7-e25. doi: 10.1016/j.annemergmed.2014.02.008.

14 Hohl CM, Zed PJ, Brubacher JR, et al. Do emergency physicians attribute drug-related emergency department visits to medication-related problems? *Ann Emerg Med* 2010;55:493-502. doi:10.1016/j.annemergmed.2009.10.008.

15 Gandhi TK, Weingart SN, Borus J, et al. Adverse drug events in ambulatory care. *New Engl J Med* 2003;348:1556-64. doi:10.1056/NEJMsa020703

16 Walsh KA, O'Riordan D, Kearney PM, et al. Improving the appropriateness of prescribing in older patients: a systematic review and meta-analysis of pharmacists' interventions in secondary care. *Age Ageing* 2016;45:201-9. doi:10.1093/ageing/afv190.

17 Kaboli PJ, Hoth AB, McClimon BJ, et al. Clinical pharmacists and inpatient medical care: a systematic review. *Arch Intern Med* 2006;166:955-64. doi:10.1001/archinte.166.9.955.

18 Holland R, Desborough J, Goodyer L, et al. Does pharmacist-led medication review help to reduce hospital admissions and deaths in older people? A systematic review and meta-analysis. *Br J Clin Pharmacol* 2007;65(3):303-16. doi:10.111/j.1365-2125.2007.03071.x.

19 Koshman SL, CHarrois TL, Simpson SH, et al. Pharmacist care of patients with heart failure: a systematic review of randomized trials. *Arch Intern Med* 2008;168(7):687-94. doi:10.1001/archinte.168.7.687.

20 Renaudin P, Boyer L, Esteve MA, et al. Do pharmacist-led medication reviews in hospitals help reduce hospital readmissions? A systematic review and meta-analysis. *Br J Clin Pharm* 2016;82:1660-73. doi:10.111/bcp.13085.

21 Thomas R, Huntley AL, Mann M, et al. Pharmacist-led interventions to reduce unplanned admissions for older people: a systematic review and meta-analysis of randamised controlled trials. *Age Ageing* 2014;43:174-87. doi:10.1093/ageing/aft169.

22 Nazareth I, Burton A, Shulman S, et al. A pharmacy discharge plan for hospitalized elderly patients: a randomized controlled trial. *Age Ageing* 2001;30:33-40. doi:10.1093/ageing/30.1.33.

23 Gillespie U, Alassaad A, Henrohn D, et al. A comprehensive pharmacist intervention to reduce morbidity in patients 80 years or older: a randomized controlled trial. *Arch Intern Med* 2009;169(9):894-900. doi:10.1001/archinternmed.2009.71.

24 McMahon CG, Cahir CA, Kenny RA, et al. Inappropriate prescribing in older fallers presenting to an Irish emergency department. *Age Ageing* 2014;43:44-50. doi:10.1093/ageing/aft114.

25 Kragh A, Elmståhl S, Atroshi I. Older adults' medication use 6 months before and after hip fracture: A population-based cohort study. *J Am Geriatr Soc* 2011;59:863-8. doi:10.1111/j.1532-5415.2011.03372.x.

26 Lai SW, Liao KF, Liao CC, et al. Polypharmacy correlates with increased risk for hip fracture in the elderly. A population-based study. *Medicine* 2010;89:295-9. doi:10.1097/MD.0b013e3181fl5efc.

27 Chan AW, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586. doi:10.1136/bmj.e7586.

28 Gnjidic D, Hilmer SN, Blyth FM, et al. Polypharmacy cutoff and outcomes: five or more medicines were used to identify community-dwelling older men at risk of different adverse outcomes. *J Clin Epidemiol* 2012;65:989-95. doi:10.1016/j.jclinepi.2012.02.018.

29 Hosomi N, Nagai Y, Kohriyama T, et al. The Japan Statin Treatment Against Recurrent Stroke (J-STARS): a multicenter, randomized, open-label, parallel-group study. *EBioMedicine* 2015;2(9):1071-8. doi:10.1016/j.ebiom.2015.08.006.

30 Nakagawa S, Kume N. Pharmacy practice in Japan. *Can J Hosp Pharm* 2017;70(3):232-42. doi:10.4212/cjhp.v70i3.1663.

31 Wood L, Egger M, Gluud LL, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *BMJ* 2008;336(7644):601-5. doi:10.1136/bmj.39465.451748.AD.

32 Lisby M, Thomsen A, Nielsen LP, et al. The effect of systematic review in elderly patients admitted to an acute ward of internal medicine. *Basic Clin Pharmacol Toxicol* 2010;106(5):422-7. doi:10.1111/j.1742-7843.2009.00511.x.

33 McMullin ST, Hennenfent JA, Ritchie DJ, et al. A prospective, randomized trial to assess the cost impact of pharmacist-initiated interventions. *Arch Intern Med* 1999;159(19):2306-9. doi:10.1001/archinte.159.19.2306.

34 Spinewine A, Swine C, Dhillon S, et al. Effect of a collaborative approach on the quality of prescribing for geriatric inpatients: a randomized, controlled trial. *J Am Geriatr Soc* 2007;55(5):658-65. doi:10.1111/j.1532-5415.2007.01132.x.

35 Lipton HL, Bird JA. The impact of clinical pharmacists' consultations on geriatric patients' compliance and medical care use: a randomized controlled trial. *Gerontologist* 1994;34(3):307-15. doi:10.1093/geront/34.3.307.

36 Mekonnen AB, McLachlan AJ, Brien JE. Effectiveness of pharmacist-led medication reconciliation programmes on clinical outcomes at hospital transitions: a systematic review and meta-analysis. *BMJ Open* 2016;6:e010003. doi:10.1136/bmjopen-2015-010003.

584 **Table 1.** Time schedule of participant enrolment, interventions, and assessments.

	STUDY PERIOD					
	Enrolment	Allocation	Post-allocation			
TIMEPOINT*	$-t_1$	0	t_1	t_2	t_3	t_4
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Allocation		X				
INTERVENTIONS:						
Pharmacist intervention		⟺				
Usual care (control)		⟺				
ASSESSMENTS:						
Number of medications	X		X	X	X	X
Number of PIP†	X		X	X	X	X
Number of PPO†	X		X	X	X	X
Adverse drug events			X			
Discharge destination			X			
Duration of hospital stay			X			
All-cause death			X	X	X	X
Readmission				X	X	X
ED visit				X	X	X

Myocardial infarction			X	X	X	X
Ischaemic stroke			X	X	X	X
Fracture			X	X	X	X

*t_1, within 72 hours after admission; t_1, at discharge; t_2, six months after randomisation; t_3, 12 months after randomisation; t_4, 24 months after randomisation.

†PIP and PPO are defined based on the 2015 STOPP/START Criteria.

ED, emergency department; PIP, potentially inappropriate prescribing; PPO, potential prescribing omission.

Table 2. Variables, measures, and analysis methods.

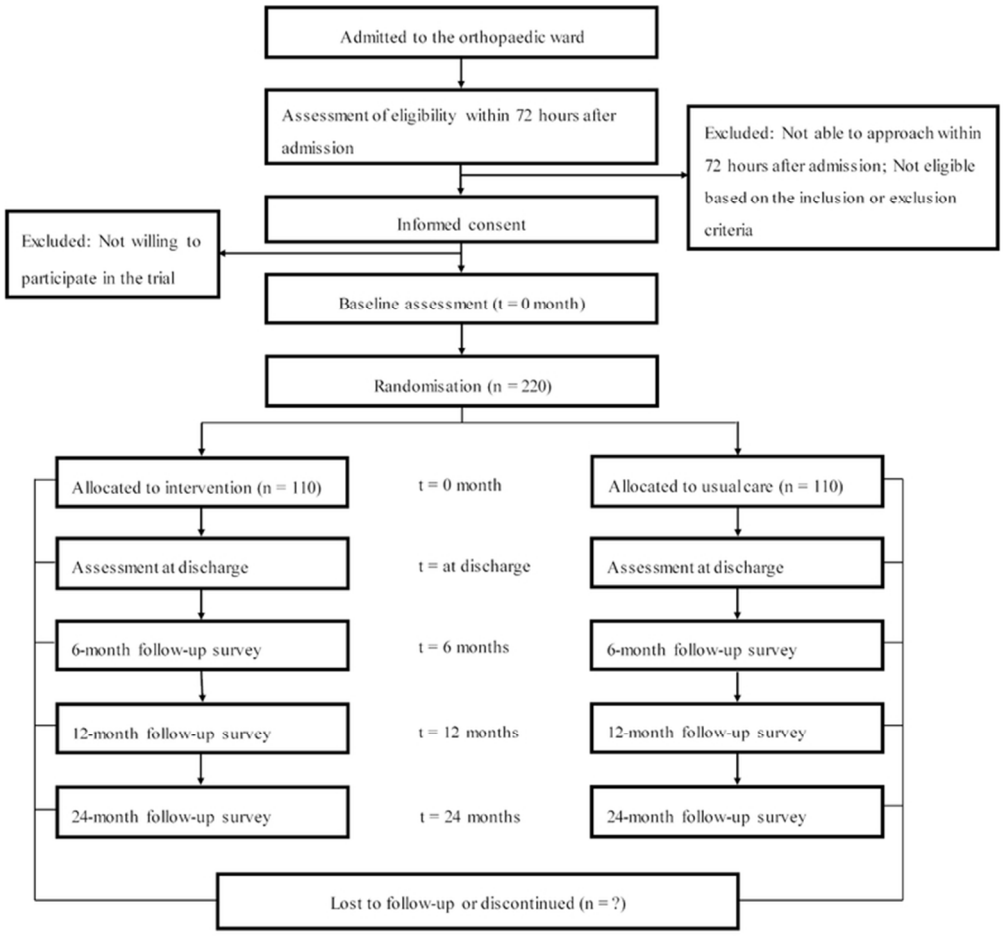
Variable/outcome	Hypothesis	Measured outcomes	Methods of analysis
Primary			
Readmission* at 12 months	Improvement occurred	Readmission rate % [binary]	Chi-squared test
Secondary			
Number of medications at discharge and at 6, 12, and 24 months	Decline occurred	Total number of medications [continuous]	T-test
PIP† at discharge and at 6, 12, and 24 months	Decline occurred	Total number of PIP [continuous]	T-test
	Improvement occurred	Proportion of patients who take any PIP % [binary]	Chi-squared test
PPO† at discharge and at 6, 12, and 24 months	Decline occurred	Total number of PPO [continuous]	T-test
	Improvement occurred	Proportion of patients who take any PPO % [binary]	Chi-squared test
Readmission* at 6 and 24 months	Improvement occurred	Readmission rate % [binary]	Chi-squared test
ED visit at 6, 12, and 24 months	Improvement occurred	Proportion of patients who visit ED % [binary]	Chi-squared test
All-cause death at 6, 12, and 24 months	Improvement occurred	All-cause mortality % [binary]	Chi-squared test
Acute myocardial infarction at 6, 12, and 24 months	Improvement occurred	Proportion of patients whom acute myocardial infarction occurred % [binary]	Chi-squared test
Acute ischaemic stroke at 6, 12, and 24 months	Improvement occurred	Proportion of patients whom acute ischaemic stroke occurred % [binary]	Chi-squared test
Any fractures at 6, 12, and 24 months	Improvement occurred	Proportion of patients whom any fractures occurred % [binary]	Chi-squared test

*Includes both planned and unplanned hospitalisation.

†PIP and PPO are defined based on the 2015 STOPP/START Criteria.

ED, emergency department; PIP, potentially inappropriate prescribing; PPO, potential prescribing omission.

Figure 1. Flow diagram of the participant.



Flow diagram of the participant.

67x64mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page Number on which item is reported
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	4
Protocol version	3	Date and version identifier	NA
Funding	4	Sources and types of financial, material, and other support	29
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	28
	5b	Name and contact information for the trial sponsor	NA
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	NA
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6-9
	6b	Explanation for choice of comparators	17
Objectives	7	Specific objectives or hypotheses	8-9
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	10
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	11
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	11-12
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	15-17
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	15-17
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	15-18
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	19-20

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	18-19, Figure 1, Table 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12, 21
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	12-13
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	14
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	14
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	14
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	14-15
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	18-19
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	19
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	22-23
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	21-22, Table 2
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	21-22, Table 2
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	22
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	23
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	23-24
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	24
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	25
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	25
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	25
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	25
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	29
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	22
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	25

	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary file
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

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

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Primary Subject Heading:	Geriatric medicine
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Keywords:	CLINICAL PHARMACOLOGY, ORTHOPAEDIC & TRAUMA SURGERY, GERIATRIC MEDICINE

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

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Running title: Pharmacist interventions

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ABSTRACT

Introduction: Given that polypharmacy and potentially inappropriate prescribing are common in elderly orthopaedic patients, pharmacist interventions to improve medication practices among this population are important. However, past studies have reported mixed results regarding the effectiveness of pharmacist-led interventions in inpatient elderly care. Furthermore, few randomised controlled trials have evaluated patient-relevant outcomes as a primary endpoint. Therefore, we will evaluate whether a pharmacist-led intervention could reduce readmission of hospitalised elderly orthopaedic patients with polypharmacy or potentially inappropriate prescribing.

Methods and analysis: This is an ongoing single-centre, prospective, non-blinded, randomised controlled trial designed to evaluate the superiority of a pharmacist-led intervention for hospitalised elderly patients compared with usual care. The trial will include newly admitted orthopaedic patients 70 years of age and older with polypharmacy or at least one potentially inappropriate prescription, as identified by the 2015 STOPP criteria. Usual care includes medication reconciliation, patient education, and monitoring, as well as providing information about discharge medications. Pharmacist interventions, in addition to usual care, include advising the patient's physician to stop unnecessary or inappropriate medications and start necessary

medications. The primary outcome is the one-year readmission rate. Secondary outcomes are the proportion of patients who undergo emergency department visits and the occurrences of all-cause death, a new fracture, myocardial infarction, and ischaemic stroke. The study started in November 2017, and up to approximately 220 patients will be enrolled.

Ethics and dissemination: The protocol was approved by the Medical Ethics Committee of the National Hospital Organization Tochigi Medical Center (No. 29-22). The trial was registered at the UMIN clinical registry. The results of this trial will be submitted for publication in a peer-reviewed journal.

Trial registration number: UMIN000029404 (registered October 3, 2017).

Key words: Emergency, Orthopaedic ward, Pharmacist intervention, Polypharmacy, Potentially inappropriate prescribing

Strengths and limitations of this study

- This randomised controlled trial will evaluate the effectiveness of pharmacist interventions for hospitalised orthopaedic elderly patients, using patient-relevant outcomes as the primary outcomes.

- This is a single-centre study with a small sample size and short-term follow-up.
- Orthopaedic patients who are admitted electively or discharged within less than seven days after admission will be excluded.
- Orthopaedic patients who are prescribed fewer than five medications and are taking no potentially inappropriate medications at admission will be excluded.

INTRODUCTION

In recent decades, as the population has aged, polypharmacy and multi-morbidities have become more complicated problems among elderly patients.[1-3] Polypharmacy in elderly patients is associated with inappropriate prescribing[4] and adverse events, such as adverse drug events and death.[5] Because adverse drug events are a primary cause of preventable hospital admissions among elderly patients,[6] strategies to prevent drug-related events has been proposed in recent decades.[7-9] These strategies include deprescribing for polypharmacy[9] and reducing potentially inappropriate prescribing and potential prescription omissions.[7,8]

Polypharmacy and potentially inappropriate prescribing among elderly patients are particularly common in acute care settings compared with primary care settings.[10-12] Therefore, it is important to improve the appropriateness of medications used during hospitalisation. In fact, the American College of Emergency Physicians Geriatric Emergency Department Guidelines recommend a multidisciplinary team intervention for all elderly patients who present to the emergency department and are prescribed more than five medications or at least one potentially inappropriate medication, regardless of the presenting complaint.[13] Given that physicians are often unaware of adverse drug events,[14,15] the role of hospital pharmacists in improving

polypharmacy and potentially inappropriate prescribing in hospitalised elderly patients is important. Nonetheless, past studies have reported mixed results regarding the effectiveness of a pharmacist-led intervention in improving the appropriateness of medications in inpatient elderly care. Although pharmacist intervention can improve the appropriateness of medications in hospitalised elderly patients,[16] the conclusions of past systematic reviews and meta-analyses have been inconsistent regarding whether patient-relevant outcomes, such as mortality and readmission, were improved by these interventions.[17-20] One recent meta-analysis that included seven randomised controlled trials that evaluated the effectiveness of a pharmacist-led intervention in inpatient elderly care also reported little impact of pharmacist interventions on readmission rates.[21] However, most trials included in this meta-analysis were considered to have a high risk of bias. Furthermore, only two of the seven randomised controlled trials included in the meta-analysis evaluated patient-relevant outcomes as primary endpoints.[22,23] In one of those two trials, a comprehensive pharmacist intervention for hospitalised elderly patients with polypharmacy led to a significant reduction in hospital visits.[23] Therefore, it is still too early to conclude that pharmacist-led interventions for hospitalised elderly patients do not improve patient-relevant outcomes. Furthermore, most studies have targeted internal medicine

patients, while few studies have ever investigated the effectiveness of pharmacist interventions for elderly patients hospitalised in an orthopaedic ward.[21] The prevalence of polypharmacy and potentially inappropriate prescribing are particularly high in elderly orthopaedic patients, and these practices often continue after recovery from a fracture.[24,25] Furthermore, polypharmacy is associated with an increased risk of fall and fracture.[5,26] Therefore, pharmacist interventions for improving the appropriateness of medications in hospitalised elderly orthopaedic patients may be associated with better patient outcomes compared with other settings. Thus, we will conduct a randomised controlled trial to evaluate whether a pharmacist-led intervention reduces readmission in hospitalised elderly orthopaedic patients with polypharmacy or potentially inappropriate prescribing.

Objectives

Primary objective

Our primary objective is to determine whether pharmacist intervention for elderly orthopaedic patients with polypharmacy or potentially inappropriate prescribing at admission reduces one-year readmission rates compared with usual care. Based on a

past study,[23] we selected a readmission time frame of one year for the primary objective.

Secondary objectives

The key secondary objectives are to determine whether pharmacist intervention for elderly orthopaedic patients with polypharmacy or potentially inappropriate prescribing at admission reduces patient-relevant outcomes, such as all-cause death, myocardial infarction, ischaemic stroke, and any fractures, compared with usual care. Other secondary objectives are to determine whether pharmacist intervention for elderly orthopaedic patients with polypharmacy or potentially inappropriate prescribing at admission reduces the total number of medications, potentially inappropriate prescribing, and potential prescription omissions.

Literature search and review

We performed a literature search and review of pharmacist interventions in elderly hospitalised orthopaedic patients. We used the terms “pharmacist”, “polypharmacy”,

"medication review", and "inappropriate prescribing" alone and in combination to search the PubMed and Google Scholar databases until 5 August 2017 without limits for the year when the articles were published. We restricted our review to full-text articles published in English or Japanese. We also identified references from the relevant articles. We primarily selected randomised controlled trials, systematic reviews, and meta-analyses. We found a recent systematic review regarding the effectiveness of pharmacist-led intervention on patient outcomes in elderly hospitalised patients.[21] Based on this systematic review, we designed this trial.

METHODS AND ANALYSIS

Trial design

This study is a single-centre, prospective, non-blinded, randomised, controlled, superiority trial with two parallel groups. All participants who provide consent for participation and fulfil the inclusion criteria will be randomly assigned to the pharmacist intervention group or the usual care group with a 1:1 allocation. The study was approved by the Medical Ethics Committee of the National Hospital Organization Tochigi Medical Center (No. 29-22) and will be conducted in accordance with the Declaration of Helsinki. Standard Protocol Items: The Recommendations for

Interventional Trials (SPIRIT checklist)[27] was followed in designing the study protocol (supplementary appendix). Figure 1 summarises the design of the trial, and each of the trial aspects is described in detail below.

Study setting

This study will be conducted in the orthopaedic ward at the National Hospital Organization Tochigi Medical Center. Our hospital is a 350-bed acute care community hospital and is one of five main hospitals that serve approximately 0.5 million individuals in Utsunomiya in the Tochigi prefecture in Japan.

Eligibility criteria

Eligible patients are those who meet all the following inclusion criteria and who do not have any listed exclusion criteria. Based on the American College of Emergency Physicians Geriatric Emergency Department Guidelines,[11] the number of medications taken or the presence of potentially inappropriate prescribing at admission will be used as the inclusion criteria. However, the minimum number of medications for inclusion will be five, based on a past study showing that taking five or more medications was a

useful parameter for estimating medication-related adverse effects related to frailty, disability, and mortality among men aged 70 years and older.[28] As-needed medications will be not be considered in the medication count.

Inclusion criteria

1. Age 70 years and older
2. Polypharmacy (defined as 5 or more medications) or at least one potentially inappropriate prescription (as defined by the 2015 STOPP criteria[8]) upon admission

Exclusion criteria

1. Elective admission
2. Inability to contact patient within 72 hours after their admission
3. Expected hospital stay duration of < one week

Study duration, enrolment and number of sites

The study will be conducted at a single hospital in Japan. The planned sample size is approximately 220 patients. This study began after November 2017. The planned

follow-up duration for each patient will be two years after the randomisation. Our investigation period is projected to be three years. However, unless we can recruit the planned number of patients within three years after beginning this study, we will extend the investigation duration to achieve the planned number of patients.

Screening and registration

All elderly patients who are hospitalised in an orthopaedic ward in our hospital will be screened for eligibility for the trial by one of three pharmacists (KS, ST, or MK) every weekday morning. Patients who are hospitalised on weekends will be screened on the following Monday morning. If the screened patients are not eligible, we will document the reason for ineligibility for the trial and the number of ineligible patients. All patients who fulfil the inclusion criteria and have no exclusion criteria will be registered by one of three pharmacists in the central data centre at the National Hospital Organization Tochigi Medical Center. Unless written informed consent is provided by the patients, we will document the reasons why the patients did not provide consent to participate in the trial and document the number of patients who declined to participate in the trial.

Randomisation and allocation concealment

All patients who provide consent for participation and who fulfil the inclusion criteria will be randomised. Randomisation will be requested by one of three pharmacists (KS, ST, or MK) to the independent randomisation centre at the National Hospital Organization Tochigi Medical Center via webmail. Participants will be randomly assigned to either the pharmacist intervention group or the usual care group. Randomisation will be performed as block randomisation with a 1:1 allocation. The computer-generated random allocation sequence will be provided by an independent staff pharmacist who is not involved in the treatment of patients or with the assessment of patient outcomes. The randomisation will not be stratified. The block sizes will be concealed until the primary outcome is analysed. Throughout the study, the randomisation list will also be concealed until the end of the study.

Blinding

Due to the nature of the intervention, neither the participants nor the clinical pharmacists can be blinded to the allocation. Patients will be informed of the group to which they have been randomly allocated. Assessments regarding the outcomes will be

conducted by an assessor who knows the treatment allocation. The analysis regarding the primary outcome will be conducted by independent investigators who are blinded to the treatment allocation and are not involved in the assessment of patient outcomes.

Pharmacist intervention group

Before starting the study, three study pharmacists (KS, ST, and MK) were trained during a three-month period from May 2017 to July 2017. To standardise the intervention by these pharmacists, approximately 16 sessions (one hour per session) regarding medication use in elderly patients based on the 2015 STOPP/START criteria[8] were provided by one internal medicine physician (JK). Therefore, these pharmacists will perform the interventions by following the 2015 STOPP/START criteria. However, the use of these criteria for the pharmacist intervention will not be mandatory because some 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.[29] One of these trained pharmacists (KS, ST, or MK) will treat the participants from admission to discharge at the following three stages.

Intervention at admission

A comprehensive list of current medications will be compiled within 72 hours after admission. A drug review will be performed, and advice regarding the following factors will be provided to one of five orthopaedic physicians who care for patients: (1) deprescribing inappropriate or unnecessary medications, (2) starting effective or necessary medications, and (3) modifying medication dosages. However, the final decision to adhere to the advice provided by pharmacists will be determined by the orthopaedic physician in charge. Pharmacists will document whether the orthopaedic physicians follow their advice. If the orthopaedic physicians accept the advice but defer action to the primary care physicians, pharmacists will send the discharge summary including their advice to the primary care physicians.

Intervention during hospitalisation

During the hospital stay, patients will be educated about the harms and benefits of their medications. Pharmacists will also provide information about the rationale for medication use and therapeutic goals. Patients will be monitored after starting or stopping medications.

Intervention at discharge

Information about discharge medications (e.g., rationale for changes and monitoring needs for newly started or stopped medications) will be summarised in a written document by the pharmacists. Patients will receive discharge counselling with this summary. The summary will also be sent to the primary care physicians and community pharmacists.

Usual care group

Usual care typically includes the same elements as those received by the intervention group but is less extensive. In the usual care group, a comprehensive list of current medications will be compiled by the pharmacists (KS, ST, or MK) within 72 hours after

admission. Patients will be monitored and educated about newly started medications by their physician and will receive discharge counselling. However, unlike in the intervention group, advice from pharmacists about deprescribing and starting medications will not be provided to the patient's physician, except in cases of apparent harmful effects of medications that are judged to be symptomatic by pharmacists. Furthermore, pharmacists will neither prepare the summary about discharge medications nor send it to the primary care physicians and community pharmacists. However, at the discretion of the pharmacist providing advice about medications for the physicians, the summary about discharge medications will be prepared. These procedures are the standard practice for pharmacists in most Japanese hospitals.[30]

Data collection

One of the pharmacists (ST, KS, or MK) will collect the demographic and baseline medical information from the patients and/or their caregivers at admission and summarise this information on a patient registration form. Participants will be followed and assessed for two years after study entry (Table 1). One of the pharmacists (ST, KS, or MK) will assess outcomes at discharge. We will survey the participants or their

caregivers regarding information about primary and secondary outcomes by sending letters at 6 months, 12 months, and 24 months after randomisation. If the participants do not respond to the survey appropriately, we will contact them or their caregivers by telephone to minimise the effect of missing data on study outcomes. Furthermore, to collect more accurate data, we will also use data from electronic medical records of our hospital if the participants are admitted or visit our hospital regularly during the study period.

Outcomes

Primary outcome

The primary outcome is the readmission rate within one year after randomisation. The readmission rate is defined as the proportion of participants who are re-hospitalised regardless of the cause of hospitalisation (all-cause readmission). Patients who visit an emergency department but are not hospitalised will not be counted. We will evaluate the difference in the readmission rate within one year after randomisation between the two treatment groups.

Secondary outcomes

The secondary outcomes are readmission rates within 6 and 24 months after randomisation. We will evaluate the differences in the readmission rates at 6 and 24 months between the two treatment groups. The other secondary outcomes are provided below. These outcomes will be evaluated at discharge and at 6 months, 12 months and 24 months after randomisation. We will evaluate the differences between the two treatment groups regarding these outcomes at discharge, 6 months, 12 months and 24 months.

- Any-cause death
- Total number of medications
- Potentially inappropriate prescribing based on the 2015 STOPP criteria[8]
- Potential prescribing omission based on the 2015 START criteria[8]
- Any fractures
- Ischaemic stroke
- Myocardial infarction
- Emergency department visits

Statistical analysis

Sample size calculation

We estimated that a sample of 200 patients would provide the study with a power of at least 80% to show a relative risk reduction of 33% for the primary outcome in the intervention group compared with the usual care group (at a two-sided alpha level of 0.05), assuming that the proportion of patients who are readmitted within one year is 60% in the usual care group (based on a previous study[23]). Assuming that the dropout rate is 10%, we would need to enrol approximately 220 patients.

Statistical analysis

The baseline characteristics of the study population will be summarised using descriptive statistics. The intervention group will be compared against the usual group for all primary and secondary outcomes (Table 2). We will use a chi-squared test for binary outcomes and Student's t-test for continuous outcomes. We will calculate the relative risk and number needed to treat with corresponding 95% confidence intervals to compare dichotomous variables, and the difference in the means will be used for an

additional analysis of continuous variables. For all tests, we will use 2-sided p-values with an alpha < 0.05 for the level of significance.

Analyses for all outcomes will include all patients who have undergone randomisation and have provided valid informed consent (intention-to-treat population). Regarding the procedure for missing data, we will exclude the data from participants who are lost to follow-up or whose outcomes are missing. These analyses will be performed using IBM SPSS Statistics Base version 21.0 (IBM Corporation, Nihonbashi, Tokyo, Japan) or Excel statistical software package version 2.11 (Bellcurve for Excel; Social Survey Research Information Co., Ltd., Tokyo, Japan). All analyses will be conducted by investigators who are blinded to the study group allocations.

Data management

The trial data of the study participants will be transmitted to and stored in the research database at National Hospital Organization Tochigi Medical Center. This data will not include the participants' identifying information. Instead, individual participants and research data will be identified by unique study identification numbers. At the end of the study, the data will be locked. The data will be stored for at least five years after study completion. Access to the stored data will be limited to investigators. The data

will be stored using codes assigned by the investigators and kept on password-protected computers.

Monitoring

Data monitoring

The risk associated with participation in this study is low, because our aim is to improve the quality of medications in patients. According to the Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects (as of March 2015), our intervention corresponds with a non-invasive procedure. Therefore, we will not need a data monitoring committee. However, an independent staff pharmacist who is not involved with the trial intervention will monitor the data periodically to ensure safety.

Adverse events

In our study, an adverse event will be defined as any undesirable medical occurrence in a participant without regard to the possibility of a causal relationship. Data on adverse events will be collected after the participants have provided consent and enrolled in the study. If a participant experiences an adverse event after the informed consent document

is signed and the participant has not yet started to receive the study intervention, the event will be reported as not being related to the study intervention. All adverse events that occur after entry into the study and for two years after randomisation will be recorded. A serious adverse event for this study is any undesirable medical occurrence that is believed by the investigators to be causally related to the study intervention and results in any of the following: a life-threatening condition (that is, immediate risk of death) or severe or permanent disability.

Auditing

According to the Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects (as of March 2015), our intervention corresponds with a non-invasive procedure. Furthermore, past studies investigating the effectiveness of a pharmacist intervention have reported few adverse events.[16-23] Therefore, we will not need auditing.

Ethics and dissemination

This study protocol was approved by the Medical Ethics Committee of the National Hospital Organization Tochigi Medical Center (Tochigi, Japan). They judged the study design, ethics, and safety. Substantial amendments to the study protocol must be approved by the Medical Ethics Committee of the National Hospital Organization Tochigi Medical Center. The trial was registered at the UMIN clinical registry on October 3, 2017. We will obtain informed consent from the trial participants or their authorised surrogates according to the Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects (as of March 2015). One of three pharmacists (ST, KS, or MK) will introduce the trial to patients and discuss the trial with all patients using the information sheets about the nature, purpose, and possible risks and benefits of the trial, which was approved by the Medical Ethics Committee of the National Hospital Organization Tochigi Medical Center. Then, the pharmacists will obtain written informed consent from patients willing to participate in the trial. To assure confidentiality, trial participants will be allocated a unique trial identification number throughout the trial. A manuscript with the results of this study will be published in a peer-reviewed journal.

Patient involvement

No patients were involved in determining the research question or outcome measures nor were any patients involved in developing plans to design or implement the study. No patients were involved in evaluating the burden of the intervention. There are no plans to disseminate the results of this research to study participants or the relevant patient community.

DISCUSSION

Given that polypharmacy and potentially inappropriate prescribing among elderly patients is common in acute care settings,[10] it is important to improve the appropriateness of medications during hospitalisation. Therefore, the role of hospital pharmacists in improving polypharmacy and potentially inappropriate prescribing in hospitalised elderly patients is important. Nonetheless, there are conflicting results regarding the effectiveness with which pharmacist interventions in elderly inpatient care can improve polypharmacy and potentially inappropriate prescribing to affect patient-relevant outcomes.[17-21] Given that few past randomised controlled trials have evaluated a patient-relevant outcome as a primary endpoint,[22,23] it is important to conduct a randomised controlled trial to evaluate whether a pharmacist-led intervention

improves patient-relevant outcomes, such as readmission and death, in hospitalised elderly orthopaedic patients with polypharmacy or potentially inappropriate prescribing.

There are several limitations to this study. First, the non-blinded study design may overestimate the effectiveness of pharmacist intervention.[31] However, due to the nature of the intervention, it is difficult for both participants and clinical pharmacists to be blinded to the allocation. Second, this study is a single-centre trial. Although most past randomised controlled trials were also single-centre trials,[21,23,32-35] the external validity of this study is limited. Therefore, an additional randomised controlled trial may be needed. Third, we will exclude elderly orthopaedic patients who are admitted electively or who are taking less than five prescribed medications or have no potentially inappropriate prescriptions. Furthermore, elderly patients admitted to other specialty wards, such as internal medicine or general surgery, will also be excluded. Therefore, it is unclear whether the findings of this trial will be applicable to elderly patients who are admitted electively or to other wards besides the orthopaedic ward. Fourth, medication reconciliation is included in the usual care group in this study. The possible beneficial effect of medical reconciliation for hospitalised patients[36] may mitigate the effectiveness of the pharmacist intervention in this study. Finally, we will not assess the cost-effectiveness of the intervention.

Although these limitations are important, this study is one of a few randomised controlled trials to investigate the effectiveness of a pharmacist-led intervention and use a patient-relevant outcome as the primary outcome for hospitalised elderly patients. Given that the burdens of polypharmacy and multi-morbidities among elderly patients have increased in recent years, this trial will provide important information on improving the acute care of elderly patients with polypharmacy or potentially inappropriate prescribing.

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Competing interests: All authors have completed the ICMJE unified disclosure from competing interest form at www.icmje.org/coi_disclosure.pdf (available upon request from the corresponding author). All authors declare that they have no conflicts of interest.

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Ethical approval: This study was approved by the Medical Ethics Committee of the National Hospital Organization Tochigi Medical Center (No. 29-22).

REFERENCES

1 Wolff JL, Starfield B, Anderson G. Prevalence, expenditures, and complications of multiple chronic conditions in the elderly. *Arch Intern Med* 2002;162:2269-76. doi:10.1001/archinte.162.20.2269.

2 Kaufman DW, Kelly JP, Rosenberg L et al. Recent patterns of medication use in the ambulatory adult population of the United States: The Slone survey. *JAMA*

2002;287:337-44. doi:10.1001/jama.287.3.337.

3 Boyd CM, Dare J, Boult C, et al. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases. *JAMA* 2005;294:716-24. doi:10.1001/jama.294.6.716.

4 Steinman MA, Landefeld CS, Rosenthal GE, et al. Polypharmacy and prescribing quality in older people. *J Am Geriatr Soc* 2006;54:1516-23. doi:10.1111/j.1532-5415.2006.00889.x.

5 Fried TR, O'Leary J, Towle V, et al. Health outcomes associated with polypharmacy in community-dwelling older adults: a systematic review. *J Am Geriatr Soc* 2014;62:2261-72. doi:10.1111/jgs.13153.

6 Beijer HJ, de Blaey CJ. Hospitalisations caused by adverse drug reactions (ADR): a meta-analysis of observational studies. *Pharm World Sci* 2002;24:46-54. doi:10.1023/A:1015570104121.

7 The American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 updated Beers Criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc* 2015;63:2227-46. doi:10.1111/jgs.13702.

8 O'Mahony D, O'Sullivan D, Byrne S, et al. STOPP/START criteria for potentially

inappropriate prescribing in older people: version 2. *Age Ageing* 2015;44:213-8. doi:10.1093/ageing/aful145.

9 Scott IA, Hilmer SN, Reeve E, et al. Reducing inappropriate polypharmacy: the process of deprescribing. *JAMA Intern Med* 2015;175(5):827-34. doi:10.1001/jamainternmed.2015.0324.

10 Gallagher P, Lang PO, Cherubini A, et al. Prevalence of potentially inappropriate prescribing in an acutely ill population of older patients admitted to six European hospitals. *Eur J Clin Pharmacol* 2011;67:1175-88. doi:10.1007/s00228-011-1061-0.

11 Tommelein E, Mehuys E, Petrovic M, et al. Potentially inappropriate prescribing in community-dwelling older people across Europe: a systematic literature review. *Eur J Clin Pharmacol* 2015;71(12):1415-27. doi:10.1007/s00228-015-1954-4.

12 Opondo D, Eslami S, Visscher S, et al. Inappropriateness of medication prescriptions to elderly patients in the primary care setting: a systematic review. *PLoS ONE* 2012;7(8):e43617. doi:10.1371/journal.pone.0043617.

13 The American College of Emergency Physicians, the American Geriatrics Society, Emergency Nurses Association and the Society for Academic Emergency Medicine. Geriatric emergency department guidelines. *Ann Emerg Med* 2014;63:e7-e25. doi: 10.1016/j.annemergmed.2014.02.008.

14 Hohl CM, Zed PJ, Brubacher JR, et al. Do emergency physicians attribute drug-related emergency department visits to medication-related problems? *Ann Emerg Med* 2010;55:493-502. doi:10.1016/j.annemergmed.2009.10.008.

15 Gandhi TK, Weingart SN, Borus J, et al. Adverse drug events in ambulatory care. *New Engl J Med* 2003;348:1556-64. doi:10.1056/NEJMsa020703

16 Walsh KA, O'Riordan D, Kearney PM, et al. Improving the appropriateness of prescribing in older patients: a systematic review and meta-analysis of pharmacists' interventions in secondary care. *Age Ageing* 2016;45:201-9. doi:10.1093/ageing/afv190.

17 Kaboli PJ, Hoth AB, McClimon BJ, et al. Clinical pharmacists and inpatient medical care: a systematic review. *Arch Intern Med* 2006;166:955-64. doi:10.1001/archinte.166.9.955.

18 Holland R, Desborough J, Goodyer L, et al. Does pharmacist-led medication review help to reduce hospital admissions and deaths in older people? A systematic review and meta-analysis. *Br J Clin Pharmacol* 2007;65(3):303-16. doi:10.111/j.1365-2125.2007.03071.x.

19 Koshman SL, CHarrois TL, Simpson SH, et al. Pharmacist care of patients with heart failure: a systematic review of randomized trials. *Arch Intern Med* 2008;168(7):687-94. doi:10.1001/archinte.168.7.687.

20 Renaudin P, Boyer L, Esteve MA, et al. Do pharmacist-led medication reviews in hospitals help reduce hospital readmissions? A systematic review and meta-analysis. *Br J Clin Pharm* 2016;82:1660-73. doi:10.111/bcp.13085.

21 Thomas R, Huntley AL, Mann M, et al. Pharmacist-led interventions to reduce unplanned admissions for older people: a systematic review and meta-analysis of randamised controlled trials. *Age Ageing* 2014;43:174-87. doi:10.1093/ageing/aft169.

22 Nazareth I, Burton A, Shulman S, et al. A pharmacy discharge plan for hospitalized elderly patients: a randomized controlled trial. *Age Ageing* 2001;30:33-40. doi:10.1093/ageing/30.1.33.

23 Gillespie U, Alassaad A, Henrohn D, et al. A comprehensive pharmacist intervention to reduce morbidity in patients 80 years or older: a randomized controlled trial. *Arch Intern Med* 2009;169(9):894-900. doi:10.1001/archinternmed.2009.71.

24 McMahon CG, Cahir CA, Kenny RA, et al. Inappropriate prescribing in older fallers presenting to an Irish emergency department. *Age Ageing* 2014;43:44-50. doi:10.1093/ageing/aft114.

25 Kragh A, Elmståhl S, Atroshi I. Older adults' medication use 6 months before and after hip fracture: A population-based cohort study. *J Am Geriatr Soc* 2011;59:863-8. doi:10.1111/j.1532-5415.2011.03372.x.

26 Lai SW, Liao KF, Liao CC, et al. Polypharmacy correlates with increased risk for hip fracture in the elderly. A population-based study. *Medicine* 2010;89:295-9. doi:10.1097/MD.0b013e3181fl5efc.

27 Chan AW, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586. doi:10.1136/bmj.e7586.

28 Gnjidic D, Hilmer SN, Blyth FM, et al. Polypharmacy cutoff and outcomes: five or more medicines were used to identify community-dwelling older men at risk of different adverse outcomes. *J Clin Epidemiol* 2012;65:989-95. doi:10.1016/j.jclinepi.2012.02.018.

29 Hosomi N, Nagai Y, Kohriyama T, et al. The Japan Statin Treatment Against Recurrent Stroke (J-STARS): a multicenter, randomized, open-label, parallel-group study. *EBioMedicine* 2015;2(9):1071-8. doi:10.1016/j.ebiom.2015.08.006.

30 Nakagawa S, Kume N. Pharmacy practice in Japan. *Can J Hosp Pharm* 2017;70(3):232-42. doi:10.4212/cjhp.v70i3.1663.

31 Wood L, Egger M, Gluud LL, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *BMJ* 2008;336(7644):601-5. doi:10.1136/bmj.39465.451748.AD.

32 Lisby M, Thomsen A, Nielsen LP, et al. The effect of systematic review in elderly patients admitted to an acute ward of internal medicine. *Basic Clin Pharmacol Toxicol* 2010;106(5):422-7. doi:10.1111/j.1742-7843.2009.00511.x.

33 McMullin ST, Hennenfent JA, Ritchie DJ, et al. A prospective, randomized trial to assess the cost impact of pharmacist-initiated interventions. *Arch Intern Med* 1999;159(19):2306-9. doi:10.1001/archinte.159.19.2306.

34 Spinewine A, Swine C, Dhillon S, et al. Effect of a collaborative approach on the quality of prescribing for geriatric inpatients: a randomized, controlled trial. *J Am Geriatr Soc* 2007;55(5):658-65. doi:10.1111/j.1532-5415.2007.01132.x.

35 Lipton HL, Bird JA. The impact of clinical pharmacists' consultations on geriatric patients' compliance and medical care use: a randomized controlled trial. *Gerontologist* 1994;34(3):307-15. doi:10.1093/geront/34.3.307.

36 Mekonnen AB, McLachlan AJ, Brien JE. Effectiveness of pharmacist-led medication reconciliation programmes on clinical outcomes at hospital transitions: a systematic review and meta-analysis. *BMJ Open* 2016;6:e010003. doi:10.1136/bmjopen-2015-010003.

585 **Table 1.** Time schedule of participant enrolment, interventions, and assessments.

	STUDY PERIOD					
	Enrolment	**Allocation**	**Post-allocation**			
TIMEPOINT*	$-t_1$	**0**	t_1	t_2	t_3	t_4
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Allocation		X				
INTERVENTIONS:						
Pharmacist intervention		⟺	⟺			
Usual care (control)		⟺	⟺			
ASSESSMENTS:						
Number of medications	X		X	X	X	X
Number of PIP†	X		X	X	X	X
Number of PPO†	X		X	X	X	X
Adverse drug events			X			
Discharge destination			X			
Duration of hospital stay			X			
All-cause death			X	X	X	X
Readmission‡				X	X	X
ED visit				X	X	X

Myocardial infarction			X	X	X	X
Ischaemic stroke			X	X	X	X
Fracture			X	X	X	X

*t_1, within 72 hours after admission; t_1, at discharge; t_2, six months after randomisation; t_3, 12 months after randomisation; t_4, 24 months after randomisation.

†PIP and PPO are defined based on the 2015 STOPP/START Criteria.

‡Includes all-cause hospitalisation regardless of the cause of hospitalisation.

ED, emergency department; PIP, potentially inappropriate prescribing; PPO, potential prescribing omission.

593 **Table 2.** Variables, measures, and analysis methods.

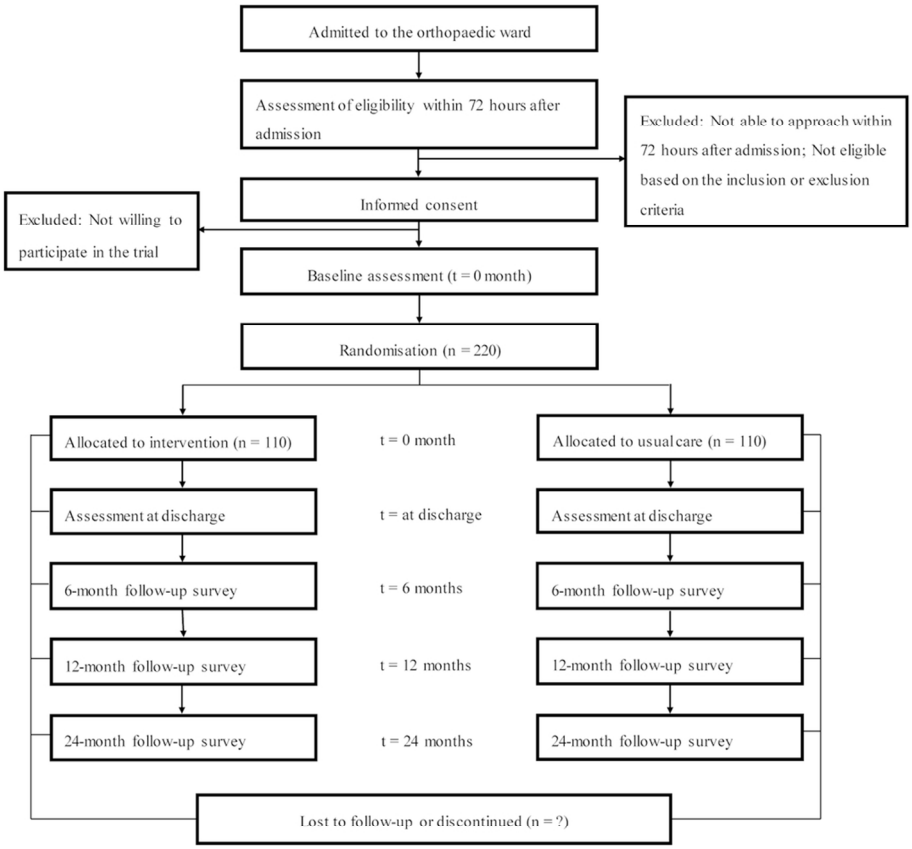
Variable/outcome	Hypothesis	Measured outcomes	Methods of analysis
Primary			
Readmission* at 12 months	Improvement occurred	Readmission rate % [binary]	Chi-squared test
Secondary			
Number of medications at discharge and at 6, 12, and 24 months	Decline occurred	Total number of medications [continuous]	T-test
PIP† at discharge and at 6, 12, and 24 months	Decline occurred	Total number of PIP [continuous]	T-test
	Improvement occurred	Proportion of patients who take any PIP % [binary]	Chi-squared test
PPO† at discharge and at 6, 12, and 24 months	Decline occurred	Total number of PPO [continuous]	T-test
	Improvement occurred	Proportion of patients who take any PPO % [binary]	Chi-squared test
Readmission* at 6 and 24 months	Improvement occurred	Readmission rate % [binary]	Chi-squared test
ED visit at 6, 12, and 24 months	Improvement occurred	Proportion of patients who visit ED % [binary]	Chi-squared test
All-cause death at 6, 12, and 24 months	Improvement occurred	All-cause mortality % [binary]	Chi-squared test
Acute myocardial infarction at 6, 12, and 24 months	Improvement occurred	Proportion of patients whom acute myocardial infarction occurred % [binary]	Chi-squared test
Acute ischaemic stroke at 6, 12, and 24 months	Improvement occurred	Proportion of patients whom acute ischaemic stroke occurred % [binary]	Chi-squared test
Any fractures at 6, 12, and 24 months	Improvement occurred	Proportion of patients whom any fractures occurred % [binary]	Chi-squared test

*Includes all-cause hospitalisation regardless of the cause of hospitalisation.

†PIP and PPO are defined based on the 2015 STOPP/START Criteria.

ED, emergency department; PIP, potentially inappropriate prescribing; PPO, potential prescribing omission.

Figure 1. Flow diagram of the participant.



Flow diagram of the participant.

99x99mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page Number on which item is reported
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	4
Protocol version	3	Date and version identifier	NA
Funding	4	Sources and types of financial, material, and other support	29
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	28
	5b	Name and contact information for the trial sponsor	NA
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	NA
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6-9
	6b	Explanation for choice of comparators	17
Objectives	7	Specific objectives or hypotheses	8-9
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	10
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	11
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	11-12
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	15-17
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	15-17
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	15-18
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	19-20

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	18-19, Figure 1, Table 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12, 21
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	12-13
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	14
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	14
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	14
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	14-15
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	18-19
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	19
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	22-23
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	21-22, Table 2
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	21-22, Table 2
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	22
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	23
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	23-24
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	24
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	25
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	25
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	25
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
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Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	25

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