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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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Manuscripts

1 **A study protocol for a single-centre, prospective, non-blinded, randomised,**
2 **12-month, parallel-group superiority study to compare the efficacy of pharmacist**
3 **intervention versus usual care for elderly patients hospitalised in orthopaedic**
4 **wards**

5
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6 21 **ABSTRACT**
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8 22 **Introduction:** Given that polypharmacy and potentially inappropriate prescribing are
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11 23 common in elderly orthopaedic patients, pharmacist interventions to improve
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14 24 medication practices among this population are important. However, past studies have
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16
17 25 reported mixed results regarding the effectiveness of pharmacist-led interventions in
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20 26 inpatient elderly care. Furthermore, few randomised controlled trials have evaluated
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23 27 patient-relevant outcomes as a primary endpoint. Therefore, we will evaluate whether a
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26 28 pharmacist-led intervention could reduce readmission of hospitalised elderly
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28
29 29 orthopaedic patients with polypharmacy or potentially inappropriate prescribing.
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31 30 **Methods and analysis:** This is an ongoing single-centre, prospective, non-blinded,
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33
34 31 randomised controlled trial designed to evaluate the superiority of a pharmacist-led
35
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37 32 intervention for hospitalised elderly patients compared with usual care. The trial will
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40 33 include newly admitted orthopaedic patients 70 years of age and older with
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43 34 polypharmacy or at least one potentially inappropriate prescription. Usual care includes
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46 35 medication reconciliation, patient education, and monitoring, as well as providing
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49 36 information about discharge medications. Pharmacist interventions, in addition to usual
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52 37 care, include advising the patient's physician to stop unnecessary or inappropriate
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55 38 medications and start necessary medications. The primary outcome is the one-year
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6 39 readmission rate. Secondary outcomes are the proportion of patients who undergo
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8
9 40 emergency department visits and the occurrences of all-cause death, a new fracture,
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11 41 myocardial infarction, and ischaemic stroke. The study started in November 2017, and
12
13
14 42 up to approximately 220 patients will be enrolled.
15

16
17 43 **Ethics and dissemination:** The protocol was approved by the Medical Ethics
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19
20 44 Committee of the National Hospital Organization Tochigi Medical Center (No. 29-22).
21
22
23 45 The trial was registered at the UMIN clinical registry. The results of the primary trials
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26 46 and each of the secondary outcomes will be submitted for publication in a
27
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29 47 peer-reviewed journal.

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31 48 **Trial registration number:** UMIN000029404 (registered October 3, 2017).
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34 49
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37 50 **Key words:** Emergency, Orthopaedic ward, Pharmacist intervention, Polypharmacy,
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39
40 51 Potentially inappropriate prescribing
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42 52 43 44 45 53 **Strengths and limitations of this study**

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48 54 ● This randomised controlled trial will evaluate the effectiveness of pharmacist
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51 55 interventions for hospitalised orthopaedic elderly patients, using
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54 56 patient-relevant outcomes as the primary outcomes.
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6 57 ● This is a single-centre study with a small sample size and short-term
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9 58 follow-up.
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11 59 ● Orthopaedic patients who are admitted electively or discharged within less
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14 60 than seven days after admission will be excluded.
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17 61 ● Orthopaedic patients who are prescribed fewer than five medications and are
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20 62 taking no potentially inappropriate medications at admission will be excluded.
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63 INTRODUCTION

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

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

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6 81 polypharmacy and potentially inappropriate prescribing in hospitalised elderly patients
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9 82 is important. Nonetheless, past studies have reported mixed results regarding the
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11 83 effectiveness of a pharmacist-led intervention in improving the appropriateness of
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14 84 medications in inpatient elderly care. Although pharmacist intervention can improve the
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16
17 85 appropriateness of medications in hospitalised elderly patients,[16] the conclusions of
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20 86 past systematic reviews and meta-analyses have been inconsistent regarding whether
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23 87 patient-relevant outcomes, such as mortality and readmission, were improved by these
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26 88 interventions.[17-20] One recent meta-analysis that included seven randomised
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29 89 controlled trials that evaluated the effectiveness of a pharmacist-led intervention in
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32 90 inpatient elderly care also reported little impact of pharmacist interventions on
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35 91 readmission rates.[21] However, most trials included in this meta-analysis were
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38 92 considered to have a high risk of bias. Furthermore, only two of the seven randomised
39
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41 93 controlled trials included in the meta-analysis evaluated patient-relevant outcomes as
42
43
44 94 primary endpoints.[22,23] In one of those two trials, a comprehensive pharmacist
45
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47 95 intervention for hospitalised elderly patients with polypharmacy led to a significant
48
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50 96 reduction in hospital visits.[23] Therefore, it is still too early to conclude that
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53 97 pharmacist-led interventions for hospitalised elderly patients do not improve
54
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56 98 patient-relevant outcomes. Furthermore, most studies have targeted internal medicine
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6 99 patients, while few studies have ever investigated the effectiveness of pharmacist
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9 100 interventions for elderly patients hospitalised in an orthopaedic ward.[21] The
10
11 101 prevalence of polypharmacy and potentially inappropriate prescribing are particularly
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14 102 high in elderly orthopaedic patients, and these practices often continue after recovery
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16
17 103 from a fracture.[24,25] Furthermore, polypharmacy is associated with an increased risk
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20 104 of fall and fracture.[5,26] Therefore, pharmacist interventions for improving the
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23 105 appropriateness of medications in hospitalised elderly orthopaedic patients may be
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26 106 associated with better patient outcomes compared with other settings. Thus, we will
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29 107 conduct a randomised controlled trial to evaluate whether a pharmacist-led intervention
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32 108 reduces readmission in hospitalised elderly orthopaedic patients with polypharmacy or
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35 109 potentially inappropriate prescribing.
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111 **Objectives**

112 *Primary objective*

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

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9 117 *Secondary objectives*
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13 118 The key secondary objectives are to determine whether pharmacist intervention for
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16 119 elderly orthopaedic patients with polypharmacy or potentially inappropriate prescribing
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19 120 at admission reduces patient-relevant outcomes, such as all-cause death, myocardial
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21
22 121 infarction, ischaemic stroke, and any fractures, compared with usual care. Other
23
24
25 122 secondary objectives are to determine whether pharmacist intervention for elderly
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28 123 orthopaedic patients with polypharmacy or potentially inappropriate prescribing at
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31 124 admission reduces the total number of medications, potentially inappropriate
32
33 125 prescribing, and potential prescription omissions.
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40 127 **Literature search and review**
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43 128 We performed a literature search and review of pharmacist interventions in elderly
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46 129 hospitalised orthopaedic patients. We used the terms “pharmacist”, “polypharmacy”,
47
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49 130 “medication review”, and “inappropriate prescribing” alone and in combination to
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52 131 search the PubMed and Google Scholar databases through 5 August 2017. We restricted
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55 132 our review to full-text articles published in English or Japanese. We also identified
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6 133 references from the relevant articles. We primarily selected randomised controlled trials,
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9 134 systematic reviews, and meta-analyses. We found a recent systematic review regarding
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11 135 the effectiveness of pharmacist-led intervention on patient outcomes in elderly
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14 136 hospitalised patients.[21] Based on this systematic review, we designed this trial.
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19 20 138 **METHODS AND ANALYSIS**

21 22 139 **Trial design**

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26 140 This study is a single-centre, prospective, non-blinded, randomised, controlled,
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29 141 superiority trial with two parallel groups. All participants who provide consent for
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32 142 participation and fulfil the inclusion criteria will be randomly assigned to the pharmacist
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34
35 143 intervention group or the usual care group with a 1:1 allocation. The study was
36
37
38 144 approved by the Medical Ethics Committee of the National Hospital Organization
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41 145 Tochigi Medical Center (No. 29-22) and will be conducted in accordance with the
42
43
44 146 Declaration of Helsinki. Standard Protocol Items: The Recommendations for
45
46
47 147 Interventional Trials (SPIRIT checklist)[27] was followed in designing the study
48
49 148 protocol (supplementary appendix). Figure 1 summarises the design of the trial, and
50
51
52 149 each of the trial aspects is described in detail below.
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6 151 **Study setting**
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9 152 This study will be conducted in the orthopaedic ward at the National Hospital
10
11
12 153 Organization Tochigi Medical Center. Our hospital is a 350-bed acute care community
13
14
15 154 hospital and is one of five main hospitals that serve approximately 0.5 million
16
17
18 155 individuals in Utsunomiya in the Tochigi prefecture in Japan.
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24 157 **Eligibility criteria**
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26
27 158 Eligible patients are those who meet all of the following inclusion criteria and who do
28
29
30 159 not have any listed exclusion criteria. Based on the American College of Emergency
31
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33 160 Physicians Geriatric Emergency Department Guidelines[11], the number of medications
34
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36 161 taken or the presence of potentially inappropriate prescribing at admission will be used
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39 162 as the inclusion criteria. However, the minimum number of medications for inclusion
40
41
42 163 will be five, based on a past study showing that taking five or more medications was a
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45 164 useful parameter for estimating medication-related adverse effects related to frailty,
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48 165 disability, and mortality among men aged 70 years and older.[28]
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52 167 *Inclusion criteria*
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54
55 168 1. Age 70 years and older
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6 169 2. Polypharmacy (defined as 5 or more medications) or at least one potentially
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9 170 inappropriate prescription (as defined by the 2015 STOPP criteria[8]) upon
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11 171 admission
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173 *Exclusion criteria*

174 1. Elective admission

175 2. Inability to contact patient within 72 hours after their admission

176 3. Expected hospital stay duration of < one week

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178 **Study duration, enrolment and number of sites**

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

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186 **Screening and registration**

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6 187 All elderly patients who are hospitalised in an orthopaedic ward in our hospital will be
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8
9 188 screened for eligibility for the trial by one of three pharmacists (KS, ST, MK) every
10
11 189 weekday morning. Patients who are hospitalised on weekends will be screened on the
12
13
14 190 following Monday morning. If the screened patients are not eligible, we will document
15
16
17 191 the reason for ineligibility for the trial and the number of ineligible patients. All patients
18
19
20 192 who fulfil the inclusion criteria and have no exclusion criteria will be registered by one
21
22
23 193 of three pharmacists (KS, ST, MK) in the central data centre at the National Hospital
24
25
26 194 Organization Tochigi Medical Center. Unless written informed consent is provided by
27
28
29 195 the patients, we will document the reasons why the patients did not provide consent to
30
31 196 participate in the trial and document the number of patients who declined to participate
32
33
34 197 in the trial.
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41 **Randomisation and allocation concealment**

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45 200 All patients who provide consent for participation and who fulfil the inclusion criteria
46
47
48 201 will be randomised. Randomisation will be requested by one of three pharmacists (KS,
49
50
51 202 ST, MK) to the independent randomisation centre at the National Hospital Organization
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53
54 203 Tochigi Medical Center via webmail. Participants will be randomly assigned to either
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6 204 the pharmacist intervention group or the usual care group. Randomisation will be
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9 205 performed as block randomisation with a 1:1 allocation. The computer-generated
10
11 206 random allocation sequence will be provided by an independent staff pharmacist who is
12
13
14 207 not involved in the treatment of patients or with the assessment of patient outcomes.
15
16
17 208 The randomisation will not be stratified. The block sizes will be concealed until the
18
19
20 209 primary outcome is analysed. Throughout the study, the randomisation list will also be
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23 210 concealed until the end of the study.
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30 212 **Blinding**

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33 213 Due to the nature of the intervention, neither the participants nor the clinical
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36 214 pharmacists can be blinded to the allocation. Patients will be informed of the group to
37
38
39 215 which they have been randomly allocated. Assessments regarding the outcomes will be
40
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42 216 conducted by an assessor who knows the treatment allocation. The analysis regarding
43
44
45 217 the primary outcome will be conducted by independent investigators who are blinded to
46
47
48 218 the treatment allocation and are not involved in the assessment of patient outcomes.
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51 219

52 53 54 55 220 **Pharmacist intervention group**

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6 221 Before starting the study, three study pharmacists (KS, ST, MK) were trained during a
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9 222 three-month period from May 2017 to July 2017. Approximately 16 sessions (one hour
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11 223 per session) on medication use in elderly patients based on the 2015 STOPP/START
12
13
14 224 criteria[8] were provided by one internal medicine physician (JK). Therefore, these
15
16
17 225 pharmacists are aware of the 2015 STOPP/START criteria, however, the use of these
18
19
20 226 criteria for the pharmacist intervention will not be mandatory. One of these trained
21
22
23 227 pharmacists (KS, ST, MK) will treat the participants from admission to discharge at the
24
25
26 228 following three stages.

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32 230 *Intervention at admission*

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36 231 A comprehensive list of current medications will be compiled within 72 hours after
37
38
39 232 admission. A drug review will be performed, and advice about the following factors will
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41
42 233 be given to the patient's physician: (1) deprescribing inappropriate or unnecessary
43
44
45 234 medications, (2) starting effective or necessary medications, and (3) modifying
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48 235 medication dosages. However, the final decision to adhere to the advice provided by
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51 236 pharmacists will be made by the physician in charge. Pharmacists will document
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54 237 whether the physicians follow their advice.

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9 239 *Intervention during hospitalisation*
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13 240 During the hospital stay, patients will be educated about the harms and benefits of their
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16 241 medications. Pharmacists will also provide information about the rationale for
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19 242 medication use and therapeutic goals. Patients will be monitored after starting or
20

21
22 243 stopping medications.
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29 245 *Intervention at discharge*
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32 246 Information about discharge medications (e.g., rationale for changes and monitoring
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34
35 247 needs for newly started or stopped medications) will be summarised in a written
36

37
38 248 document by the pharmacists. Patients will receive discharge counselling with this
39

40
41 249 summary. The summary will also be sent to the primary care physicians and community
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44 250 pharmacists.
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51 252 **Usual care group**
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6 253 Usual care typically includes the same elements as those received by the intervention
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9 254 group but is less extensive. In the usual care group, a comprehensive list of current
10
11 255 medications will be compiled by the pharmacists (KS, ST, MK) within 72 hours after
12
13
14 256 admission. Patients will be monitored and educated about newly started medications by
15
16
17 257 their physician and will receive discharge counselling. However, unlike in the
18
19
20 258 intervention group, advice from pharmacists about deprescribing and starting
21
22
23 259 medications will not be provided to the patient's physician, except for in cases of
24
25
26 260 apparent harmful effects of medications. Furthermore, pharmacists will neither prepare
27
28
29 261 the summary about discharge medications nor send it to the primary care physicians and
30
31
32 262 community pharmacists. However, at the discretion of the pharmacist providing advice
33
34
35 263 about medications for the physicians, the summary about discharge medications will be
36
37
38 264 prepared. These procedures are the standard practice for pharmacists in most Japanese
39
40 265 hospitals.[29]

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46 47 267 **Data collection**

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49
50 268 One of the pharmacists (ST, KS, MK) will collect the demographic and baseline
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53 269 medical information from the patients and/or their caregivers at admission and
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6 270 summarise this information on a patient registration form. Participants will be followed
7
8
9 271 and assessed for two years after study entry (Table 1). One of the pharmacists (ST, KS,
10
11 272 MK) will assess outcomes at discharge. We will survey the participants or their
12
13
14 273 caregivers regarding information about primary and secondary outcomes by sending
15
16
17 274 letters at 6 months, 12 months, and 24 months after randomisation. If the participants do
18
19
20 275 not respond to the survey, we will try to contact them or their caregivers by telephone to
21
22
23 276 minimise the effect of missing data on study outcomes.
24
25

26 277

278 **Outcomes**

279 *Primary outcome*

280 The primary outcome is the readmission rate within one year after randomisation.
281 Readmission includes both planned and unplanned admissions. We will evaluate the
282 difference between the two treatment groups in the proportion of participants who are
283 readmitted within one year after randomisation. We will also evaluate the differences in
284 readmission rates between the groups at 6 and 24 months.
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6 286 *Secondary outcomes*
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9 287 The secondary outcomes are provided below. These outcomes will be evaluated at
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11
12 288 discharge and at 6 months, 12 months and 24 months after randomisation. We will
13
14
15 289 evaluate the differences between the two treatment groups regarding these outcomes at
16
17
18 290 discharge, 6 months, 12 months and 24 months.

19
20
21 291 • Any-cause death
22

23
24
25 292 • Total number of medications
26

27
28
29 293 • Potentially inappropriate prescribing based on the 2015 STOPP criteria[8]
30

31
32 294 • Potential prescribing omission based on the 2015 START criteria[8]
33
34

35
36 295 • Any fractures
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39 296 • Ischaemic stroke
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43 297 • Myocardial infarction
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47 298 • Emergency department visits
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53 300 **Statistical analysis**
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6 301 *Sample size calculation*

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8 302 We estimated that a sample of 200 patients would provide the study with a power of at
9
10
11 303 least 80% to show a relative risk reduction of 33% for the primary outcome in the
12
13
14 304 intervention group compared with the usual care group (at a two-sided alpha level of
15
16
17 305 0.05), assuming that the proportion of patients who are readmitted within one year is
18
19
20 306 60% in the usual care group (based on a previous study[23]). Assuming that the dropout
21
22
23 307 rate is 10%, we would need to enrol approximately 220 patients.
24

25
26 308

27
28 309 *Statistical analysis*

29
30
31 310 The baseline characteristics of the study population will be summarised using
32
33
34 311 descriptive statistics. The intervention group will be compared against the usual group
35
36
37 312 for all primary and secondary outcomes (Table 2). We will use a chi-squared test for
38
39
40 313 binary outcomes and Student's t-test for continuous outcomes. We will calculate the
41
42
43 314 relative risk and number needed to treat with corresponding 95% confidence intervals to
44
45
46 315 compare dichotomous variables, and the difference in the means will be used for an
47
48
49 316 additional analysis of continuous variables. For all tests, we will use 2-sided p-values
50
51 317 with an alpha < 0.05 for the level of significance.
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6 318 Analyses for all outcomes will include all patients who have undergone
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9 319 randomisation and have provided valid informed consent (intention-to-treat population).
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11 320 Regarding the procedure for missing data, we will exclude the data from participants
12
13
14 321 who are lost to follow-up or whose outcomes are missing. These analyses will be
15
16
17 322 performed using IBM SPSS Statistics Base version 21.0 (IBM Corporation, Nihonbashi,
18
19
20 323 Tokyo, Japan) or Excel statistical software package version 2.11 (Bellcurve for Excel;
21
22
23 324 Social Survey Research Information Co., Ltd., Tokyo, Japan). All analyses will be
24
25
26 325 conducted by investigators who are blinded to the study group allocations.
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31 327 **Data management**

32
33
34 328 The trial data about study participants will be transmitted to and stored in the research
35
36
37 329 database at National Hospital Organization Tochigi Medical Center. This will not
38
39
40 330 include the participants' identifying information. Rather, individual participants and
41
42
43 331 research data will be identified by a unique study identification number. At the end of
44
45
46 332 the study, the data will be locked. Data will be stored for at least five years after study
47
48
49 333 completion. Access to stored data will be limited to investigators. Data will be stored
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51
52 334 using codes assigned by the investigators. Data will be kept on password-protected
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55 335 computers.
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9 337 **Monitoring**

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11 338 *Data monitoring*

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15 339 The risk associated with participation in this study is low, because our aim is to improve
16
17 340 the quality of medications in patients. According to the Japanese Ethical Guidelines for
18
19 341 Medical and Health Research Involving Human Subjects (as of March 2015), our
20
21 342 intervention corresponds with a non-invasive procedure. Therefore, we will not need a
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23 343 data monitoring committee. However, an independent staff pharmacist who is not
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25 344 involved with the trial intervention will monitor the data periodically to ensure safety.
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36 346 *Adverse events*

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40 347 In our study, an adverse event will be defined as any undesirable medical occurrence in
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42 348 a participant without regard to the possibility of a causal relationship. Data on adverse
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44 349 events will be collected after the participants have provided consent and enrolled in the
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46 350 study. If a participant experiences an adverse event after the informed consent document
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48 351 is signed and the participant has not yet started to receive the study intervention, the
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50 352 event will be reported as not being related to the study intervention. All adverse events
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6 353 that occur after entry into the study and for two years after randomisation will be
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9 354 recorded. A serious adverse event for this study is any undesirable medical occurrence
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11 355 that is believed by the investigators to be causally related to the study intervention and
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14 356 results in any of the following: a life-threatening condition (that is, immediate risk of
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17 357 death) or severe or permanent disability.
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22 23 24 359 *Auditing*

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28 360 According to the Japanese Ethical Guidelines for Medical and Health Research
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31 361 Involving Human Subjects (as of March 2015), our intervention corresponds with a
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34 362 non-invasive procedure. Furthermore, past studies investigating the effectiveness of a
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37 363 pharmacist intervention have reported few adverse events.[16-23] Therefore, we will
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40 364 not need auditing.
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44 45 366 **Ethics and dissemination**

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48 367 This study protocol was approved by the Medical Ethics Committee of the National
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51 368 Hospital Organization Tochigi Medical Center (Tochigi, Japan). They judged the study
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54 369 design, ethics, and safety. Substantial amendments of the study protocol must be
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6 370 approved by the Medical Ethics Committee of the National Hospital Organization
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9 371 Tochigi Medical Center. The trial was registered at the UMIN clinical registry on
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11 372 October 3, 2017. We will obtain informed consent from the trial participants or their
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14 373 authorised surrogates according to the Japanese Ethical Guidelines for Medical and
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17 374 Health Research Involving Human Subjects (as of March 2015). One of three
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20 375 pharmacists (ST, KS, MK) will introduce the trial to patients and discuss the trial with
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23 376 all patients using the information sheets about the nature, purpose, and possible risks
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26 377 and benefits of the trial, which was approved by the Medical Ethics Committee of the
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29 378 National Hospital Organization Tochigi Medical Center. Then, the pharmacists will
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32 379 obtain written informed consent from patients willing to participate in the trial. To
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34 380 assure confidentiality, trial participants will be allocated a unique trial identification
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37 381 number throughout the trial.

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40 382 A manuscript with the results of the primary study will be published in a
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43 383 peer-reviewed journal. Separate manuscripts will be written on each of the secondary
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46 384 aims, and these manuscripts will also be submitted for publication in peer-reviewed
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49 385 journals.

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54 387 **DISCUSSION**

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6 388 Given that polypharmacy and potentially inappropriate prescribing among
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9 389 elderly patients is common in acute care settings,[10] it is important to improve the
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11 390 appropriateness of medications during hospitalisation. Therefore, the role of hospital
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14 391 pharmacists in improving polypharmacy and potentially inappropriate prescribing in
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17 392 hospitalised elderly patients is important. Nonetheless, there are conflicting results
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20 393 regarding the effectiveness with which pharmacist interventions in elderly inpatient care
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23 394 can improve polypharmacy and potentially inappropriate prescribing to affect
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26 395 patient-relevant outcomes.[17-21] Given that few past randomised controlled trials have
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29 396 evaluated a patient-relevant outcome as a primary endpoint,[22,23] it is important to
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31 397 conduct a randomised controlled trial to evaluate whether a pharmacist-led intervention
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34 398 improves patient-relevant outcomes, such as readmission and death, in hospitalised
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37 399 elderly orthopaedic patients with polypharmacy or potentially inappropriate prescribing.

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41 400 There are several limitations to this study. First, the non-blinded study design
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43 401 may overestimate the effectiveness of pharmacist intervention.[30] However, due to the
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46 402 nature of the intervention, it is difficult for both participants and clinical pharmacists to
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49 403 be blinded to the allocation. Second, this study is a single-centre trial. Although most
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52 404 past randomised controlled trials were also a single-centre trials,[21,23,31-34] the
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55 405 external validity of this study is limited. Therefore, an additional randomised controlled

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6 406 trial may be needed. Third, we will exclude elderly orthopaedic patients who are
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9 407 admitted electively or who are taking less than five prescribed medications or have no
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11 408 potentially inappropriate prescriptions. Furthermore, elderly patients admitted to other
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14 409 specialty wards, such as internal medicine or general surgery, will also be excluded.
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17 410 Therefore, it is unclear whether the findings of this trial will be applicable to elderly
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20 411 patients who are admitted electively or to other wards besides the orthopaedic ward.
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23 412 Finally, we will not assess the cost-effectiveness of the intervention.
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26 413 Although these limitations are important, this study is one of a few randomised
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28 414 controlled trials to investigate the effectiveness of a pharmacist-led intervention and use
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31 415 a patient-relevant outcome as the primary outcome for hospitalised elderly patients.
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34 416 Given that the burdens of polypharmacy and multi-morbidities among elderly patients
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37 417 have increased in recent years, this trial will provide important information on
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40 418 improving the acute care of elderly patients with polypharmacy or potentially
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43 419 inappropriate prescribing.
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51 421 **Acknowledgements:** None.
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6 423 **Contributors:** KS and JK conceived the project. JK performed the literature search and
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8
9 424 review. KS, JK, ST, and MK designed the study. KS and JK wrote the draft of the
10
11 425 protocol for the study. All authors contributed equally to writing the original protocol
12
13
14 426 for this study. KS is the chief investigator of this study. JK wrote the draft of this
15
16
17 427 manuscript. All authors provided final approval for submission of this manuscript for
18
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20 428 publication consideration.
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25 430 **Competing interests:** All authors have completed the ICMJE unified disclosure from
26
27
28 431 competing interest form at www.icmje.org/coi_disclosure.pdf (available upon request
29
30
31 432 from the corresponding author). All authors declare that they have no conflicts of
32
33
34 433 interest.
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39 435 **Funding:** This study is investigator initiated and self-funded. It is not supported by a
40
41
42 436 specific grant from any funding agency in the public, commercial, or not-for-profit
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45 437 sector.
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51 439 **Ethical approval:** This study was approved by the Medical Ethics Committee of the
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54 440 National Hospital Organization Tochigi Medical Center (No. 29-22).
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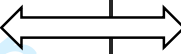

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551 **Table 1.** Time schedule of participant enrolment, interventions, and assessments.

	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

552 * t_1 , within 72 hours after admission; t_1 , at discharge; t_2 , six months after randomisation;

553 t_3 , 12 months after randomisation; t_4 , 24 months after randomisation.

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

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

556 prescribing omission.

557

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

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5 559 *Includes both planned and unplanned hospitalization.
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7 560 †PIP and PPO are defined based on the 2015 STOPP/START Criteria.
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9 561 ED, emergency department; PIP, potentially inappropriate prescribing; PPO, potential

10 562 prescribing omission.
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563 **Figure 1.** Flow diagram of the participant.

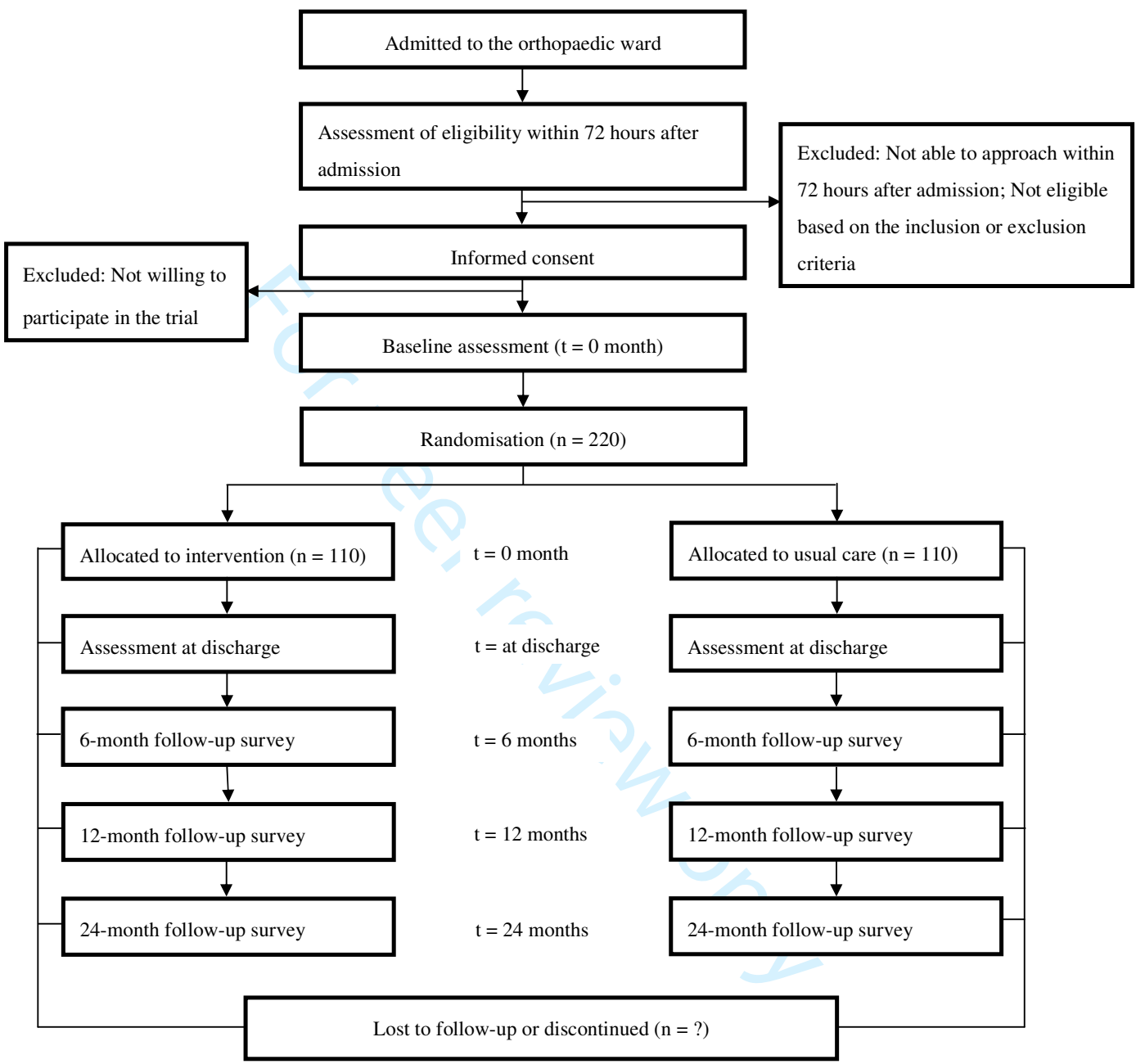
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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

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			

1 2 3 4 5 6	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
7 8		6b	Explanation for choice of comparators	17
9 10	Objectives	7	Specific objectives or hypotheses	8-9
11 12 13 14 15	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
16 17	Methods: Participants, interventions, and outcomes			
18 19 20 21 22 23	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
24 25 26 27 28	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
29 30 31 32 33 34 35 36 37 38	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
39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	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			

1 2 3 4 5 6 7 8 9 10	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
11 12 13 14 15 16		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
17 18 19 20 21 22 23 24	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
25 26 27 28 29	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
30 31 32		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	20-21, Table 2
33 34 35 36 37 38		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
39	Methods: Monitoring			
40 41 42 43 44 45 46 47 48	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
49 50 51 52 53 54 55 56 57 58 59 60		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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" 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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Manuscripts

1 **A study protocol for a single-centre, prospective, non-blinded, randomised,**
2 **12-month, parallel-group superiority study to compare the efficacy of pharmacist**
3 **intervention *versus* usual care for elderly patients hospitalised in orthopaedic**
4 **wards**

5
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12
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6 21 **ABSTRACT**

7
8 22 **Introduction:** Given that polypharmacy and potentially inappropriate prescribing are
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11 23 common in elderly orthopaedic patients, pharmacist interventions to improve
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14 24 medication practices among this population are important. However, past studies have
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17 25 reported mixed results regarding the effectiveness of pharmacist-led interventions in
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20 26 inpatient elderly care. Furthermore, few randomised controlled trials have evaluated
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23 27 patient-relevant outcomes as a primary endpoint. Therefore, we will evaluate whether a
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26 28 pharmacist-led intervention could reduce readmission of hospitalised elderly
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28
29 29 orthopaedic patients with polypharmacy or potentially inappropriate prescribing.

30 30 **Methods and analysis:** This is an ongoing single-centre, prospective, non-blinded,
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32
33 31 randomised controlled trial designed to evaluate the superiority of a pharmacist-led
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36 32 intervention for hospitalised elderly patients compared with usual care. The trial will
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39 33 include newly admitted orthopaedic patients 70 years of age and older with
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42 34 polypharmacy or at least one potentially inappropriate prescription, as identified by the
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45 35 2015 STOPP criteria. Usual care includes medication reconciliation, patient education,
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48 36 and monitoring, as well as providing information about discharge medications.
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51 37 Pharmacist interventions, in addition to usual care, include advising the patient's
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54 38 physician to stop unnecessary or inappropriate medications and start necessary
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6 39 medications. The primary outcome is the one-year readmission rate. Secondary
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8
9 40 outcomes are the proportion of patients who undergo emergency department visits and
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11 41 the occurrences of all-cause death, a new fracture, myocardial infarction, and ischaemic
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13
14 42 stroke. The study started in November 2017, and up to approximately 220 patients will
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16
17 43 be enrolled.

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20 44 **Ethics and dissemination:** The protocol was approved by the Medical Ethics
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22 45 Committee of the National Hospital Organization Tochigi Medical Center (No. 29-22).
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24
25 46 The trial was registered at the UMIN clinical registry. The results of this trial will be
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28 47 submitted for publication in a peer-reviewed journal.

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31 48 **Trial registration number:** UMIN000029404 (registered October 3, 2017).
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37 50 **Key words:** Emergency, Orthopaedic ward, Pharmacist intervention, Polypharmacy,
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39 51 Potentially inappropriate prescribing
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43 52

44 45 53 **Strengths and limitations of this study**

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48 54 ● This randomised controlled trial will evaluate the effectiveness of pharmacist
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51 55 interventions for hospitalised orthopaedic elderly patients, using
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54 56 patient-relevant outcomes as the primary outcomes.

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6 57 ● This is a single-centre study with a small sample size and short-term
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9 58 follow-up.
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11 59 ● Orthopaedic patients who are admitted electively or discharged within less
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14 60 than seven days after admission will be excluded.
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17 61 ● Orthopaedic patients who are prescribed fewer than five medications and are
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20 62 taking no potentially inappropriate medications at admission will be excluded.
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63 INTRODUCTION

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

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

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6 81 polypharmacy and potentially inappropriate prescribing in hospitalised elderly patients
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8 82 is important. Nonetheless, past studies have reported mixed results regarding the
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11 83 effectiveness of a pharmacist-led intervention in improving the appropriateness of
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14 84 medications in inpatient elderly care. Although pharmacist intervention can improve the
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17 85 appropriateness of medications in hospitalised elderly patients,[16] the conclusions of
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20 86 past systematic reviews and meta-analyses have been inconsistent regarding whether
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23 87 patient-relevant outcomes, such as mortality and readmission, were improved by these
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26 88 interventions.[17-20] One recent meta-analysis that included seven randomised
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29 89 controlled trials that evaluated the effectiveness of a pharmacist-led intervention in
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32 90 inpatient elderly care also reported little impact of pharmacist interventions on
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35 91 readmission rates.[21] However, most trials included in this meta-analysis were
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38 92 considered to have a high risk of bias. Furthermore, only two of the seven randomised
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41 93 controlled trials included in the meta-analysis evaluated patient-relevant outcomes as
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44 94 primary endpoints.[22,23] In one of those two trials, a comprehensive pharmacist
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47 95 intervention for hospitalised elderly patients with polypharmacy led to a significant
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50 96 reduction in hospital visits.[23] Therefore, it is still too early to conclude that
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53 97 pharmacist-led interventions for hospitalised elderly patients do not improve
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56 98 patient-relevant outcomes. Furthermore, most studies have targeted internal medicine

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6 99 patients, while few studies have ever investigated the effectiveness of pharmacist
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9 100 interventions for elderly patients hospitalised in an orthopaedic ward.[21] The
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11 101 prevalence of polypharmacy and potentially inappropriate prescribing are particularly
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14 102 high in elderly orthopaedic patients, and these practices often continue after recovery
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17 103 from a fracture.[24,25] Furthermore, polypharmacy is associated with an increased risk
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20 104 of fall and fracture.[5,26] Therefore, pharmacist interventions for improving the
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23 105 appropriateness of medications in hospitalised elderly orthopaedic patients may be
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26 106 associated with better patient outcomes compared with other settings. Thus, we will
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29 107 conduct a randomised controlled trial to evaluate whether a pharmacist-led intervention
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32 108 reduces readmission in hospitalised elderly orthopaedic patients with polypharmacy or
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35 109 potentially inappropriate prescribing.
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111 **Objectives**

112 *Primary objective*

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

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6 116 past study,[23] we selected a readmission time frame of one year for the primary

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9 117 objective.

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16 119 *Secondary objectives*

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19 120 The key secondary objectives are to determine whether pharmacist intervention for

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22 121 elderly orthopaedic patients with polypharmacy or potentially inappropriate prescribing

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25 122 at admission reduces patient-relevant outcomes, such as all-cause death, myocardial

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27
28 123 infarction, ischaemic stroke, and any fractures, compared with usual care. Other

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31 124 secondary objectives are to determine whether pharmacist intervention for elderly

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34 125 orthopaedic patients with polypharmacy or potentially inappropriate prescribing at

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37 126 admission reduces the total number of medications, potentially inappropriate

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39 127 prescribing, and potential prescription omissions.

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46 129 **Literature search and review**

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50 130 We performed a literature search and review of pharmacist interventions in elderly

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53 131 hospitalised orthopaedic patients. We used the terms “pharmacist”, “polypharmacy”,

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6 132 “medication review”, and “inappropriate prescribing” alone and in combination to
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9 133 search the PubMed and Google Scholar databases until 5 August 2017 without limits for
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11 134 the year when the articles were published. We restricted our review to full-text articles
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14 135 published in English or Japanese. We also identified references from the relevant
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17 136 articles. We primarily selected randomised controlled trials, systematic reviews, and
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20 137 meta-analyses. We found a recent systematic review regarding the effectiveness of
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23 138 pharmacist-led intervention on patient outcomes in elderly hospitalised patients.[21]
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26 139 Based on this systematic review, we designed this trial.
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32 141 **METHODS AND ANALYSIS**

33 34 35 142 **Trial design**

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37 143 This study is a single-centre, prospective, non-blinded, randomised, controlled,
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40 144 superiority trial with two parallel groups. All participants who provide consent for
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43 145 participation and fulfil the inclusion criteria will be randomly assigned to the pharmacist
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46 146 intervention group or the usual care group with a 1:1 allocation. The study was
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49 147 approved by the Medical Ethics Committee of the National Hospital Organization
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52 148 Tochigi Medical Center (No. 29-22) and will be conducted in accordance with the
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55 149 Declaration of Helsinki. Standard Protocol Items: The Recommendations for
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6 150 Interventional Trials (SPIRIT checklist)[27] was followed in designing the study
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9 151 protocol (supplementary appendix). Figure 1 summarises the design of the trial, and
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12 152 each of the trial aspects is described in detail below.
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19 154 **Study setting**

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22 155 This study will be conducted in the orthopaedic ward at the National Hospital
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25 156 Organization Tochigi Medical Center. Our hospital is a 350-bed acute care community
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28 157 hospital and is one of five main hospitals that serve approximately 0.5 million
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31 158 individuals in Utsunomiya in the Tochigi prefecture in Japan.
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37 160 **Eligibility criteria**

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40 161 Eligible patients are those who meet all the following inclusion criteria and who do not
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43 162 have any listed exclusion criteria. Based on the American College of Emergency
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46 163 Physicians Geriatric Emergency Department Guidelines,[11] the number of medications
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49 164 taken or the presence of potentially inappropriate prescribing at admission will be used
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52 165 as the inclusion criteria. However, the minimum number of medications for inclusion
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55 166 will be five, based on a past study showing that taking five or more medications was a
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6 167 useful parameter for estimating medication-related adverse effects related to frailty,
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9 168 disability, and mortality among men aged 70 years and older.[28] As-needed
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11 169 medications will be not be counted.
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20 171 *Inclusion criteria*

21 172 1. Age 70 years and older

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23 173 2. Polypharmacy (defined as 5 or more medications) or at least one potentially

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25 174 inappropriate prescription (as defined by the 2015 STOPP criteria[8]) upon

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28 175 admission
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34 177 *Exclusion criteria*

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37 178 1. Elective admission

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39 179 2. Inability to contact patient within 72 hours after their admission

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41 180 3. Expected hospital stay duration of < one week
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48 182 **Study duration, enrolment and number of sites**

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51 183 The study will be conducted at a single hospital in Japan. The planned sample size is

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53 184 approximately 220 patients. This study began after November 2017. The planned
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6 185 follow-up duration for each patient will be two years after the randomisation. Our
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9 186 investigation period is projected to be three years. However, unless we can recruit the
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12 187 planned number of patients within three years after beginning this study, we will extend
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15 188 the investigation duration to achieve the planned number of patients.
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22 **Screening and registration**

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24 191 All elderly patients who are hospitalised in an orthopaedic ward in our hospital will be
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26 192 screened for eligibility for the trial by one of three pharmacists (KS, ST, or MK) every
27
28
29 193 weekday morning. Patients who are hospitalised on weekends will be screened on the
30
31
32 194 following Monday morning. If the screened patients are not eligible, we will document
33
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35 195 the reason for ineligibility for the trial and the number of ineligible patients. All patients
36
37
38 196 who fulfil the inclusion criteria and have no exclusion criteria will be registered by one
39
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41 197 of three pharmacists in the central data centre at the National Hospital Organization
42
43
44 198 Tochigi Medical Center. Unless written informed consent is provided by the patients,
45
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47 199 we will document the reasons why the patients did not provide consent to participate in
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49 200 the trial and document the number of patients who declined to participate in the trial.
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6 202 **Randomisation and allocation concealment**
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9 203 All patients who provide consent for participation and who fulfil the inclusion criteria
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12 204 will be randomised. Randomisation will be requested by one of three pharmacists (KS,
13
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15 205 ST, or MK) to the independent randomisation centre at the National Hospital
16
17
18 206 Organization Tochigi Medical Center via webmail. Participants will be randomly
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21 207 assigned to either the pharmacist intervention group or the usual care group.
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24 208 Randomisation will be performed as block randomisation with a 1:1 allocation. The
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27 209 computer-generated random allocation sequence will be provided by an independent
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30 210 staff pharmacist who is not involved in the treatment of patients or with the assessment
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33 211 of patient outcomes. The randomisation will not be stratified. The block sizes will be
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36 212 concealed until the primary outcome is analysed. Throughout the study, the
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39 213 randomisation list will also be concealed until the end of the study.
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45 215 **Blinding**
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48 216 Due to the nature of the intervention, neither the participants nor the clinical
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51 217 pharmacists can be blinded to the allocation. Patients will be informed of the group to
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54 218 which they have been randomly allocated. Assessments regarding the outcomes will be
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6 219 conducted by an assessor who knows the treatment allocation. The analysis regarding
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8 220 the primary outcome will be conducted by independent investigators who are blinded to
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11 221 the treatment allocation and are not involved in the assessment of patient outcomes.
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18 223 **Pharmacist intervention group**

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22 224 Before starting the study, three study pharmacists (KS, ST, and MK) were trained
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25 225 during a three-month period from May 2017 to July 2017. To standardise the
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28 226 intervention by these pharmacists, approximately 16 sessions (one hour per session)
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30
31 227 regarding medication use in elderly patients based on the 2015 STOPP/START
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33 228 criteria[8] were provided by one internal medicine physician (JK). Therefore, these
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35
36 229 pharmacists will perform the interventions by following the 2015 STOPP/START
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38
39 230 criteria. However, the use of these criteria for the pharmacist intervention will not be
40
41
42 231 mandatory because some criteria have uncertain applicability to Japanese patients. For
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45 232 example, according to the 2015 START criteria, statin therapy is recommended for
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48 233 patients with a past history of cerebral vascular disease unless the patient's status is
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51 234 end-of-life or the patient is aged >85 years. However, the effectiveness of statin therapy
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53 235 for ischaemic stroke patients without dyslipidaemia has not been clearly demonstrated
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6 236 in Japan.[29] One of these trained pharmacists (KS, ST, or MK) will treat the

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9 237 participants from admission to discharge at the following three stages.

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16 239 *Intervention at admission*

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19 240 A comprehensive list of current medications will be compiled within 72 hours after

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22 241 admission. A drug review will be performed, and advice regarding the following factors

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25 242 will be provided to one of five orthopaedic physicians who care for patients: (1)

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28 243 deprescribing inappropriate or unnecessary medications, (2) starting effective or

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31 244 necessary medications, and (3) modifying medication dosages. However, the final

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34 245 decision to adhere to the advice provided by pharmacists will be determined by the

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37 246 orthopaedic physician in charge. Pharmacists will document whether the orthopaedic

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40 247 physicians follow their advice. If the orthopaedic physicians accept the advice but defer

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43 248 action to the primary care physicians, pharmacists will send the discharge summary

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45 249 including their advice to the primary care physicians.

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52 251 *Intervention during hospitalisation*

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6 252 During the hospital stay, patients will be educated about the harms and benefits of their
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9 253 medications. Pharmacists will also provide information about the rationale for
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11 254 medication use and therapeutic goals. Patients will be monitored after starting or
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14 255 stopping medications.
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21 257 *Intervention at discharge*

25 258 Information about discharge medications (e.g., rationale for changes and monitoring
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28 259 needs for newly started or stopped medications) will be summarised in a written
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31 260 document by the pharmacists. Patients will receive discharge counselling with this
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34 261 summary. The summary will also be sent to the primary care physicians and community
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37 262 pharmacists.
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43 264 **Usual care group**

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47 265 Usual care typically includes the same elements as those received by the intervention
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50 266 group but is less extensive. In the usual care group, a comprehensive list of current
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53 267 medications will be compiled by the pharmacists (KS, ST, or MK) within 72 hours after
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6 268 admission. Patients will be monitored and educated about newly started medications by
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9 269 their physician and will receive discharge counselling. However, unlike in the
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11 270 intervention group, advice from pharmacists about deprescribing and starting
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14 271 medications will not be provided to the patient's physician, except in cases of apparent
15
16
17 272 harmful effects of medications that are judged to be symptomatic by pharmacists.
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20 273 Furthermore, pharmacists will neither prepare the summary about discharge medications
21
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23 274 nor send it to the primary care physicians and community pharmacists. However, at the
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26 275 discretion of the pharmacist providing advice about medications for the physicians, the
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29 276 summary about discharge medications will be prepared. These procedures are the
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31 277 standard practice for pharmacists in most Japanese hospitals.[30]
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279 **Data collection**

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

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6 285 caregivers regarding information about primary and secondary outcomes by sending
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9 286 letters at 6 months, 12 months, and 24 months after randomisation. If the participants do
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11 287 not respond to the survey appropriately, we will contact them or their caregivers by
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13
14 288 telephone to minimise the effect of missing data on study outcomes. Furthermore, to
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17 289 collect more accurate data, we will also use data from electronic medical records of our
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20 290 hospital if the participants are admitted or visit our hospital regularly during the study
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23 291 period.
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30 293 **Outcomes**

31 32 33 294 *Primary outcome*

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37 295 The primary outcome is the readmission rate within one year after randomisation. The
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40 296 readmission rate is defined as the proportion of participants who are readmitted.
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43 297 Readmission includes both planned and unplanned admissions. We will evaluate the
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46 298 difference in the readmission rate within one year after randomisation between the two
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49 299 treatment groups.
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6 301 *Secondary outcomes*
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9 302 The secondary outcomes are readmission rates within 6 and 24 months after
10
11 303 randomisation. We will evaluate the differences in the readmission rates at 6 and 24
12
13 304 months between the two treatment groups. The other secondary outcomes are provided
14
15 305 below. These outcomes will be evaluated at discharge and at 6 months, 12 months and
16
17 306 24 months after randomisation. We will evaluate the differences between the two
18
19 307 treatment groups regarding these outcomes at discharge, 6 months, 12 months and 24
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21 308 months.
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30 309 • Any-cause death
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33 310 • Total number of medications
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37 311 • Potentially inappropriate prescribing based on the 2015 STOPP criteria[8]
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40 312 • Potential prescribing omission based on the 2015 START criteria[8]
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44 313 • Any fractures
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47 314 • Ischaemic stroke
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50 315 • Myocardial infarction
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53 316 • Emergency department visits
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8 318 **Statistical analysis**

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11 319 *Sample size calculation*

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14 320 We estimated that a sample of 200 patients would provide the study with a power of at
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17 321 least 80% to show a relative risk reduction of 33% for the primary outcome in the
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20 322 intervention group compared with the usual care group (at a two-sided alpha level of
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23 323 0.05), assuming that the proportion of patients who are readmitted within one year is
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26 324 60% in the usual care group (based on a previous study[23]). Assuming that the dropout
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29 325 rate is 10%, we would need to enrol approximately 220 patients.

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34 327 *Statistical analysis*

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37 328 The baseline characteristics of the study population will be summarised using
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40 329 descriptive statistics. The intervention group will be compared against the usual group
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43 330 for all primary and secondary outcomes (Table 2). We will use a chi-squared test for
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46 331 binary outcomes and Student's t-test for continuous outcomes. We will calculate the
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49 332 relative risk and number needed to treat with corresponding 95% confidence intervals to
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52 333 compare dichotomous variables, and the difference in the means will be used for an

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6 334 additional analysis of continuous variables. For all tests, we will use 2-sided p-values
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9 335 with an alpha < 0.05 for the level of significance.

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11 336 Analyses for all outcomes will include all patients who have undergone
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14 337 randomisation and have provided valid informed consent (intention-to-treat population).
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17 338 Regarding the procedure for missing data, we will exclude the data from participants
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20 339 who are lost to follow-up or whose outcomes are missing. These analyses will be
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23 340 performed using IBM SPSS Statistics Base version 21.0 (IBM Corporation, Nihonbashi,
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25
26 341 Tokyo, Japan) or Excel statistical software package version 2.11 (Bellcurve for Excel;
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29 342 Social Survey Research Information Co., Ltd., Tokyo, Japan). All analyses will be
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31 343 conducted by investigators who are blinded to the study group allocations.
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37 345 **Data management**

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40 346 The trial data of the study participants will be transmitted to and stored in the research
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43 347 database at National Hospital Organization Tochigi Medical Center. This data will not
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46 348 include the participants' identifying information. Instead, individual participants and
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49 349 research data will be identified by unique study identification numbers. At the end of
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52 350 the study, the data will be locked. The data will be stored for at least five years after
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55 351 study completion. Access to the stored data will be limited to investigators. The data
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6 352 will be stored using codes assigned by the investigators and kept on password-protected
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9 353 computers.

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15 355 **Monitoring**

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18 356 *Data monitoring*

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21 357 The risk associated with participation in this study is low, because our aim is to improve
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24 358 the quality of medications in patients. According to the Japanese Ethical Guidelines for
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27 359 Medical and Health Research Involving Human Subjects (as of March 2015), our
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30 360 intervention corresponds with a non-invasive procedure. Therefore, we will not need a
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33 361 data monitoring committee. However, an independent staff pharmacist who is not
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36 362 involved with the trial intervention will monitor the data periodically to ensure safety.

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43 364 *Adverse events*

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46 365 In our study, an adverse event will be defined as any undesirable medical occurrence in
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49 366 a participant without regard to the possibility of a causal relationship. Data on adverse
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52 367 events will be collected after the participants have provided consent and enrolled in the
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55 368 study. If a participant experiences an adverse event after the informed consent document

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6 369 is signed and the participant has not yet started to receive the study intervention, the
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9 370 event will be reported as not being related to the study intervention. All adverse events
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11 371 that occur after entry into the study and for two years after randomisation will be
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14 372 recorded. A serious adverse event for this study is any undesirable medical occurrence
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17 373 that is believed by the investigators to be causally related to the study intervention and
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20 374 results in any of the following: a life-threatening condition (that is, immediate risk of
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23 375 death) or severe or permanent disability.
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30 377 *Auditing*

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33 378 According to the Japanese Ethical Guidelines for Medical and Health Research
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36 379 Involving Human Subjects (as of March 2015), our intervention corresponds with a
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39 380 non-invasive procedure. Furthermore, past studies investigating the effectiveness of a
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42 381 pharmacist intervention have reported few adverse events.[16-23] Therefore, we will
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45 382 not need auditing.
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51 384 **Ethics and dissemination**

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6 385 This study protocol was approved by the Medical Ethics Committee of the National
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8 386 Hospital Organization Tochigi Medical Center (Tochigi, Japan). They judged the study
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11 387 design, ethics, and safety. Substantial amendments to the study protocol must be
12
13
14 388 approved by the Medical Ethics Committee of the National Hospital Organization
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17 389 Tochigi Medical Center. The trial was registered at the UMIN clinical registry on
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20 390 October 3, 2017. We will obtain informed consent from the trial participants or their
21
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23 391 authorised surrogates according to the Japanese Ethical Guidelines for Medical and
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26 392 Health Research Involving Human Subjects (as of March 2015). One of three
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29 393 pharmacists (ST, KS, or MK) will introduce the trial to patients and discuss the trial
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32 394 with all patients using the information sheets about the nature, purpose, and possible
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35 395 risks and benefits of the trial, which was approved by the Medical Ethics Committee of
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38 396 the National Hospital Organization Tochigi Medical Center. Then, the pharmacists will
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41 397 obtain written informed consent from patients willing to participate in the trial. To
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44 398 assure confidentiality, trial participants will be allocated a unique trial identification
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47 399 number throughout the trial. A manuscript with the results of this study will be
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50 400 published in a peer-reviewed journal.

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54 402 **Patient involvement**

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6 403 No patients were involved in determining the research question or outcome measures
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9 404 nor were they involved in developing plans to design or implement the study. No
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11 405 patients were involved in evaluating the burden of the intervention. There are no plans
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14 406 to disseminate the results of this research to study participants or the relevant patient
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17 407 community.
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22 409 **DISCUSSION**

25 410 Given that polypharmacy and potentially inappropriate prescribing among
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28 411 elderly patients is common in acute care settings,[10] it is important to improve the
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31 412 appropriateness of medications during hospitalisation. Therefore, the role of hospital
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34 413 pharmacists in improving polypharmacy and potentially inappropriate prescribing in
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37 414 hospitalised elderly patients is important. Nonetheless, there are conflicting results
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40 415 regarding the effectiveness with which pharmacist interventions in elderly inpatient care
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43 416 can improve polypharmacy and potentially inappropriate prescribing to affect
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46 417 patient-relevant outcomes.[17-21] Given that few past randomised controlled trials have
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49 418 evaluated a patient-relevant outcome as a primary endpoint,[22,23] it is important to
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51 419 conduct a randomised controlled trial to evaluate whether a pharmacist-led intervention
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6 420 improves patient-relevant outcomes, such as readmission and death, in hospitalised
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8 421 elderly orthopaedic patients with polypharmacy or potentially inappropriate prescribing.
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11
12 422 There are several limitations to this study. First, the non-blinded study design
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15 423 may overestimate the effectiveness of pharmacist intervention.[31] However, due to the
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17 424 nature of the intervention, it is difficult for both participants and clinical pharmacists to
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19 425 be blinded to the allocation. Second, this study is a single-centre trial. Although most
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21 426 past randomised controlled trials were also single-centre trials,[21,23,32-35] the
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23 427 external validity of this study is limited. Therefore, an additional randomised controlled
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26 428 trial may be needed. Third, we will exclude elderly orthopaedic patients who are
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29 429 admitted electively or who are taking less than five prescribed medications or have no
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32 430 potentially inappropriate prescriptions. Furthermore, elderly patients admitted to other
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35 431 specialty wards, such as internal medicine or general surgery, will also be excluded.
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38 432 Therefore, it is unclear whether the findings of this trial will be applicable to elderly
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41 433 patients who are admitted electively or to other wards besides the orthopaedic ward.
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44 434 Fourth, medication reconciliation is included in the usual care group in this study. The
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47 435 possible beneficial effect of medical reconciliation for hospitalised patients[36] may
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50 436 mitigate the effectiveness of the pharmacist intervention in this study. Finally, we will
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53 437 not assess the cost-effectiveness of the intervention.
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6 438 Although these limitations are important, this study is one of a few randomised
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9 439 controlled trials to investigate the effectiveness of a pharmacist-led intervention and use
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11 440 a patient-relevant outcome as the primary outcome for hospitalised elderly patients.

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14 441 Given that the burdens of polypharmacy and multi-morbidities among elderly patients
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17 442 have increased in recent years, this trial will provide important information on
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20 443 improving the acute care of elderly patients with polypharmacy or potentially
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23 444 inappropriate prescribing.

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27
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33
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35
36
37 449 review. KS, JK, ST, and MK designed the study. KS and JK wrote the draft of the
38
39
40 450 protocol for the study. All authors contributed equally to writing the original protocol
41
42
43 451 for this study. KS is the chief investigator of this study. JK wrote the draft of this
44
45
46 452 manuscript. All authors provided final approval for submission of this manuscript for
47
48
49 453 publication consideration.

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6 455 **Competing interests:** All authors have completed the ICMJE unified disclosure from
7
8
9 456 competing interest form at www.icmje.org/coi_disclosure.pdf (available upon request
10
11 457 from the corresponding author). All authors declare that they have no conflicts of
12
13
14 458 interest.

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21
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25 462 sector.

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31 464 **Ethical approval:** This study was approved by the Medical Ethics Committee of the
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33 465 National Hospital Organization Tochigi Medical Center (No. 29-22).

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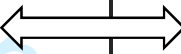

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584 **Table 1.** Time schedule of participant enrolment, interventions, and assessments.

	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

585 * t_1 , within 72 hours after admission; t_1 , at discharge; t_2 , six months after randomisation;

586 t_3 , 12 months after randomisation; t_4 , 24 months after randomisation.

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

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

589 prescribing omission.

590

591 **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

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5 592 *Includes both planned and unplanned hospitalisation.
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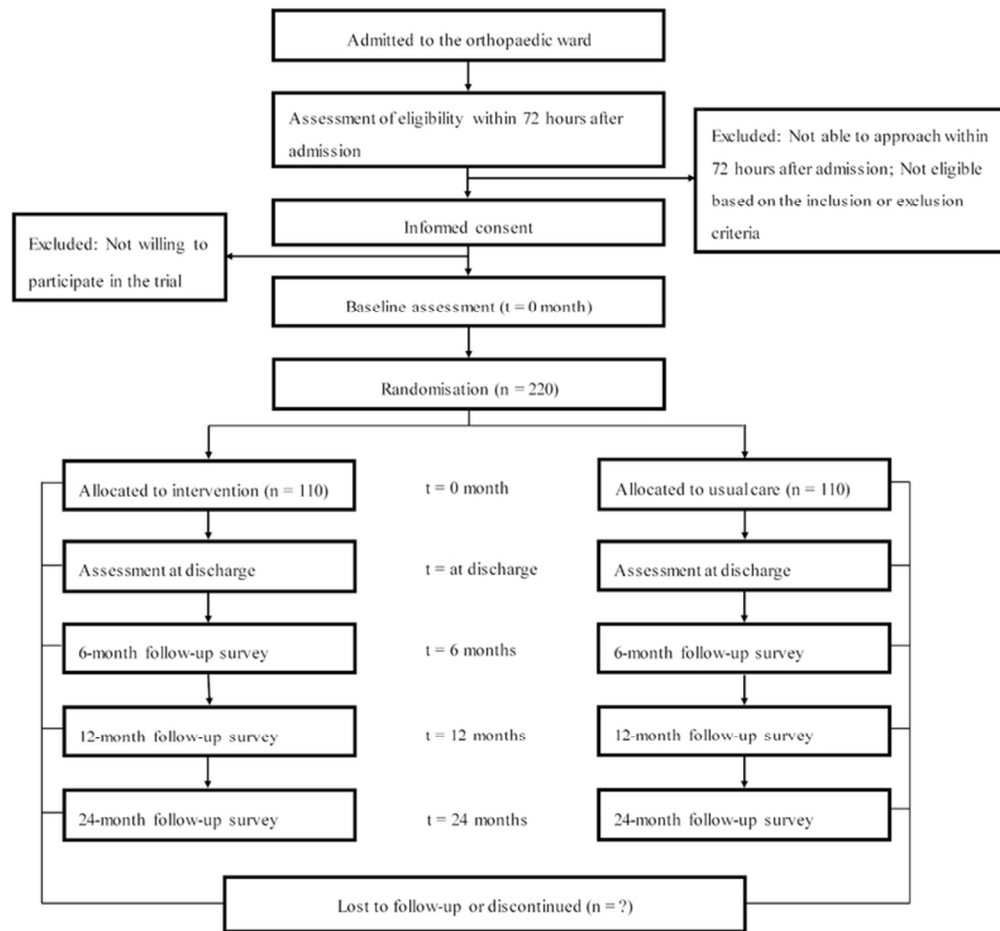
7 593 †PIP and PPO are defined based on the 2015 STOPP/START Criteria.
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9 594 ED, emergency department; PIP, potentially inappropriate prescribing; PPO, potential
10 595 prescribing omission.
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596 **Figure 1.** Flow diagram of the participant.

For peer review only



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			

1 2 3 4 5 6 7 8 9 10	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
11 12 13 14 15 16		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
17 18 19 20 21 22 23 24	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
25 26 27 28 29	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
30 31 32		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	21-22, Table 2
33 34 35 36 37 38		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
39	Methods: Monitoring			
40 41 42 43 44 45 46 47 48	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
49 50 51 52 53 54 55 56 57 58 59 60		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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" 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

Journal:	<i>BMJ Open</i>
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Primary Subject Heading:	Geriatric medicine
Secondary Subject Heading:	Pharmacology and therapeutics
Keywords:	CLINICAL PHARMACOLOGY, ORTHOPAEDIC & TRAUMA SURGERY, GERIATRIC MEDICINE

SCHOLARONE™
Manuscripts

1 **A study protocol for a single-centre, prospective, non-blinded, randomised,**
2 **12-month, parallel-group superiority study to compare the efficacy of pharmacist**
3 **intervention *versus* usual care for elderly patients hospitalised in orthopaedic**
4 **wards**

5
6 Junpei Komagamine, MD¹; Kenichi Sugawara²; Miho Kaminaga²; Shinpei Tatsumi²

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9 Center, 1-10-37, Nakatomatsuri, Utsunomiya, Tochigi 3208580, Japan.

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12
13 **Running title:** Pharmacist interventions

14 **Word count:** 278 (abstract) and 3691 (main text)

15 **Source of support:** None

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6 17 **Corresponding author:** Junpei Komagamine, MD, Department of Internal Medicine,
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6 21 **ABSTRACT**

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8 22 **Introduction:** Given that polypharmacy and potentially inappropriate prescribing are
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11 23 common in elderly orthopaedic patients, pharmacist interventions to improve
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14 24 medication practices among this population are important. However, past studies have
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17 25 reported mixed results regarding the effectiveness of pharmacist-led interventions in
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20 26 inpatient elderly care. Furthermore, few randomised controlled trials have evaluated
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23 27 patient-relevant outcomes as a primary endpoint. Therefore, we will evaluate whether a
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26 28 pharmacist-led intervention could reduce readmission of hospitalised elderly
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29 29 orthopaedic patients with polypharmacy or potentially inappropriate prescribing.

30 30 **Methods and analysis:** This is an ongoing single-centre, prospective, non-blinded,
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33 31 randomised controlled trial designed to evaluate the superiority of a pharmacist-led
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36 32 intervention for hospitalised elderly patients compared with usual care. The trial will
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39 33 include newly admitted orthopaedic patients 70 years of age and older with
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42 34 polypharmacy or at least one potentially inappropriate prescription, as identified by the
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45 35 2015 STOPP criteria. Usual care includes medication reconciliation, patient education,
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48 36 and monitoring, as well as providing information about discharge medications.
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51 37 Pharmacist interventions, in addition to usual care, include advising the patient's
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54 38 physician to stop unnecessary or inappropriate medications and start necessary
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6 39 medications. The primary outcome is the one-year readmission rate. Secondary
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9 40 outcomes are the proportion of patients who undergo emergency department visits and
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11 41 the occurrences of all-cause death, a new fracture, myocardial infarction, and ischaemic
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14 42 stroke. The study started in November 2017, and up to approximately 220 patients will
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17 43 be enrolled.

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20 44 **Ethics and dissemination:** The protocol was approved by the Medical Ethics
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22 45 Committee of the National Hospital Organization Tochigi Medical Center (No. 29-22).
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25 46 The trial was registered at the UMIN clinical registry. The results of this trial will be
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28 47 submitted for publication in a peer-reviewed journal.

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31 48 **Trial registration number:** UMIN000029404 (registered October 3, 2017).
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37 50 **Key words:** Emergency, Orthopaedic ward, Pharmacist intervention, Polypharmacy,
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39 51 Potentially inappropriate prescribing
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42 43 44 45 53 **Strengths and limitations of this study**

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48 54 ● This randomised controlled trial will evaluate the effectiveness of pharmacist
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51 55 interventions for hospitalised orthopaedic elderly patients, using
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54 56 patient-relevant outcomes as the primary outcomes.

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6 57 ● This is a single-centre study with a small sample size and short-term
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9 58 follow-up.
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11 59 ● Orthopaedic patients who are admitted electively or discharged within less
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14 60 than seven days after admission will be excluded.
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17 61 ● Orthopaedic patients who are prescribed fewer than five medications and are
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20 62 taking no potentially inappropriate medications at admission will be excluded.
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63 INTRODUCTION

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

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

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6 81 polypharmacy and potentially inappropriate prescribing in hospitalised elderly patients
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9 82 is important. Nonetheless, past studies have reported mixed results regarding the
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11 83 effectiveness of a pharmacist-led intervention in improving the appropriateness of
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14 84 medications in inpatient elderly care. Although pharmacist intervention can improve the
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17 85 appropriateness of medications in hospitalised elderly patients,[16] the conclusions of
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20 86 past systematic reviews and meta-analyses have been inconsistent regarding whether
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23 87 patient-relevant outcomes, such as mortality and readmission, were improved by these
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26 88 interventions.[17-20] One recent meta-analysis that included seven randomised
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29 89 controlled trials that evaluated the effectiveness of a pharmacist-led intervention in
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32 90 inpatient elderly care also reported little impact of pharmacist interventions on
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35 91 readmission rates.[21] However, most trials included in this meta-analysis were
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38 92 considered to have a high risk of bias. Furthermore, only two of the seven randomised
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41 93 controlled trials included in the meta-analysis evaluated patient-relevant outcomes as
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44 94 primary endpoints.[22,23] In one of those two trials, a comprehensive pharmacist
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47 95 intervention for hospitalised elderly patients with polypharmacy led to a significant
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50 96 reduction in hospital visits.[23] Therefore, it is still too early to conclude that
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53 97 pharmacist-led interventions for hospitalised elderly patients do not improve
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56 98 patient-relevant outcomes. Furthermore, most studies have targeted internal medicine

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6 99 patients, while few studies have ever investigated the effectiveness of pharmacist
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9 100 interventions for elderly patients hospitalised in an orthopaedic ward.[21] The
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11 101 prevalence of polypharmacy and potentially inappropriate prescribing are particularly
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14 102 high in elderly orthopaedic patients, and these practices often continue after recovery
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17 103 from a fracture.[24,25] Furthermore, polypharmacy is associated with an increased risk
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20 104 of fall and fracture.[5,26] Therefore, pharmacist interventions for improving the
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23 105 appropriateness of medications in hospitalised elderly orthopaedic patients may be
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26 106 associated with better patient outcomes compared with other settings. Thus, we will
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29 107 conduct a randomised controlled trial to evaluate whether a pharmacist-led intervention
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32 108 reduces readmission in hospitalised elderly orthopaedic patients with polypharmacy or
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35 109 potentially inappropriate prescribing.
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111 **Objectives**

112 *Primary objective*

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

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6 116 past study,[23] we selected a readmission time frame of one year for the primary
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9 117 objective.

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16 119 *Secondary objectives*

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19 120 The key secondary objectives are to determine whether pharmacist intervention for
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22 121 elderly orthopaedic patients with polypharmacy or potentially inappropriate prescribing
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25 122 at admission reduces patient-relevant outcomes, such as all-cause death, myocardial
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28 123 infarction, ischaemic stroke, and any fractures, compared with usual care. Other
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31 124 secondary objectives are to determine whether pharmacist intervention for elderly
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34 125 orthopaedic patients with polypharmacy or potentially inappropriate prescribing at
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37 126 admission reduces the total number of medications, potentially inappropriate
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39 127 prescribing, and potential prescription omissions.
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46 129 **Literature search and review**

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50 130 We performed a literature search and review of pharmacist interventions in elderly
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53 131 hospitalised orthopaedic patients. We used the terms “pharmacist”, “polypharmacy”,
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6 132 “medication review”, and “inappropriate prescribing” alone and in combination to
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9 133 search the PubMed and Google Scholar databases until 5 August 2017 without limits for
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11 134 the year when the articles were published. We restricted our review to full-text articles
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14 135 published in English or Japanese. We also identified references from the relevant
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17 136 articles. We primarily selected randomised controlled trials, systematic reviews, and
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20 137 meta-analyses. We found a recent systematic review regarding the effectiveness of
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23 138 pharmacist-led intervention on patient outcomes in elderly hospitalised patients.[21]
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26 139 Based on this systematic review, we designed this trial.
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32 141 **METHODS AND ANALYSIS**

33 34 35 142 **Trial design**

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37 143 This study is a single-centre, prospective, non-blinded, randomised, controlled,
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40 144 superiority trial with two parallel groups. All participants who provide consent for
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43 145 participation and fulfil the inclusion criteria will be randomly assigned to the pharmacist
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46 146 intervention group or the usual care group with a 1:1 allocation. The study was
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49 147 approved by the Medical Ethics Committee of the National Hospital Organization
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52 148 Tochigi Medical Center (No. 29-22) and will be conducted in accordance with the
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55 149 Declaration of Helsinki. Standard Protocol Items: The Recommendations for
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6 150 Interventional Trials (SPIRIT checklist)[27] was followed in designing the study
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9 151 protocol (supplementary appendix). Figure 1 summarises the design of the trial, and
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12 152 each of the trial aspects is described in detail below.
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19 154 **Study setting**

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22 155 This study will be conducted in the orthopaedic ward at the National Hospital
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25 156 Organization Tochigi Medical Center. Our hospital is a 350-bed acute care community
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28 157 hospital and is one of five main hospitals that serve approximately 0.5 million
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31 158 individuals in Utsunomiya in the Tochigi prefecture in Japan.
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37 160 **Eligibility criteria**

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40 161 Eligible patients are those who meet all the following inclusion criteria and who do not
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43 162 have any listed exclusion criteria. Based on the American College of Emergency
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46 163 Physicians Geriatric Emergency Department Guidelines,[11] the number of medications
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49 164 taken or the presence of potentially inappropriate prescribing at admission will be used
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52 165 as the inclusion criteria. However, the minimum number of medications for inclusion
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55 166 will be five, based on a past study showing that taking five or more medications was a
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6 167 useful parameter for estimating medication-related adverse effects related to frailty,
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9 168 disability, and mortality among men aged 70 years and older.[28] As-needed
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11 169 medications will be not be considered in the medication count.
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17 171 *Inclusion criteria*

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19
20 172 1. Age 70 years and older
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23 173 2. Polypharmacy (defined as 5 or more medications) or at least one potentially
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25 174 inappropriate prescription (as defined by the 2015 STOPP criteria[8]) upon
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28 175 admission
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34 177 *Exclusion criteria*

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37 178 1. Elective admission
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40 179 2. Inability to contact patient within 72 hours after their admission
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43 180 3. Expected hospital stay duration of < one week
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48 182 **Study duration, enrolment and number of sites**

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51 183 The study will be conducted at a single hospital in Japan. The planned sample size is
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54 184 approximately 220 patients. This study began after November 2017. The planned
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6 185 follow-up duration for each patient will be two years after the randomisation. Our
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8
9 186 investigation period is projected to be three years. However, unless we can recruit the
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11
12 187 planned number of patients within three years after beginning this study, we will extend
13
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15 188 the investigation duration to achieve the planned number of patients.
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20 190 **Screening and registration**

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22
23 191 All elderly patients who are hospitalised in an orthopaedic ward in our hospital will be
24
25
26 192 screened for eligibility for the trial by one of three pharmacists (KS, ST, or MK) every
27
28
29 193 weekday morning. Patients who are hospitalised on weekends will be screened on the
30
31
32 194 following Monday morning. If the screened patients are not eligible, we will document
33
34
35 195 the reason for ineligibility for the trial and the number of ineligible patients. All patients
36
37
38 196 who fulfil the inclusion criteria and have no exclusion criteria will be registered by one
39
40
41 197 of three pharmacists in the central data centre at the National Hospital Organization
42
43
44 198 Tochigi Medical Center. Unless written informed consent is provided by the patients,
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46
47 199 we will document the reasons why the patients did not provide consent to participate in
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49
50 200 the trial and document the number of patients who declined to participate in the trial.
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6 202 **Randomisation and allocation concealment**
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9 203 All patients who provide consent for participation and who fulfil the inclusion criteria
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11
12 204 will be randomised. Randomisation will be requested by one of three pharmacists (KS,
13
14
15 205 ST, or MK) to the independent randomisation centre at the National Hospital
16
17
18 206 Organization Tochigi Medical Center via webmail. Participants will be randomly
19
20
21 207 assigned to either the pharmacist intervention group or the usual care group.
22
23
24 208 Randomisation will be performed as block randomisation with a 1:1 allocation. The
25
26
27 209 computer-generated random allocation sequence will be provided by an independent
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29
30 210 staff pharmacist who is not involved in the treatment of patients or with the assessment
31
32
33 211 of patient outcomes. The randomisation will not be stratified. The block sizes will be
34
35
36 212 concealed until the primary outcome is analysed. Throughout the study, the
37
38
39 213 randomisation list will also be concealed until the end of the study.
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45 215 **Blinding**
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48 216 Due to the nature of the intervention, neither the participants nor the clinical
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51 217 pharmacists can be blinded to the allocation. Patients will be informed of the group to
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53
54 218 which they have been randomly allocated. Assessments regarding the outcomes will be
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6 219 conducted by an assessor who knows the treatment allocation. The analysis regarding
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8 220 the primary outcome will be conducted by independent investigators who are blinded to
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11 221 the treatment allocation and are not involved in the assessment of patient outcomes.
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18 223 **Pharmacist intervention group**

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22 224 Before starting the study, three study pharmacists (KS, ST, and MK) were trained
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24
25 225 during a three-month period from May 2017 to July 2017. To standardise the
26
27
28 226 intervention by these pharmacists, approximately 16 sessions (one hour per session)
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31 227 regarding medication use in elderly patients based on the 2015 STOPP/START
32
33 228 criteria[8] were provided by one internal medicine physician (JK). Therefore, these
34
35
36 229 pharmacists will perform the interventions by following the 2015 STOPP/START
37
38
39 230 criteria. However, the use of these criteria for the pharmacist intervention will not be
40
41
42 231 mandatory because some criteria have uncertain applicability to Japanese patients. For
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45 232 example, according to the 2015 START criteria, statin therapy is recommended for
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47
48 233 patients with a past history of cerebral vascular disease unless the patient's status is
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51 234 end-of-life or the patient is aged >85 years. However, the effectiveness of statin therapy
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54 235 for ischaemic stroke patients without dyslipidaemia has not been clearly demonstrated
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6 236 in Japan.[29] One of these trained pharmacists (KS, ST, or MK) will treat the

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9 237 participants from admission to discharge at the following three stages.

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16 239 *Intervention at admission*

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19 240 A comprehensive list of current medications will be compiled within 72 hours after

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22 241 admission. A drug review will be performed, and advice regarding the following factors

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24
25 242 will be provided to one of five orthopaedic physicians who care for patients: (1)

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28 243 deprescribing inappropriate or unnecessary medications, (2) starting effective or

29
30
31 244 necessary medications, and (3) modifying medication dosages. However, the final

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34 245 decision to adhere to the advice provided by pharmacists will be determined by the

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37 246 orthopaedic physician in charge. Pharmacists will document whether the orthopaedic

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40 247 physicians follow their advice. If the orthopaedic physicians accept the advice but defer

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43 248 action to the primary care physicians, pharmacists will send the discharge summary

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46 249 including their advice to the primary care physicians.

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52 251 *Intervention during hospitalisation*

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6 252 During the hospital stay, patients will be educated about the harms and benefits of their
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9 253 medications. Pharmacists will also provide information about the rationale for
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11 254 medication use and therapeutic goals. Patients will be monitored after starting or
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14 255 stopping medications.
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18 256

21 257 *Intervention at discharge*

25 258 Information about discharge medications (e.g., rationale for changes and monitoring
26
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28 259 needs for newly started or stopped medications) will be summarised in a written
29
30
31 260 document by the pharmacists. Patients will receive discharge counselling with this
32
33
34 261 summary. The summary will also be sent to the primary care physicians and community
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36
37 262 pharmacists.
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43 264 **Usual care group**

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47 265 Usual care typically includes the same elements as those received by the intervention
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49
50 266 group but is less extensive. In the usual care group, a comprehensive list of current
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53 267 medications will be compiled by the pharmacists (KS, ST, or MK) within 72 hours after
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6 268 admission. Patients will be monitored and educated about newly started medications by
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9 269 their physician and will receive discharge counselling. However, unlike in the
10
11 270 intervention group, advice from pharmacists about deprescribing and starting
12
13
14 271 medications will not be provided to the patient's physician, except in cases of apparent
15
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17 272 harmful effects of medications that are judged to be symptomatic by pharmacists.
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20 273 Furthermore, pharmacists will neither prepare the summary about discharge medications
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22
23 274 nor send it to the primary care physicians and community pharmacists. However, at the
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26 275 discretion of the pharmacist providing advice about medications for the physicians, the
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28
29 276 summary about discharge medications will be prepared. These procedures are the
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31 277 standard practice for pharmacists in most Japanese hospitals.[30]
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279 **Data collection**

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

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6 285 caregivers regarding information about primary and secondary outcomes by sending
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9 286 letters at 6 months, 12 months, and 24 months after randomisation. If the participants do
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11 287 not respond to the survey appropriately, we will contact them or their caregivers by
12
13
14 288 telephone to minimise the effect of missing data on study outcomes. Furthermore, to
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17 289 collect more accurate data, we will also use data from electronic medical records of our
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20 290 hospital if the participants are admitted or visit our hospital regularly during the study
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23 291 period.
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30 293 **Outcomes**

31 32 33 294 *Primary outcome*

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37 295 The primary outcome is the readmission rate within one year after randomisation. The
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40 296 readmission rate is defined as the proportion of participants who are re-hospitalised
41
42
43 297 regardless of the cause of hospitalisation (all-cause readmission). Patients who visit an
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46 298 emergency department but are not hospitalised will not be counted. We will evaluate the
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49 299 difference in the readmission rate within one year after randomisation between the two
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51 300 treatment groups.
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6 302 *Secondary outcomes*
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9 303 The secondary outcomes are readmission rates within 6 and 24 months after
10
11
12 304 randomisation. We will evaluate the differences in the readmission rates at 6 and 24
13
14
15 305 months between the two treatment groups. The other secondary outcomes are provided
16
17
18 306 below. These outcomes will be evaluated at discharge and at 6 months, 12 months and
19
20
21 307 24 months after randomisation. We will evaluate the differences between the two
22
23
24 308 treatment groups regarding these outcomes at discharge, 6 months, 12 months and 24
25
26
27 309 months.

30 310 • Any-cause death

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33 311 • Total number of medications

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37 312 • Potentially inappropriate prescribing based on the 2015 STOPP criteria[8]
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41 313 • Potential prescribing omission based on the 2015 START criteria[8]
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44 314 • Any fractures

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48 315 • Ischaemic stroke
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51 316 • Myocardial infarction
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55 317 • Emergency department visits
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9 319 **Statistical analysis**

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11 320 *Sample size calculation*

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14 321 We estimated that a sample of 200 patients would provide the study with a power of at
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17 322 least 80% to show a relative risk reduction of 33% for the primary outcome in the
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19
20 323 intervention group compared with the usual care group (at a two-sided alpha level of
21
22
23 324 0.05), assuming that the proportion of patients who are readmitted within one year is
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26 325 60% in the usual care group (based on a previous study[23]). Assuming that the dropout
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29 326 rate is 10%, we would need to enrol approximately 220 patients.

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34 328 *Statistical analysis*

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37 329 The baseline characteristics of the study population will be summarised using
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40 330 descriptive statistics. The intervention group will be compared against the usual group
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42
43 331 for all primary and secondary outcomes (Table 2). We will use a chi-squared test for
44
45
46 332 binary outcomes and Student's t-test for continuous outcomes. We will calculate the
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49 333 relative risk and number needed to treat with corresponding 95% confidence intervals to
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52 334 compare dichotomous variables, and the difference in the means will be used for an

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6 335 additional analysis of continuous variables. For all tests, we will use 2-sided p-values
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9 336 with an alpha < 0.05 for the level of significance.

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11 337 Analyses for all outcomes will include all patients who have undergone
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13
14 338 randomisation and have provided valid informed consent (intention-to-treat population).
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17 339 Regarding the procedure for missing data, we will exclude the data from participants
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20 340 who are lost to follow-up or whose outcomes are missing. These analyses will be
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22
23 341 performed using IBM SPSS Statistics Base version 21.0 (IBM Corporation, Nihonbashi,
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25
26 342 Tokyo, Japan) or Excel statistical software package version 2.11 (Bellcurve for Excel;
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28
29 343 Social Survey Research Information Co., Ltd., Tokyo, Japan). All analyses will be
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31 344 conducted by investigators who are blinded to the study group allocations.
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37 346 **Data management**

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40 347 The trial data of the study participants will be transmitted to and stored in the research
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43 348 database at National Hospital Organization Tochigi Medical Center. This data will not
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45
46 349 include the participants' identifying information. Instead, individual participants and
47
48
49 350 research data will be identified by unique study identification numbers. At the end of
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52 351 the study, the data will be locked. The data will be stored for at least five years after
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55 352 study completion. Access to the stored data will be limited to investigators. The data
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6 353 will be stored using codes assigned by the investigators and kept on password-protected
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9 354 computers.

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15 356 **Monitoring**

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18 357 *Data monitoring*

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21 358 The risk associated with participation in this study is low, because our aim is to improve
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24 359 the quality of medications in patients. According to the Japanese Ethical Guidelines for
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27 360 Medical and Health Research Involving Human Subjects (as of March 2015), our
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30 361 intervention corresponds with a non-invasive procedure. Therefore, we will not need a
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33 362 data monitoring committee. However, an independent staff pharmacist who is not
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36 363 involved with the trial intervention will monitor the data periodically to ensure safety.

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43 365 *Adverse events*

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46 366 In our study, an adverse event will be defined as any undesirable medical occurrence in
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49 367 a participant without regard to the possibility of a causal relationship. Data on adverse
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52 368 events will be collected after the participants have provided consent and enrolled in the
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55 369 study. If a participant experiences an adverse event after the informed consent document

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6 370 is signed and the participant has not yet started to receive the study intervention, the
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9 371 event will be reported as not being related to the study intervention. All adverse events
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11 372 that occur after entry into the study and for two years after randomisation will be
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14 373 recorded. A serious adverse event for this study is any undesirable medical occurrence
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17 374 that is believed by the investigators to be causally related to the study intervention and
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20 375 results in any of the following: a life-threatening condition (that is, immediate risk of
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23 376 death) or severe or permanent disability.
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30 378 *Auditing*

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33 379 According to the Japanese Ethical Guidelines for Medical and Health Research
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36 380 Involving Human Subjects (as of March 2015), our intervention corresponds with a
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39 381 non-invasive procedure. Furthermore, past studies investigating the effectiveness of a
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42 382 pharmacist intervention have reported few adverse events.[16-23] Therefore, we will
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45 383 not need auditing.
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51 385 **Ethics and dissemination**

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6 386 This study protocol was approved by the Medical Ethics Committee of the National
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9 387 Hospital Organization Tochigi Medical Center (Tochigi, Japan). They judged the study
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11 388 design, ethics, and safety. Substantial amendments to the study protocol must be
12
13
14 389 approved by the Medical Ethics Committee of the National Hospital Organization
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17 390 Tochigi Medical Center. The trial was registered at the UMIN clinical registry on
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20 391 October 3, 2017. We will obtain informed consent from the trial participants or their
21
22
23 392 authorised surrogates according to the Japanese Ethical Guidelines for Medical and
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25
26 393 Health Research Involving Human Subjects (as of March 2015). One of three
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29 394 pharmacists (ST, KS, or MK) will introduce the trial to patients and discuss the trial
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31
32 395 with all patients using the information sheets about the nature, purpose, and possible
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34 396 risks and benefits of the trial, which was approved by the Medical Ethics Committee of
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36
37 397 the National Hospital Organization Tochigi Medical Center. Then, the pharmacists will
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40 398 obtain written informed consent from patients willing to participate in the trial. To
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43 399 assure confidentiality, trial participants will be allocated a unique trial identification
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46 400 number throughout the trial. A manuscript with the results of this study will be
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49 401 published in a peer-reviewed journal.
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54 403 **Patient involvement**
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6 404 No patients were involved in determining the research question or outcome measures
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9 405 nor were any patients involved in developing plans to design or implement the study.
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11 406 No patients were involved in evaluating the burden of the intervention. There are no
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14 407 plans to disseminate the results of this research to study participants or the relevant
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17 408 patient community.
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23 410 **DISCUSSION**

24
25 411 Given that polypharmacy and potentially inappropriate prescribing among
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28 412 elderly patients is common in acute care settings,[10] it is important to improve the
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31 413 appropriateness of medications during hospitalisation. Therefore, the role of hospital
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34 414 pharmacists in improving polypharmacy and potentially inappropriate prescribing in
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37 415 hospitalised elderly patients is important. Nonetheless, there are conflicting results
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40 416 regarding the effectiveness with which pharmacist interventions in elderly inpatient care
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43 417 can improve polypharmacy and potentially inappropriate prescribing to affect
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46 418 patient-relevant outcomes.[17-21] Given that few past randomised controlled trials have
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49 419 evaluated a patient-relevant outcome as a primary endpoint,[22,23] it is important to
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51 420 conduct a randomised controlled trial to evaluate whether a pharmacist-led intervention
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6 421 improves patient-relevant outcomes, such as readmission and death, in hospitalised
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8 422 elderly orthopaedic patients with polypharmacy or potentially inappropriate prescribing.
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11
12 423 There are several limitations to this study. First, the non-blinded study design
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15 424 may overestimate the effectiveness of pharmacist intervention.[31] However, due to the
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18 425 nature of the intervention, it is difficult for both participants and clinical pharmacists to
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21 426 be blinded to the allocation. Second, this study is a single-centre trial. Although most
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24 427 past randomised controlled trials were also single-centre trials,[21,23,32-35] the
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27 428 external validity of this study is limited. Therefore, an additional randomised controlled
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30 429 trial may be needed. Third, we will exclude elderly orthopaedic patients who are
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33 430 admitted electively or who are taking less than five prescribed medications or have no
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36 431 potentially inappropriate prescriptions. Furthermore, elderly patients admitted to other
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39 432 specialty wards, such as internal medicine or general surgery, will also be excluded.
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41
42 433 Therefore, it is unclear whether the findings of this trial will be applicable to elderly
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44
45 434 patients who are admitted electively or to other wards besides the orthopaedic ward.
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47
48 435 Fourth, medication reconciliation is included in the usual care group in this study. The
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51 436 possible beneficial effect of medical reconciliation for hospitalised patients[36] may
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54 437 mitigate the effectiveness of the pharmacist intervention in this study. Finally, we will
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57 438 not assess the cost-effectiveness of the intervention.
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6 439 Although these limitations are important, this study is one of a few randomised
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9 440 controlled trials to investigate the effectiveness of a pharmacist-led intervention and use
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11 441 a patient-relevant outcome as the primary outcome for hospitalised elderly patients.

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14 442 Given that the burdens of polypharmacy and multi-morbidities among elderly patients
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17 443 have increased in recent years, this trial will provide important information on
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20 444 improving the acute care of elderly patients with polypharmacy or potentially
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22
23 445 inappropriate prescribing.

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27
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35
36
37 450 review. KS, JK, ST, and MK designed the study. KS and JK wrote the draft of the
38
39
40 451 protocol for the study. All authors contributed equally to writing the original protocol
41
42
43 452 for this study. KS is the chief investigator of this study. JK wrote the draft of this
44
45
46 453 manuscript. All authors provided final approval for submission of this manuscript for
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49 454 publication consideration.

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6 456 **Competing interests:** All authors have completed the ICMJE unified disclosure from
7
8
9 457 competing interest form at www.icmje.org/coi_disclosure.pdf (available upon request
10
11 458 from the corresponding author). All authors declare that they have no conflicts of
12
13
14 459 interest.

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21
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23
24 463 sector.

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31 465 **Ethical approval:** This study was approved by the Medical Ethics Committee of the
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33 466 National Hospital Organization Tochigi Medical Center (No. 29-22).

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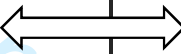

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585 **Table 1.** Time schedule of participant enrolment, interventions, and assessments.

	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

586 * t_1 , within 72 hours after admission; t_1 , at discharge; t_2 , six months after randomisation;

587 t_3 , 12 months after randomisation; t_4 , 24 months after randomisation.

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

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

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

591 prescribing omission.

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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

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5 594 *Includes all-cause hospitalisation regardless of the cause of hospitalisation.
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7 595 †PIP and PPO are defined based on the 2015 STOPP/START Criteria.
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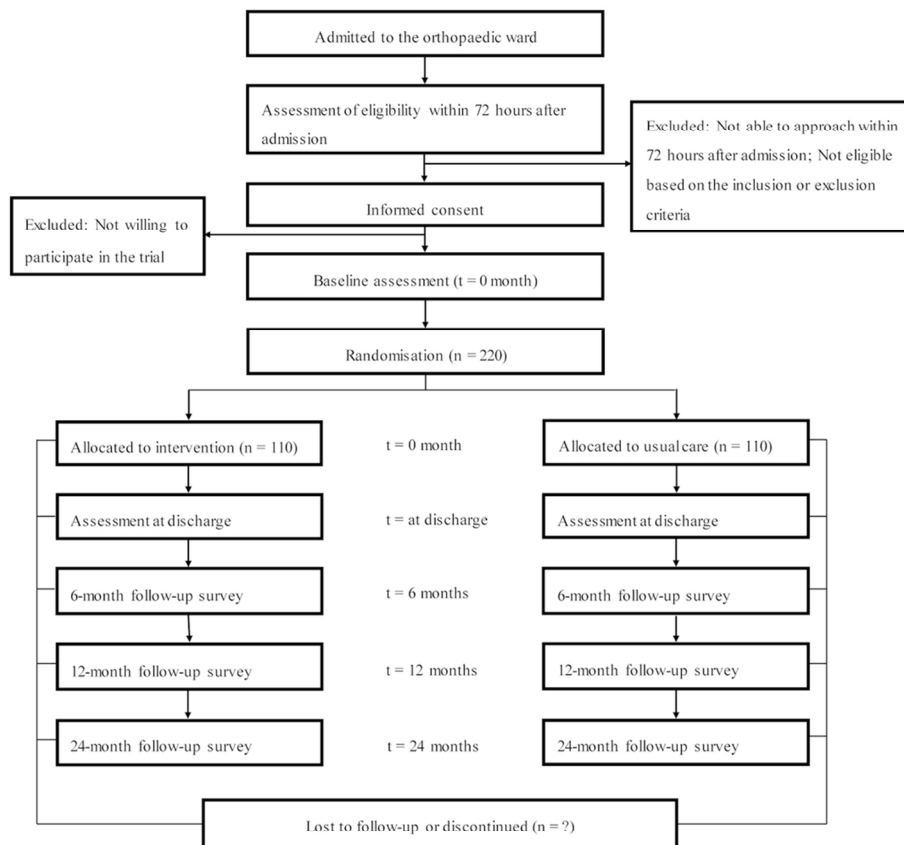
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598 **Figure 1.** Flow diagram of the participant.

For peer review only



Flow diagram of the participant.

99x99mm (300 x 300 DPI)





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			

1 2 3 4 5 6 7 8 9 10 11	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
12 13 14 15 16 17		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
18 19 20 21 22 23 24 25	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
26 27 28 29 30 31	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
32 33 34		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	21-22, Table 2
35 36 37 38 39 40		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
41 42	Methods: Monitoring			
43 44 45 46 47 48 49 50 51 52	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
53 54 55 56 57 58 59 60		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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.



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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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.