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## Protocol of a randomized controlled trial on the efficacy of medication optimization in elderly inpatients: Medication optimization Protocol Efficacy for Geriatric inpatients (MPEG) trial

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3 **Protocol of a randomized controlled trial on the efficacy of medication optimization in elderly**  
4 **inpatients: Medication optimization Protocol Efficacy for Geriatric inpatients (MPEG) trial**  
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## ABSTRACT

**Introduction:** Whether medication optimization improves clinical outcomes in elderly individuals remains unclear. The current study aims to evaluate the effect of multidisciplinary team-based medication optimization on survival, re-hospitalization, and unscheduled hospital visits in elderly patients.

**Methods and analysis:** We report the protocol of a single center, open-label, randomized controlled trial. The enrolled subjects will be medical inpatients, aged 65 years or older, admitted to a community hospital, and receiving five or more regular medications. The participants will be randomly assigned to receive either an intervention for medication optimization or the usual care. The intervention will consist of a multidisciplinary team-based medication review, followed by a medication optimization proposal based on the Screening Tool of Older Persons' potentially inappropriate Prescriptions/Screening Tool to Alert doctors to the Right Treatment (STOPP/START) criteria and an implicit medication optimization protocol. Medication optimization summaries will be sent to primary care physicians and community pharmacists upon discharge. The primary outcome will be a composite of death, unscheduled hospital visits, and re-hospitalization until 48 weeks after randomization. Secondary outcomes will include each of the primary endpoints, the number of prescribed medications, QoL score, level of long-term care required, drug-related adverse events, death during hospitalization, and injury due to falls. Participants will be followed-up for 48 weeks with bimonthly telephone interviews to assess the primary and secondary outcomes. A log-rank test stratified by randomization factors will be used to compare the incidence of composite endpoint. The study was initiated in 2019 and a minimum of 500 patients will be enrolled.

**Ethics and dissemination:** The study protocol has been approved by the Institutional Ethical Committee of St. Marianna University School of Medicine (No.4129). The results of the current study will be submitted to a peer-reviewed journal.

**Trial registration number:** UMIN000035265

**Keywords:** polypharmacy, deprescriptions, potentially inappropriate medication list, frail elderly

### Strengths and limitations of this study

- The MPEG trial is a large randomized controlled trial that will examine the efficacy of multidisciplinary team-based medication optimization on patient-oriented outcomes.
- The study will be adequately powered to examine the efficacy of medication optimization protocol in elderly inpatients with a 48-week follow-up period.
- The multidisciplinary team-based intervention incorporates both explicit and implicit deprescribing criteria to enhance the efficacy of medication optimization process in elderly inpatients.
- The open-label design of this study has limitations; however, it will provide a rationale for future multicenter confirmatory studies.

### INTRODUCTION

Polypharmacy is known to increase death rate, fall incidence, and healthcare utilization in elderly individuals.[1-3] Potentially inappropriate medication lists (PIMs), aiming to reduce inappropriate medication prescriptions in elderly individuals, have been a mainstay of medication optimization strategies.[4] They can be used as an explicit criterion for medication reconciliation. Among the PIMs, the Screening Tool of Older Persons' potentially inappropriate Prescriptions/Screening Tool to Alert doctors to the Right Treatment (STOPP/START) is a widely accepted criterion, incorporating the list of medicines that are potentially harmful and those that should be prescribed for elderly individuals.[5] A recent systematic review of randomized controlled trials of interventions to reduce polypharmacy using the STOPP criteria showed that the STOPP-based interventions are associated with reduced falls, emergency visits, and medical costs, and short hospital stays.[6] However, to date, no study has shown the effect of STOPP-based interventions on clinically important outcomes such as death and re-admission rates. In reality, most adverse drug reactions are caused by drugs that are not included in such criteria.[7] In addition, there could be both “appropriate” and “inappropriate” polypharmacy, depending on the patient background.

Recently, a more implicit criterion for polypharmacy, called deprescribing protocol, has been expected to improve patient outcomes. Scott et al. defined it as “the systematic process of identifying

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3 and discontinuing drugs in instances in which existing or potential harms outweigh existing or  
4 potential benefits within the context of an individual patient's care goals, current level of functioning,  
5 life expectancy, values, and preferences.”[8] The use of the deprescribing protocol has been indicated  
6 to reduce the number of prescription drugs,[9] but whether the intervention improves significant  
7 patient-oriented outcomes, such as death, hospitalization, and falls, remains controversial.[10-12] A  
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and discontinuing drugs in instances in which existing or potential harms outweigh existing or potential benefits within the context of an individual patient's care goals, current level of functioning, life expectancy, values, and preferences.”[8] The use of the deprescribing protocol has been indicated to reduce the number of prescription drugs,[9] but whether the intervention improves significant patient-oriented outcomes, such as death, hospitalization, and falls, remains controversial.[10-12] A Cochrane review had pointed out that studies, which failed to demonstrate the benefits of the deprescribing protocol, had a follow-up period of less than 1 year, which may not be sufficient to identify the true effect of the deprescribing protocol.[13] Thus, a lack of evidence regarding the effect of the deprescribing protocol on patient-oriented outcomes could be attributed to methodological limitations in previous studies.

### **Objectives**

In this study, we aim to evaluate the effect of multidisciplinary team-based medication optimization process, using both explicit and implicit criteria, on survival, re-hospitalization, and unscheduled hospital visits in elderly inpatients.

## **METHODS AND ANALYSIS**

### **MPEG trial design**

This is a single center, open-label, randomized controlled trial with a two-arm parallel design. **Figure 1** depicts the flow diagram of the progress through various phases of the study. The current trial protocol follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines, developed to provide a standardized guidance for recommended items to be included in a clinical trial protocol.[14] The study was approved by the Institutional Ethics Committee of St. Marianna University School of Medicine (No. 4129) and was registered at the UMIN Clinical Trials Registry (UMIN000035265).

### **Study setting and eligibility criteria**

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3 The present trial will be conducted in patients in the medical wards of a university-affiliated  
4 community hospital. Patients admitted to the medical wards will be screened for study eligibility by  
5 hospital receptionists, medical ward-based pharmacists, and the principal- or co-investigators.  
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9 The eligibility criteria for participants are:

- 10 1. Medical inpatients;
- 11 2. Aged 65 years or older;
- 12 3. Taking five or more regularly prescribed medications;
- 13 4. Predicted length of hospital stay after admission: 1 week or longer.

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22 Exclusion criteria include the following: inability to take medications orally; life expectancy of less  
23 than 1 month; and attending physicians disagreeing to study participation. In the current study, a  
24 regularly prescribed medication is defined as “any form of prescribed oral medications recorded in the  
25 participant’s medical record handbook, a referral letter, or electronic medical record over 28 days or  
26 longer at the time of hospital admission.” Drugs that are used “as needed” will not be counted in  
27 regular medications.  
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### 37 **Interventions**

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39 Participants will be randomly assigned to receive either a medication optimization  
40 intervention or the usual care. Both groups will be subjected to a medication review by ward-based  
41 pharmacists, along with the usual care from their attending physicians. For those assigned to the  
42 intervention group, the multidisciplinary deprescribing team, which will consist of a physician and a  
43 pharmacist, will conduct the medication optimization intervention within 48 h of allocation. Ward-  
44 based nurses will be consulted by the deprescribing team, as required, to collect any information  
45 necessary for the medication optimization proposal. All members of the deprescribing team will  
46 receive standardized instruction and guidance in advance. In addition, monthly deprescribing-team  
47 meetings will be held for monitoring and quality control of interventions.  
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58 Overall, the intervention will consist of a medication review, followed by the development of  
59 a medication optimization proposal based on the STOPP/START criteria[5] and a medication  
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3 optimization protocol (**Figure 2**). First, the study participant's baseline data (age, sex, past medical  
4 history, comorbid conditions, height, weight, blood pressure, pulse rate, oxygen saturation, body  
5 temperature, eGFR, serum sodium level, serum potassium level, and regularly prescribed  
6 medications) will be collected via a chart review and entered into a computer-based medication  
7 optimization support system, developed specifically for the trial. The medication optimization support  
8 system will automatically generate a draft of proposal according to the STOPP/START criteria.[5]  
9  
10 After reviewing the draft proposal, the deprescribing team will conduct a step-by-step discussion  
11 based on the medication optimization protocol (**Figure 3**), involving the following steps per the  
12 algorithm proposed by Scott et al.[8]  
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22 **1) Does the prescription have an appropriate indication?**

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24 All efforts will be made to ensure the indications for each drug. If no clear indication is confirmed  
25 or the drug is prescribed as a result of a prescribing cascade (e.g., proton pump inhibitor to reduce  
26 gastrointestinal adverse effects associated with non-steroidal anti-inflammatory drugs), the  
27 deprescribing team will discuss whether the drug should be deprescribed.  
28  
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33 **2) Does the harm outweigh the potential benefits?**

34  
35 Study participants' symptoms and laboratory results will be reviewed to determine any adverse  
36 effect that outweighs the expected benefits of the prescribed drug.  
37  
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39 **3) For a symptomatic medication, does the patient currently have the target symptom?**

40  
41 Symptomatic medications that control active symptoms to maintain quality of life (e.g.,  
42 painkillers and antiemetics) will be evaluated for their necessity. If the symptom is mild or  
43 intermittent or the drug is deemed ineffective, cessation, dose reduction, or "as-needed" use of the  
44 corresponding drug will be discussed.  
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49 **4) For a preventive medication, does the patient have enough life expectancy to expect benefit  
50 of preventive care?**

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52 Medications aimed to prevent the occurrence of disease (e.g. statins and glucose-lowering drugs)  
53 will be considered for their benefits, the length of time required for the expected benefit, and the  
54 participant's preference and estimated life expectancy.  
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3 The rationale for medication optimization proposal will be explained and discussed in detail with  
4 each participant or next of kin (NOK). Upon participant's agreement, the team will recommend the  
5 medication optimization plan, including its rationale, to the participant's attending physician. Whether  
6 the proposal would be accepted or not will be left to the discretion of the participant and his/her  
7 attending physician, as a part of clinical judgment. The details of each medication optimization  
8 proposal and the list of medications at discharge will be recorded to track adherence to the proposal.  
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15 Medication optimization summary, including the reason for prescription modification and  
16 relevant precautions, will be sent to the study participant's primary care physician and community  
17 pharmacists upon discharge.  
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## 24 **Outcomes**

### 25 **Primary outcome**

26 The primary outcome is a composite of all-cause death, unscheduled hospital visits, and re-  
27 hospitalization until 48 weeks after randomization. Time to the first occurrence of primary composite  
28 outcome will be recorded for the survival analysis. An unscheduled hospital visit is defined as an  
29 unexpected visit to the emergency department or outpatient clinic during the follow-up period owing to  
30 new or worsening symptoms, signs, and concerns. Any rehospitalization due to new or worsening  
31 symptoms, signs, and concerns after first hospital discharge will be recorded. A hospital transfer will  
32 be deemed as continuation of hospitalization rather than rehospitalization.  
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### 45 **Secondary outcomes**

46 The following endpoints at the baseline, 24 weeks, and 48 weeks post-randomization, will be assessed  
47 as secondary outcomes.  
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#### 51 **1. Number of regular and potentially inappropriate medications**

52 The number of prescribed medications listed in participant's medical record handbook, referral  
53 letter, or electronic medical record over a duration of 28 days or longer at the baseline, 24 weeks,  
54 and 48 weeks post-randomization will be considered as "regular medication." Any prescribed  
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3 regular medication listed in the STOPP criteria[5] will be indicated as PIM, whose number at the  
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5 baseline, 24 weeks, and 48 weeks post-randomization will be recorded simultaneously.  
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## 7 2. **Level of long-term care required**

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9 The level of long-term care required, under the Japanese long-term care (LTC) insurance system,  
10  
11 will be assessed at the baseline, 24 weeks, and 48 weeks post-randomization. The levels will be  
12  
13 assigned by the local government as follows: independent, support required 1 or 2, and care  
14  
15 required 1 to 5—where care level 5 implies the highest level of requirement for long-term care  
16  
17 and independent implies the lowest level of requirement.[15]  
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## 20 3. **Health-related quality of life**

21  
22 Self-reported general health status will be recorded at three time points using EQ5D-3L.[16] We  
23  
24 will use the Japanese version of EQ5D-3L and a Japanese scoring system that have been found to  
25  
26 be valid and reliable.[17]  
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31 In addition to the above-listed outcomes, the ones listed below, occurring within 48 weeks after  
32  
33 randomization, will be assessed including the event dates.

- 34 ➤ All-cause death
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- 36 ➤ All-cause death during initial hospitalization
- 37
- 38 ➤ Unscheduled hospital visits
- 39
- 40 ➤ Rehospitalization
- 41
- 42 ➤ Drug adverse events
- 43
- 44

45 Any potential drug-related adverse events (AEs) will be recorded according to the Japanese  
46  
47 version of CTCAE 4.0.[18] Drug names, symptom onset timing, severity, treatment,  
48  
49 consequence, and relevance to the intervention will be entered in the report form.  
50

- 51 ➤ Injury due to falls
- 52

53 For the current study, a fall was defined per Gibson et al.: “unintentionally coming to the ground  
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55 or some lower level and other than as a consequence of sustaining a violent blow, loss of  
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57 consciousness, sudden onset of paralysis as in stroke or an epileptic seizure.”[19]  
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### Sample size

Ravn-Nielsen et al., who examined the effect of multifaceted pharmacist intervention in medical wards, demonstrated a 23% reduction in hazard risk in the composite outcome of readmission or ED visits, within 180 days after inclusion, compared with that in usual care.[20] They did not find a significant difference in mortality across the groups, although a 6-month follow-up period may not be sufficient to detect a true effect. Another study conducted at residential aged care facilities revealed the deprescribing group, compared with the usual-care group, demonstrated a 40% mortality reduction within 12 months of randomization.[9] Based on these two trials and other related studies,[21-24] in this study, the investigators agreed on the requirement of at least 500 cases to provide a power of 80%, with a significance level at  $\alpha = 0.05$ , on the assumption of primary composite endpoint rates of 30% and 40% in the intervention and control groups, respectively, and a true hazard-ratio of 0.75 while allowing for a 15% dropout.

### Recruitment

We will recruit 500 subjects in the MPEG trial, based on the above-mentioned sample size calculation, to detect a significant difference in the primary outcome. Participants will be recruited from six medical wards in the study site (Kawasaki Municipal Tama Hospital). Community pharmacy and regional primary care provider outreach and advertising were conducted by the principal investigator before the study. Advertisements included information on inclusion criteria and time commitment, description of the intervention, and their chance of receiving intervention. Recruitment of participants in this trial was initiated in May 2019 and will last for 2 years or until target enrollment is reached. Multiple strategies have been adopted in the recruitment process. Local physicians and other health-care providers, including nurses and ward-based pharmacists in the study site, have been requested to refer potential participants. Participants will be given a gift card as a reward for study participation.

### Allocation

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3 The study participants, who meet the eligibility criteria, will be allocated to the intervention and  
4 usual-care groups on a one-on-one basis. Randomization will be conducted upon request from the  
5 staff member responsible for recruitment, using the computer-generated-allocation sequence as a part  
6 of HOPE eACReSS, a Clinical Data Management system. The HOPE eACReSS, developed by  
7 Fujitsu, Tokyo, Japan, ensures allocation concealment, and the randomization method uses stratified  
8 block randomization under age group blocks of 65–74, 75–84, and 85 years and above. The  
9 randomization result will be stored, printed, and immediately reported to the staff member responsible  
10 for intervention on that day.  
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### 22 **Blinding**

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24 The research assistant who performs the bimonthly telephone interview assessments will be blind to  
25 group allocation. The investigators, ward-based pharmacists, participants' attending physicians,  
26 participants, and/or their NOK will be aware of group allocation.  
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### 32 **Data collection and management**

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34 The detailed participant timeline, including schedule of enrollment, interventions, and outcome  
35 measurements, is presented in **Table 1**. Demographic characteristics at enrollment, including age, sex,  
36 date of admission, race, past medical history, comorbid conditions, smoking status, physical  
37 measurements on admission (height, weight, and vital signs), level of long-term care required, and  
38 history of falls within 3 months, will be collected via a chart review and interview by a trained  
39 research nurse and the deprescribing team. Participants' baseline medication list and laboratory  
40 findings (eGFR, serum sodium level, and serum potassium level) will also be assessed by reviewing  
41 the participants' medical record handbook, referral letter, and electronic medical record. Participants  
42 will be followed-up by a telephone interview every 8 weeks, through 48 weeks, to assess any  
43 incidence of primary and secondary outcomes. The follow-up telephone interview will be performed  
44 by a trained research assistant blinded to group allocation. If the study candidate is unable to respond  
45 to the telephone interview due to lack of capacity, a predetermined NOK will be contacted. The  
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medication lists at 24 and 48 weeks will be sent from the relevant community pharmacist upon request from the investigators.

**Table 1. Timetable of the MPEG trial**

	Baseline assessment	Enrollment	Follow-up 1	Follow-up 2	Follow-up 3	Follow-up 4	Follow-up 5	Follow-up 6
<b>Time point (week)</b>	0	0	8 ± 2	16 ± 2	24 ± 2	32 ± 2	40 ± 2	48 ± 2
<b>Enrollment</b>								
Informed consent	x							
Sociodemographic characteristics	x							
Allocation		x						
<b>Intervention</b>		x						
<b>Assessments</b>								
Subjective symptoms	x	x	x	x	x	x	x	x
Adverse events			x	x	x	x	x	x
Vital signs	x							
Height and weight	x							
Unscheduled visits			x	x	x	x	x	x
Hospital readmission			x	x	x	x	x	x
Injury due to falls			x	x	x	x	x	x
Laboratory findings (eGFR, serum sodium level, and serum potassium level)	x							
Number of prescribed medications	x				x			x
Number of prescribed potentially inappropriate medications*	x				x			x

EQ5D-3L		x			x			x
Level of care required	x				x			x

\*The number of prescribed potentially inappropriate medications listed in the STOPP/START criteria[5]

### Statistical analysis

The primary and secondary outcomes will be adjudicated using the intention-to-treat analysis. All randomized participants will be analyzed. For those who discontinue the trial before completion, all efforts will be made to follow their primary and secondary endpoints over the study duration through phone calls and health record review, if permitted. Participants who do not experience any endpoint will be censored either when lost to follow-up or at the completion of follow-up.

For the primary endpoint, survival functions for each group will be estimated using the Kaplan–Meier method, and a log-rank test (two-sided), stratified by age group, will be conducted for the primary comparison. Significance level will be set at 0.05. In addition, a Cox proportional hazards model will be used to estimate hazard ratio across the groups. The secondary outcomes, each of all-cause death, unscheduled hospital visits, and re-hospitalization until 48 weeks after randomization, will be compared by stratified log-rank test, and hazard ratio will be estimated using Cox proportional hazards models. Pre-specified subgroup analyses of the primary endpoint of indicator diseases (heart failure, pneumonia, diabetes mellitus, ischemic stroke, and urinary tract infection) and indicator drug classes (antiplatelets, antihypertensives, antidiabetics, and sedatives) will be conducted for the exploratory analyses. All statistical analyses will be performed using STATA/SE 15.0 (StataCorp LLC, College Station, TX, USA).

### Data monitoring

Central monitoring will be conducted at least once a year to check protocol compliance. The monitoring report will be submitted to the president (chairman of the ethics committee) and the investigators. Audit will be conducted, if the principal investigator deems it necessary, based on the

1  
2  
3 monitoring report. There is no predetermined interim analysis for the current study. All study results  
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5 will be analyzed by a statistician in a de-identified form.  
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### 9 **Harms**

10 For the current trial, medication modification in the intervention group will be at the discretion of the  
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12 participant and his/her attending physician, as a part of clinical practice. Thus, the risk of adverse  
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14 events related to the intervention is not expected to significantly deviate from the usual care.  
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17 However, any adverse event during the study period will be recorded according to the Japanese  
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19 version of PRO-CTCAE.[18] Investigators will report to the president (chairman of the ethics  
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21 committee) and I-DSMB on all serious adverse events during the study period.  
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24 Serious adverse events in the MPEG trial are defined as follows:  
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- 26 1) All-cause death;
- 27
- 28 2) All-cause rehospitalization;
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- 30 3) Disability.  
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### 35 **Patient and public involvement**

36 The current trial will be conducted without direct patient involvement. The Institutional Ethics  
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38 Committee of St. Marianna University School of Medicine includes patient representatives, charged  
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40 with the responsibility to protect patient rights; thus, the MPEG trial protocol was reviewed by a  
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42 patient representative. Besides the above review process, patients will not be invited to comment on  
43  
44 the study design and interpretation of the study results. Patients were not involved in the writing of  
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46 this manuscript.  
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## 52 **ETHICS AND DISSEMINATION**

### 53 **Ethics approval and consent to participate**

54 The current study protocol was approved by the Institutional Ethical Committee of St. Marianna  
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56 University School of Medicine (No. 4129). Before study participation, oral and written explanations  
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58 will be provided to all study candidates, and then written consent will be obtained. If a study  
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3 candidate is unable to provide consent due to a lack of capacity (the researcher deems it inappropriate  
4 to obtain informed consent from the study candidate), the same will be obtained from the candidate's  
5 NOK. For this trial, a candidate's NOK is defined as the candidate's closest blood relative or one who  
6 is eligible to provide consent on behalf of the subject based on their mutual relationship. If the NOK  
7 cannot visit the hospital on that day, he/she will be contacted via telephone, because an oral consent is  
8 acceptable for study enrollment, provided that a written consent can be obtained at a later date. If  
9 there is any revision to study protocol that could affect the participants' decision to participate, the  
10 principle investigator will inform the participants and confirm their intent to continue their  
11 participation.  
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### 24 **Confidentiality**

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26 The data obtained will be managed by the personal information manager, in accordance with the Act  
27 on the Protection of Personal Information, until five years after publication of the study results. Personal  
28 information, such as participants' name, date of birth, and hospital ID will be stored in a secure database  
29 (HOPE eACReSS) with password protection. All hard copies of data will be maintained in a locked  
30 cabinet. Data included in the HOPE eACReSS will be completely de-identified at the time of data entry  
31 to the web-based clinical research data management system.  
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### 41 **Dissemination plan and availability of data**

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43 The results of the current study will be disseminated to healthcare providers, policy makers, and  
44 patients, via presentations at local and national meetings, as well as by publication in a peer-reviewed  
45 journal. The datasets used and analyzed during the current study are available from the corresponding  
46 author upon reasonable request.  
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## 52 **DISCUSSION**

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55 Herein, we describe the detailed methodology of the MPEG trial, a single center, open-label,  
56 randomized controlled trial with a two-arm parallel design. The main goal of this study is to demonstrate  
57 the efficacy and feasibility of multidisciplinary team-based intervention using both explicit and implicit  
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3 criteria for medication optimization. While the benefits of deprescribing have been increasingly  
4 highlighted and appear promising in terms of reducing inappropriate prescription, controversy  
5 regarding whether the deprescribing approach actually improves clinically significant outcomes  
6 remains unanswered.[10-12] Furthermore, the definition of deprescribing varies across studies, ranging  
7 from the use of explicit criteria, such as the STOPP/START criteria[5] and Beers criteria,[25] to the  
8 more implicit “deprescribing protocol” approach proposed by Scott et al.[8] Considering the strength  
9 and weakness of explicit and implicit criteria, the complimentary use of both in the current study is  
10 expected to enhance the efficacy of medication optimization process in elderly individuals.

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20 Other methodological limitations that potentially affected the non-significant results of  
21 previous deprescribing trials are the relatively shorter follow-up period and a lack of sufficient power  
22 to detect the true effect of intervention on clinically important outcomes.[10-13] In this study, we will  
23 collect longitudinal data of approximately 500 patients for up to 48 weeks, allowing sufficient power  
24 and follow-up period to detect clinically important effects of the medication optimization intervention.  
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The results of this study will provide critical evidence regarding the effect of medication optimization  
that would enhance safety and efficient care for elderly multimorbid medical inpatients.

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### Acknowledgments

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### Authors' contributions:

Each author has contributed significantly to the study. KI, MH, AT, HM, EI, EK, YI, and TM participated integrally in the study design. KI, EI, and MT contributed primarily to statistical analyses. All authors contributed to study protocol implementation, data acquisition, and study data interpretation. KI and SMH drafted the initial manuscript, and all other authors, including CO and TM, read and approved the final manuscript.

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**Competing interest statement:** Authors declare no conflict of interests.

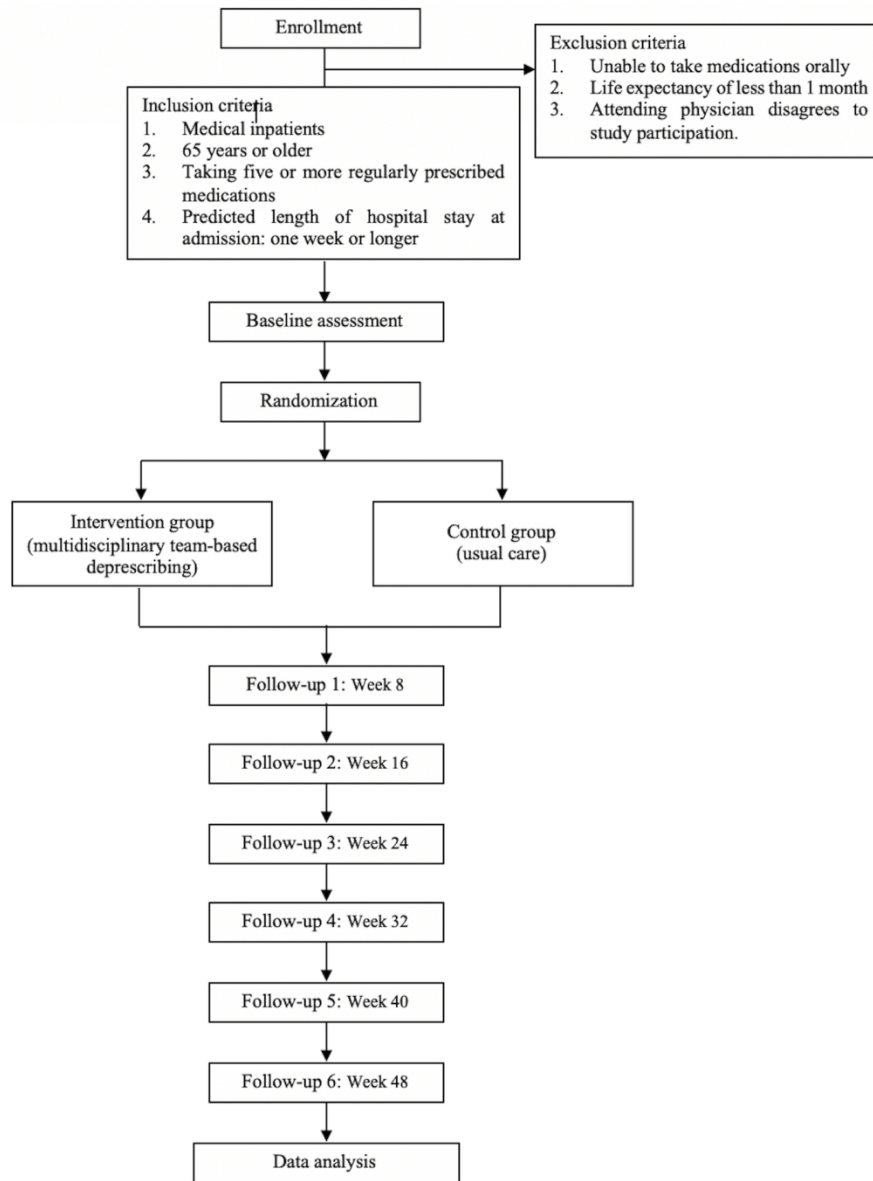
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3 **Figure legends**  
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9 **Figure 1. Flowchart summarizing the MPEG trial procedure**  
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13 **Figure 2. Scheme of multidisciplinary team-based medication optimization intervention**  
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18 **Figure 3. Medication optimization protocol for the MPEG trial**  
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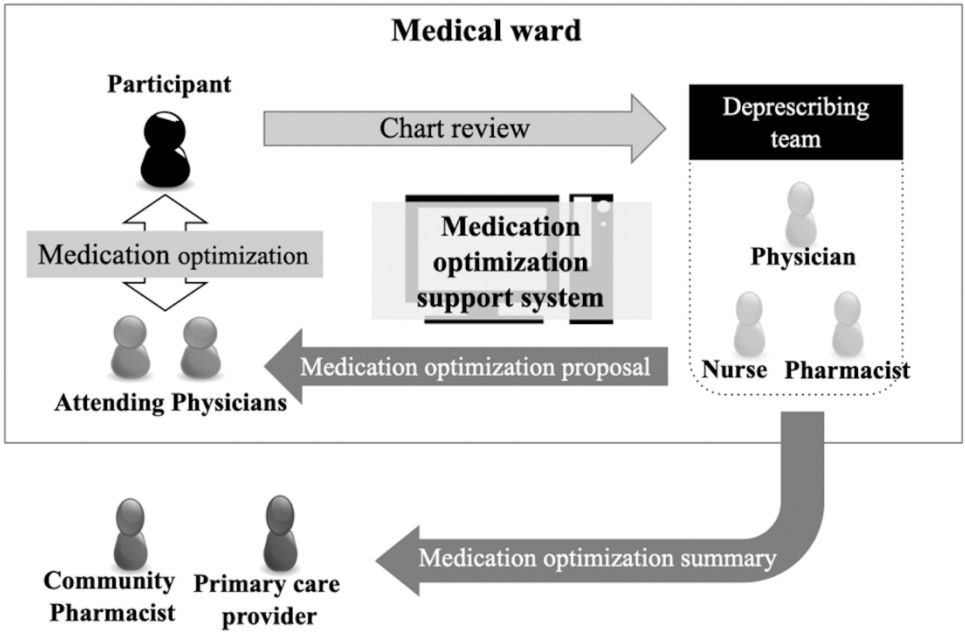
20 † Baseline information includes study participants' age, sex, past medical history, comorbid  
21 conditions, height, weight, blood pressure, pulse rate, oxygen saturation, body temperature, eGFR,  
22 serum sodium level, serum potassium level, and regularly prescribed medications.  
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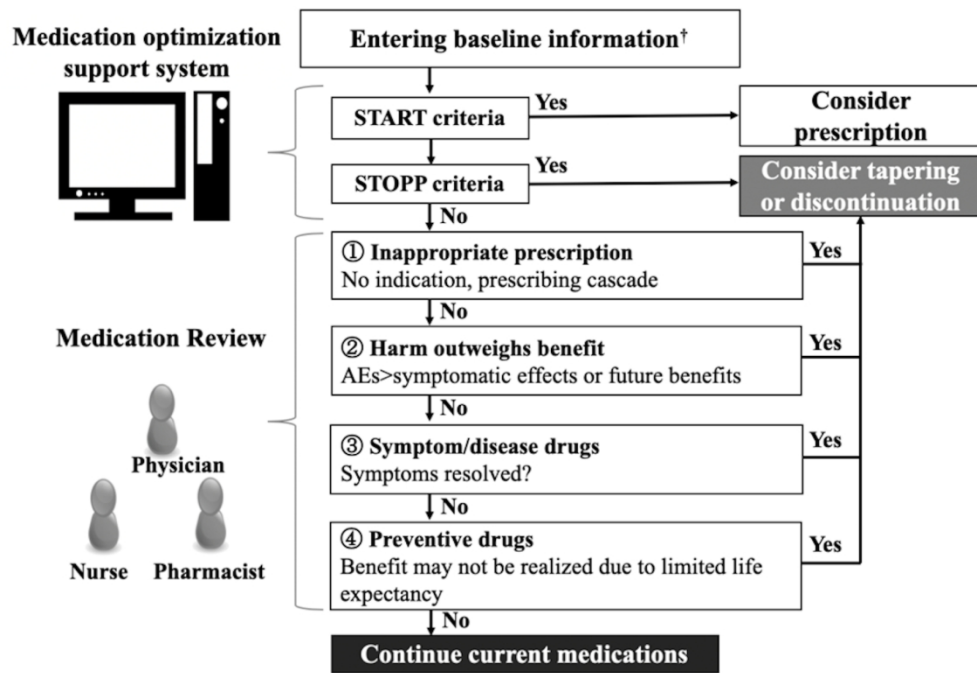
**Figure 1. Flowchart summarizing the MPEG trial procedure**



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**Figure 2. Scheme of multidisciplinary team-based medication optimization intervention**



**Figure 3. Medication optimization protocol for the MPEG trial**

† Baseline information includes study participants' age, sex, past medical history, comorbid conditions, height, weight, blood pressure, pulse rate, oxygen saturation, body temperature, eGFR, serum sodium level, serum potassium level, and regularly prescribed medications.

# Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. *Ann Intern Med.* 2013;158(3):200-207

		Reporting Item	Page Number
<b>Administrative information</b>			
Title	<a href="#">#1</a>	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	<a href="#">#2a</a>	Trial identifier and registry name. If not yet registered, name of intended registry	2, 4
Trial registration: data set	<a href="#">#2b</a>	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	<a href="#">#3</a>	Date and version identifier	2
Funding	<a href="#">#4</a>	Sources and types of financial, material, and other support	19
Roles and responsibilities: contributorship	<a href="#">#5a</a>	Names, affiliations, and roles of protocol contributors	19

1	Roles and	<a href="#">#5b</a>	Name and contact information for the trial sponsor	N/A
2	responsibilities:			
3	sponsor contact			
4	information			
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8	Roles and	<a href="#">#5c</a>	Role of study sponsor and funders, if any, in study design;	N/A
9	responsibilities:		collection, management, analysis, and interpretation of data;	
10	sponsor and funder		writing of the report; and the decision to submit the report for	
11			publication, including whether they will have ultimate authority	
12			over any of these activities	
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16	Roles and	<a href="#">#5d</a>	Composition, roles, and responsibilities of the coordinating centre,	12-13
17	responsibilities:		steering committee, endpoint adjudication committee, data	
18	committees		management team, and other individuals or groups overseeing the	
19			trial, if applicable (see Item 21a for data monitoring committee)	
20				
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23	<b>Introduction</b>			
24				
25	Background and	<a href="#">#6a</a>	Description of research question and justification for undertaking	3-4
26	rationale		the trial, including summary of relevant studies (published and	
27			unpublished) examining benefits and harms for each intervention	
28				
29				
30	Background and	<a href="#">#6b</a>	Explanation for choice of comparators	3-4
31	rationale: choice of			
32	comparators			
33				
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35				
36	Objectives	<a href="#">#7</a>	Specific objectives or hypotheses	4
37				
38	Trial design	<a href="#">#8</a>	Description of trial design including type of trial (eg, parallel	4
39			group, crossover, factorial, single group), allocation ratio, and	
40			framework (eg, superiority, equivalence, non-inferiority,	
41			exploratory)	
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44				
45	<b>Methods:</b>			
46	<b>Participants,</b>			
47	<b>interventions, and</b>			
48	<b>outcomes</b>			
49				
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51	Study setting	<a href="#">#9</a>	Description of study settings (eg, community clinic, academic	4-5
52			hospital) and list of countries where data will be collected.	
53			Reference to where list of study sites can be obtained	
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57	Eligibility criteria	<a href="#">#10</a>	Inclusion and exclusion criteria for participants. If applicable,	5
58			eligibility criteria for study centres and individuals who will	
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		perform the interventions (eg, surgeons, psychotherapists)	
1			
2	Interventions:	<a href="#">#11a</a> Interventions for each group with sufficient detail to allow	5-7
3	description	replication, including how and when they will be administered	
4			
5	Interventions:	<a href="#">#11b</a> Criteria for discontinuing or modifying allocated interventions for	14
6	modifications	a given trial participant (eg, drug dose change in response to	
7		harms, participant request, or improving / worsening disease)	
8			
9	Interventions:	<a href="#">#11c</a> Strategies to improve adherence to intervention protocols, and any	7
10	adherence	procedures for monitoring adherence (eg, drug tablet return;	
11		laboratory tests)	
12			
13	Interventions:	<a href="#">#11d</a> Relevant concomitant care and interventions that are permitted or	N/A
14	concomitant care	prohibited during the trial	
15			
16	Outcomes	<a href="#">#12</a> Primary, secondary, and other outcomes, including the specific	7-8
17		measurement variable (eg, systolic blood pressure), analysis metric	
18		(eg, change from baseline, final value, time to event), method of	
19		aggregation (eg, median, proportion), and time point for each	
20		outcome. Explanation of the clinical relevance of chosen efficacy	
21		and harm outcomes is strongly recommended	
22			
23	Participant timeline	<a href="#">#13</a> Time schedule of enrolment, interventions (including any run-ins	4,10-12,
24		and washouts), assessments, and visits for participants. A	Figure 1
25		schematic diagram is highly recommended (see Figure)	
26			
27	Sample size	<a href="#">#14</a> Estimated number of participants needed to achieve study	9
28		objectives and how it was determined, including clinical and	
29		statistical assumptions supporting any sample size calculations	
30			
31	Recruitment	<a href="#">#15</a> Strategies for achieving adequate participant enrolment to reach	9
32		target sample size	
33			
34			
35			
36	<b>Methods: Assignment</b>		
37	<b>of interventions (for</b>		
38	<b>controlled trials)</b>		
39			
40	Allocation: sequence	<a href="#">#16a</a> Method of generating the allocation sequence (eg, computer-	9-10
41	generation	generated random numbers), and list of any factors for	
42		stratification. To reduce predictability of a random sequence,	
43		details of any planned restriction (eg, blocking) should be provided	
44		in a separate document that is unavailable to those who enrol	
45		participants or assign interventions	
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1	Allocation	<a href="#">#16b</a>	Mechanism of implementing the allocation sequence (eg, central	10
2	concealment		telephone; sequentially numbered, opaque, sealed envelopes),	
3			describing any steps to conceal the sequence until interventions are	
4	mechanism		assigned	
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8	Allocation:	<a href="#">#16c</a>	Who will generate the allocation sequence, who will enrol	10
9	implementation		participants, and who will assign participants to interventions	
10				
11	Blinding (masking)	<a href="#">#17a</a>	Who will be blinded after assignment to interventions (eg, trial	10
12			participants, care providers, outcome assessors, data analysts), and	
13			how	
14				
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17	Blinding (masking):	<a href="#">#17b</a>	If blinded, circumstances under which unblinding is permissible,	N/A
18	emergency unblinding		and procedure for revealing a participant's allocated intervention	
19			during the trial	
20				
21				
22	<b>Methods: Data</b>			
23	<b>collection,</b>			
24	<b>management, and</b>			
25	<b>analysis</b>			
26				
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29	Data collection plan	<a href="#">#18a</a>	Plans for assessment and collection of outcome, baseline, and	10-12
30			other trial data, including any related processes to promote data	
31			quality (eg, duplicate measurements, training of assessors) and a	
32			description of study instruments (eg, questionnaires, laboratory	
33			tests) along with their reliability and validity, if known. Reference	
34			to where data collection forms can be found, if not in the protocol	
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39	Data collection plan:	<a href="#">#18b</a>	Plans to promote participant retention and complete follow-up,	10-12
40	retention		including list of any outcome data to be collected for participants	
41			who discontinue or deviate from intervention protocols	
42				
43				
44	Data management	<a href="#">#19</a>	Plans for data entry, coding, security, and storage, including any	10-13
45			related processes to promote data quality (eg, double data entry;	
46			range checks for data values). Reference to where details of data	
47			management procedures can be found, if not in the protocol	
48				
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51	Statistics: outcomes	<a href="#">#20a</a>	Statistical methods for analysing primary and secondary outcomes.	12
52			Reference to where other details of the statistical analysis plan can	
53			be found, if not in the protocol	
54				
55				
56	Statistics: additional	<a href="#">#20b</a>	Methods for any additional analyses (eg, subgroup and adjusted	12
57	analyses		analyses)	
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1	Statistics: analysis	<a href="#">#20c</a>	Definition of analysis population relating to protocol non-	12
2	population and missing		adherence (eg, as randomised analysis), and any statistical	
3	data		methods to handle missing data (eg, multiple imputation)	
4				
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6	<b>Methods: Monitoring</b>			
7				
8	Data monitoring:	<a href="#">#21a</a>	Composition of data monitoring committee (DMC); summary of	12-13
9	formal committee		its role and reporting structure; statement of whether it is	
10			independent from the sponsor and competing interests; and	
11			reference to where further details about its charter can be found, if	
12			not in the protocol. Alternatively, an explanation of why a DMC is	
13			not needed	
14				
15	Data monitoring:	<a href="#">#21b</a>	Description of any interim analyses and stopping guidelines,	N/A
16	interim analysis		including who will have access to these interim results and make	
17			the final decision to terminate the trial	
18				
19	Harms	<a href="#">#22</a>	Plans for collecting, assessing, reporting, and managing solicited	13
20			and spontaneously reported adverse events and other unintended	
21			effects of trial interventions or trial conduct	
22				
23	Auditing	<a href="#">#23</a>	Frequency and procedures for auditing trial conduct, if any, and	12-13
24			whether the process will be independent from investigators and the	
25			sponsor	
26				
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28				
29	<b>Ethics and</b>			
30	<b>dissemination</b>			
31				
32	Research ethics	<a href="#">#24</a>	Plans for seeking research ethics committee / institutional review	13
33	approval		board (REC / IRB) approval	
34				
35	Protocol amendments	<a href="#">#25</a>	Plans for communicating important protocol modifications (eg,	14
36			changes to eligibility criteria, outcomes, analyses) to relevant	
37			parties (eg, investigators, REC / IRBs, trial participants, trial	
38			registries, journals, regulators)	
39				
40	Consent or assent	<a href="#">#26a</a>	Who will obtain informed consent or assent from potential trial	13-14
41			participants or authorised surrogates, and how (see Item 32)	
42				
43	Consent or assent:	<a href="#">#26b</a>	Additional consent provisions for collection and use of participant	N/A
44	ancillary studies		data and biological specimens in ancillary studies, if applicable	
45				
46	Confidentiality	<a href="#">#27</a>	How personal information about potential and enrolled participants	14
47			will be collected, shared, and maintained in order to protect	
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		confidentiality before, during, and after the trial	
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2	Declaration of interests	<a href="#">#28</a> Financial and other competing interests for principal investigators	19
3		for the overall trial and each study site	
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5			
6	Data access	<a href="#">#29</a> Statement of who will have access to the final trial dataset, and	14
7		disclosure of contractual agreements that limit such access for	
8		investigators	
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11	Ancillary and post trial	<a href="#">#30</a> Provisions, if any, for ancillary and post-trial care, and for	N/A
12	care	compensation to those who suffer harm from trial participation	
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14			
15	Dissemination policy:	<a href="#">#31a</a> Plans for investigators and sponsor to communicate trial results to	14
16	trial results	participants, healthcare professionals, the public, and other	
17		relevant groups (eg, via publication, reporting in results databases,	
18		or other data sharing arrangements), including any publication	
19		restrictions	
20			
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22			
23	Dissemination policy:	<a href="#">#31b</a> Authorship eligibility guidelines and any intended use of	N/A
24	authorship	professional writers	
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26			
27	Dissemination policy:	<a href="#">#31c</a> Plans, if any, for granting public access to the full protocol,	14
28	reproducible research	participant-level dataset, and statistical code	
29			
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31	<b>Appendices</b>		
32			
33	Informed consent	<a href="#">#32</a> Model consent form and other related documentation given to	N/A
34	materials	participants and authorised surrogates	
35			
36			
37	Biological specimens	<a href="#">#33</a> Plans for collection, laboratory evaluation, and storage of	N/A
38		biological specimens for genetic or molecular analysis in the	
39		current trial and for future use in ancillary studies, if applicable	
40			
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43 None The SPIRIT checklist is distributed under the terms of the Creative Commons Attribution License CC-  
 44 BY-ND 3.0. This checklist can be completed online using <https://www.goodreports.org/>, a tool made by the  
 45 [EQUATOR Network](#) in collaboration with [Penelope.ai](#)  
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# BMJ Open

## Protocol of a randomized controlled trial on the efficacy of medication optimization in elderly inpatients: Medication optimization Protocol Efficacy for Geriatric inpatients (MPEG) trial

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3 **1 Protocol of a randomized controlled trial on the efficacy of medication optimization in elderly**  
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5 **2 inpatients: Medication optimization Protocol Efficacy for Geriatric inpatients (MPEG) trial**  
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7 **3**

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## 1 **ABSTRACT**

2 **Introduction:** Whether medication optimization improves clinical outcomes in elderly individuals  
3 remains unclear. The current study aims to evaluate the effect of multidisciplinary team-based  
4 medication optimization on survival, re-hospitalization, and unscheduled hospital visits in elderly  
5 patients.

6 **Methods and analysis:** We report the protocol of a single center, open-label, randomized controlled  
7 trial. The enrolled subjects will be medical inpatients, aged 65 years or older, admitted to a community  
8 hospital, and receiving five or more regular medications. The participants will be randomly assigned to  
9 receive either an intervention for medication optimization or the usual care. The intervention will  
10 consist of a multidisciplinary team-based medication review, followed by a medication optimization  
11 proposal based on the Screening Tool of Older Persons' potentially inappropriate  
12 Prescriptions/Screening Tool to Alert doctors to the Right Treatment (STOPP/START) criteria and an  
13 implicit medication optimization protocol. Medication optimization summaries will be sent to primary  
14 care physicians and community pharmacists upon discharge. The primary outcome will be a composite  
15 of death, unscheduled hospital visits, and re-hospitalization until 48 weeks after randomization.  
16 Secondary outcomes will include each of the primary endpoints, the number of prescribed medications,  
17 quality of life score, level of long-term care required, drug-related adverse events, death during  
18 hospitalization, and falls. Participants will be followed-up for 48 weeks with bimonthly telephone  
19 interviews to assess the primary and secondary outcomes. A log-rank test stratified by randomization  
20 factors will be used to compare the incidence of the composite endpoint. The study was initiated in  
21 2019 and a minimum of 500 patients will be enrolled.

22 **Ethics and dissemination:** The study protocol has been approved by the Institutional Ethical  
23 Committee of St. Marianna University School of Medicine (No. 4129). The results of the current  
24 study will be submitted to a peer-reviewed journal.

25 **Trial registration number:** UMIN000035265

26  
27 **Keywords:** polypharmacy, deprescriptions, potentially inappropriate medication list, frail elderly

28

## 1 **Strengths and limitations of this study**

- 2 ➤ The MPEG trial is a large randomized controlled trial that will examine the efficacy of
- 3 multidisciplinary team-based medication optimization on patient-oriented outcomes.
- 4 ➤ The study will be adequately powered to examine the efficacy of medication optimization
- 5 protocol in elderly inpatients with a 48-week follow-up period.
- 6 ➤ The multidisciplinary team-based intervention incorporates both explicit and implicit
- 7 deprescribing criteria to enhance the efficacy of medication optimization in elderly inpatients.
- 8 ➤ The open-label design of this study has limitations; however, it will provide a rationale for future
- 9 multicenter confirmatory studies.

## 11 **INTRODUCTION**

12 Polypharmacy is known to increase death rate, fall incidence, and healthcare utilization in  
13 elderly individuals.[1-3] Potentially inappropriate medication lists (PIMs), aiming to reduce  
14 inappropriate medication prescriptions in elderly individuals, have been a mainstay of medication  
15 optimization strategies.[4] They can be used as an explicit criterion for medication reconciliation.  
16 Among the PIMs, the Screening Tool of Older Persons' potentially inappropriate  
17 Prescriptions/Screening Tool to Alert doctors to the Right Treatment (STOPP/START) is a widely  
18 accepted criterion, incorporating the list of medicines that are potentially harmful and those that  
19 should be prescribed for elderly individuals.[5] A recent systematic review of randomized controlled  
20 trials of interventions to reduce polypharmacy using the STOPP criteria showed that the STOPP-  
21 based interventions are associated with reduced falls, emergency visits, and medical costs, and short  
22 hospital stays.[6] However, to date, no study has shown the effect of STOPP-based interventions on  
23 clinically important outcomes such as death and readmission rates. In reality, most adverse drug  
24 reactions are caused by drugs that are not included in such criteria.[7] In addition, there could be both  
25 “appropriate” and “inappropriate” polypharmacy, depending on the patient background.

26 Recently, a more implicit criterion for polypharmacy, called the deprescribing protocol, has  
27 been expected to improve patient outcomes. Scott et al. defined it as “the systematic process of  
28 identifying and discontinuing drugs in instances in which existing or potential harms outweigh

1 existing or potential benefits within the context of an individual patient's care goals, current level of  
2 functioning, life expectancy, values, and preferences.”[8] The use of the deprescribing protocol has  
3 been indicated to reduce the number of prescription drugs,[9] but whether the intervention improves  
4 significant patient-oriented outcomes, such as death, hospitalization, and falls, remains  
5 controversial.[10-12] A Cochrane review pointed out that studies that failed to demonstrate the  
6 benefits of the deprescribing protocol had a follow-up period of less than 1 year, which may not be  
7 sufficient to identify the true effect of the deprescribing protocol.[13] Thus, a lack of evidence  
8 regarding the effect of the deprescribing protocol on patient-oriented outcomes could be attributed to  
9 methodological limitations in previous studies.

## 10 **Objectives**

11 In this study, we aim to evaluate the effect of multidisciplinary team-based medication optimization  
12 process, using both explicit and implicit criteria, on survival, re-hospitalization, and unscheduled  
13 hospital visits in elderly inpatients.  
14

## 15 **METHODS AND ANALYSIS**

### 16 **MPEG trial design**

17 This is a single center, open-label, randomized controlled trial with a two-arm parallel design. **Figure**  
18 **1** depicts the flow diagram of the progress through various phases of the study. The current trial protocol  
19 follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines,  
20 developed to provide a standardized guidance for recommended items to be included in a clinical trial  
21 protocol.[14] The study was approved by the Institutional Ethics Committee of St. Marianna University  
22 School of Medicine (No. 4129) and was registered at the UMIN Clinical Trials Registry  
23 (UMIN000035265).  
24

### 25 **Study setting and eligibility criteria**

1  
2  
3 1 The present trial will be conducted in patients in the medical wards of a university-affiliated  
4  
5 2 community hospital. Patients admitted to the medical wards will be screened for study eligibility by  
6  
7 3 hospital receptionists, medical ward-based pharmacists, and the principal- or co-investigators.

8  
9 4 The eligibility criteria for participants are as follows:

- 10  
11 5 1. Medical inpatients;  
12  
13 6 2. Aged 65 years or older;  
14  
15 7 3. Taking five or more regularly prescribed medications;  
16  
17  
18 8 4. Predicted length of hospital stay after admission: 1 week or longer.

19  
20 9  
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22 10 Exclusion criteria include the following: inability to take medications orally; life expectancy of less  
23  
24 11 than 1 month based on attending physician's clinical judgment; and attending physicians disagreeing  
25  
26 12 on study participation. In the current study, a regularly prescribed medication is defined as "any form  
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28 13 of prescribed oral medications recorded in the participant's medical record handbook, a referral letter,  
29  
30 14 or electronic medical record over 28 days or longer at the time of hospital admission." Drugs that are  
31  
32 15 used "as needed" will not be counted in regular medications.

### 33 34 35 36 37 17 **Interventions**

38  
39 18 Participants will be randomly assigned to receive either a medication optimization  
40  
41 19 intervention or the usual care. Both groups will be subjected to medication reconciliation by ward-  
42  
43 20 based pharmacists using data provided by the medical record handbook, patient/family, or a referral  
44  
45 21 letter, along with the usual care from their attending physicians. For those assigned to the intervention  
46  
47 22 group, the multidisciplinary deprescribing team, which will consist of a physician and a pharmacist,  
48  
49 23 will conduct the medication optimization intervention within 48 h of allocation. Ward-based nurses  
50  
51 24 will be consulted by the deprescribing team, as required, to collect any information necessary for the  
52  
53 25 medication optimization proposal, including patient preference and medication adherence. All  
54  
55 26 members of the deprescribing team will receive standardized instruction and guidance in advance. In  
56  
57 27 addition, monthly deprescribing-team meetings and case-based reflection for selected cases during the  
58  
59 28 previous month will be held for monitoring and quality control of interventions.



1 Overall, the intervention will consist of a medication review, followed by the development of  
2 a medication optimization proposal based on the STOPP/START criteria[5] and a medication  
3 optimization protocol (**Figure 2**). First, the study participant's baseline data (age, sex, past medical  
4 history, comorbid conditions, height, weight, blood pressure, pulse rate, oxygen saturation, body  
5 temperature, eGFR, serum sodium level, serum potassium level, and regularly prescribed  
6 medications) will be collected via a chart review and entered into a computer-based medication  
7 optimization support system, developed specifically for the trial. The medication optimization support  
8 system will automatically generate a draft proposal according to the STOPP/START criteria.[5] After  
9 reviewing the draft proposal, the deprescribing team will conduct a step-by-step discussion based on  
10 the medication optimization protocol (**Figure 3**), involving the following steps per the algorithm  
11 proposed by Scott et al.[8]

12 **1) Does the prescription have an appropriate indication?**

13 All efforts will be made to ensure the indications for each drug. If no clear indication is confirmed  
14 or the drug is prescribed as a result of a prescribing cascade (e.g., proton pump inhibitor to reduce  
15 gastrointestinal adverse effects associated with non-steroidal anti-inflammatory drugs), the  
16 deprescribing team will discuss whether the drug should be deprescribed.

17 **2) Does the harm outweigh the potential benefits?**

18 Study participants' symptoms and laboratory results will be reviewed to determine any adverse  
19 effect that outweighs the expected benefits of the prescribed drug (e.g., calcium channel blocker  
20 in a patient with orthostatic hypotension and recurrent falls).

21 **3) For a symptomatic medication, does the patient currently have the target symptom?**

22 Symptomatic medications that control active symptoms to maintain quality of life (e.g.,  
23 painkillers and antiemetics) will be evaluated for their necessity. If the symptom is mild or  
24 intermittent or the drug is deemed ineffective, cessation, dose reduction, or "as-needed" use of the  
25 corresponding drug will be discussed.

26 **4) For a preventive medication, does the patient have enough life expectancy to expect benefit  
27 of preventive care?**

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2  
3 1 Medications aimed to prevent the occurrence of disease (e.g., statins and glucose-lowering drugs)  
4  
5 2 will be considered for their benefits, the length of time required for the expected benefit, and the  
6  
7 3 participant's preference and estimated life expectancy.  
8  
9  
10 4

11 5 The rationale for the medication optimization proposal will be explained and discussed in detail  
12  
13 6 with each participant or next of kin (NOK). Upon the participant's agreement, the team will  
14  
15 7 recommend the medication optimization plan, including its rationale, to the participant's attending  
16  
17 8 physician. Whether the proposal would be accepted or not will be left to the discretion of the  
18  
19 9 participant and his/her attending physician, as a part of clinical judgment. The details of each  
20  
21 10 medication optimization proposal and the list of medications at discharge will be recorded to track  
22  
23 11 adherence to the proposal.  
24  
25

26 12 Medication optimization summary, including the reason for prescription modification and  
27  
28 13 relevant precautions, will be sent to the study participant's primary care physician and community  
29  
30 14 pharmacists upon discharge.  
31  
32  
33 15

## 34 16 **Outcomes**

### 35 17 **Primary outcome**

36  
37 18 The primary outcome is a composite of all-cause death, unscheduled hospital visits, and re-  
38  
39 19 hospitalization until 48 weeks after randomization. Time to the first occurrence of primary composite  
40  
41 20 outcome will be recorded for the survival analysis. An unscheduled hospital visit is defined as an  
42  
43 21 unexpected visit to the emergency department or outpatient clinic during the follow-up period owing to  
44  
45 22 new or worsening symptoms, signs, and concerns. Any re-hospitalization due to new or worsening  
46  
47 23 symptoms, signs, and concerns after first hospital discharge will be recorded. A hospital transfer will  
48  
49 24 be deemed as continuation of hospitalization rather than re-hospitalization.  
50  
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### 53 26 **Secondary outcomes**

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55  
56 27 The following endpoints at the baseline, 24 weeks, and 48 weeks post-randomization will be assessed  
57  
58 28 as secondary outcomes.  
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3 **1. Number of regular and potentially inappropriate medications**  
4

5 The number of prescribed medications listed in the participant's medical record handbook,  
6 referral letter, or electronic medical record over a duration of 28 days or longer at the baseline, 24  
7 weeks, and 48 weeks post-randomization will be considered as "regular medication." Any  
8 prescribed regular medication listed in the STOPP criteria[5] will be indicated as PIM, whose  
9 number at the baseline, 24 weeks, and 48 weeks post-randomization will be recorded  
10 simultaneously.  
11

12 **2. Level of long-term care required**  
13

14 The level of long-term care required, under the Japanese long-term care (LTC) insurance system,  
15 will be assessed at the baseline, 24 weeks, and 48 weeks post-randomization. The levels will be  
16 assigned by the local government as follows: independent, support required 1 or 2, and care  
17 required 1 to 5—where care level 5 implies the highest level of requirement for long-term care  
18 and independent implies the lowest level of requirement.[15]  
19

20 **3. Health-related quality of life**  
21

22 Self-reported general health status will be recorded at three time points using EQ5D-3L.[16] We  
23 will use the Japanese version of EQ5D-3L and a Japanese scoring system that have been found to  
24 be valid and reliable.[17]  
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41 In addition to the above-listed outcomes, the ones listed below, occurring within 48 weeks after  
42 randomization, will be assessed including the event dates.  
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- 44
- 45 ➤ All-cause death
  - 46
  - 47 ➤ All-cause death during initial hospitalization
  - 48
  - 49 ➤ Unscheduled hospital visits
  - 50
  - 51 ➤ Re-hospitalization
  - 52
  - 53 ➤ Drug adverse events
  - 54

55 Any potential drug-related adverse events will be determined by consensus among the  
56 deprescribing team and attending physicians and recorded according to the Japanese version of  
57  
58  
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60

1 CTCAE 4.0.[18] Drug names, symptom onset timing, severity, treatment, consequence, and  
2 relevance to the intervention will be entered in the report form.

3 ➤ Falls

4 For the current study, a fall was defined per Gibson et al.: “unintentionally coming to the ground  
5 or some lower level and other than as a consequence of sustaining a violent blow, loss of  
6 consciousness, sudden onset of paralysis as in stroke or an epileptic seizure.”[19]

7  
8 **Sample size**

9 Ravn-Nielsen et al., who examined the effect of multifaceted pharmacist intervention in medical wards,  
10 demonstrated a 23% reduction in hazard risk in the composite outcome of readmission or ED visits  
11 within 180 days after inclusion, compared with that in usual care.[20] They did not find a significant  
12 difference in mortality across the groups, although a 6-month follow-up period may not be sufficient to  
13 detect a true effect. Another study conducted at residential aged care facilities revealed the  
14 deprescribing group, compared with the usual-care group, demonstrated a 40% mortality reduction  
15 within 12 months of randomization.[9] Based on these two trials and other related studies,[21-24] in  
16 this study, the investigators agreed on the requirement of at least 500 cases to provide a power of 80%,  
17 with a significance level at  $\alpha = 0.05$ , on the assumption of primary composite endpoint rates of 30%  
18 and 40% in the intervention and control groups, respectively, and a true hazard ratio of 0.75 while  
19 allowing for a 15% dropout.

20  
21 **Recruitment**

22 We will recruit 500 subjects in the MPEG trial, based on the above-mentioned sample size  
23 calculation, to detect a significant difference in the primary outcome. Participants will be recruited  
24 from six medical wards in the study site (Kawasaki Municipal Tama Hospital). Community pharmacy  
25 and regional primary care provider outreach and advertising were conducted by the principal  
26 investigator before the study. Advertisements included information on inclusion criteria and time  
27 commitment, description of the intervention, and the participants' chance of receiving intervention.

1 Recruitment of participants in this trial was initiated in May 2019 and will last for 2 years or until  
2 target enrollment is reached. Multiple strategies have been adopted in the recruitment process. Local  
3 physicians and other healthcare providers, including nurses and ward-based pharmacists in the study  
4 site, have been requested to refer potential participants. Participants will be given a gift card as a  
5 reward for study participation.

### 6 7 **Allocation**

8 The study participants who meet the eligibility criteria will be allocated to the intervention and usual-  
9 care groups on a one-on-one basis. Randomization will be conducted upon request from the staff  
10 member responsible for recruitment, using the computer-generated allocation sequence as a part of  
11 HOPE eACReSS, a clinical data management system. The HOPE eACReSS, developed by Fujitsu,  
12 Tokyo, Japan, ensures allocation concealment, and the randomization method uses stratified block  
13 randomization under age group blocks of 65–74, 75–84, and 85 years and above. The randomization  
14 result will be stored, printed, and immediately reported to the staff member responsible for  
15 intervention on that day.

### 16 17 **Blinding**

18 The research assistant who performs the bimonthly telephone interview assessments will be blind to  
19 group allocation. The investigators, ward-based pharmacists, participants' attending physicians,  
20 participants, and/or their NOK will be aware of group allocation.

### 21 22 **Data collection and management**

23 The detailed participant timeline, including schedule of enrollment, interventions, and outcome  
24 measurements, is presented in **Table 1**. Demographic characteristics at enrollment, including age, sex,  
25 date of admission, race, past medical history, comorbid conditions, smoking status, physical  
26 measurements on admission (height, weight, and vital signs), level of long-term care required, and  
27 history of falls within 3 months, will be collected via a chart review and interview by a trained  
28 research nurse and the deprescribing team. Participants' baseline medication list and laboratory

1 findings (eGFR, serum sodium level, and serum potassium level) will also be assessed by reviewing  
 2 the participants' medical record handbook, referral letter, and electronic medical record. Participants  
 3 will be followed-up by a telephone interview every 8 weeks, through 48 weeks, to assess any  
 4 incidence of primary and secondary outcomes. The follow-up telephone interview will be performed  
 5 by a trained research assistant blinded to group allocation. If the study candidate is unable to respond  
 6 to the telephone interview due to lack of capacity, a predetermined NOK will be contacted. The  
 7 medication lists at 24 and 48 weeks will be sent from the relevant community pharmacist upon  
 8 request from the investigators.

10 **Table 1. Timetable of the MPEG trial**

	Baseline assessment	Enrollment	Follow-up 1	Follow-up 2	Follow-up 3	Follow-up 4	Follow-up 5	Follow-up 6
<b>Time point (week)</b>	0	0	8 ± 2	16 ± 2	24 ± 2	32 ± 2	40 ± 2	48 ± 2
<b>Enrollment</b>								
Informed consent	x							
Sociodemographic characteristics	x							
Allocation		x						
<b>Intervention</b>		x						
<b>Assessments</b>								
Subjective symptoms	x	x	x	x	x	x	x	x
Adverse events			x	x	x	x	x	x
Vital signs	x							
Height and weight	x							
Unscheduled visits			x	x	x	x	x	x
Hospital readmission			x	x	x	x	x	x
Falls			x	x	x	x	x	x

Laboratory findings (eGFR, serum sodium level, and serum potassium level)	x							
Number of prescribed medications	x				x			x
Number of prescribed potentially inappropriate medications*	x				x			x
EQ5D-3L		x			x			x
Level of care required	x				x			x

\*The number of prescribed potentially inappropriate medications listed in the STOPP/START

criteria[5]

#### Statistical analysis

The primary and secondary outcomes will be adjudicated using the intention-to-treat analysis. All randomized participants will be analyzed. For those who discontinue the trial before completion, all efforts will be made to follow their primary and secondary endpoints over the study duration through phone calls and health record review, if permitted. Participants who do not experience any endpoint will be censored either when lost to follow-up or at the completion of follow-up.

For the primary endpoint, survival functions for each group will be estimated using the Kaplan–Meier method, and a log-rank test (two-sided), stratified by age group, will be conducted for the primary comparison. Significance level will be set at 0.05. In addition, a Cox proportional hazards model will be used to estimate the hazard ratio across groups. The secondary outcomes, each of all-cause death, unscheduled hospital visits, and re-hospitalization until 48 weeks after randomization, will be compared by stratified log-rank test, and the hazard ratio will be estimated using Cox proportional hazards models. Pre-specified subgroup analyses of the primary endpoint of indicator diseases (heart failure, pneumonia, diabetes mellitus, ischemic stroke, and urinary tract infection) and indicator drug classes (antiplatelets, antihypertensives, antidiabetics, and sedatives) will be conducted for the exploratory analyses. All statistical analyses will be performed using STATA/SE 15.0 (StataCorp LLC, College Station, TX,

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7 **3 Data monitoring**

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9 4 Central monitoring will be conducted at least once a year to check protocol compliance. The  
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11 5 monitoring report will be submitted to the president (chairman of the ethics committee) and the  
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13 6 investigators. Audit will be conducted, if the principal investigator deems it necessary, based on the  
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15 7 monitoring report. There is no predetermined interim analysis for the current study. All study results  
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17 8 will be analyzed by a statistician in a de-identified form.  
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22 **10 Harms**

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24 11 For the current trial, medication modification in the intervention group will be at the discretion of the  
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26 12 participant and his/her attending physician, as a part of clinical practice. Thus, the risk of adverse  
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28 13 events related to the intervention is not expected to significantly deviate from the usual care.

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30 14 However, any adverse event during the study period will be recorded according to the Japanese  
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32 15 version of PRO-CTCAE.[18] Investigators will report to the president (chairman of the ethics  
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34 16 committee) and I-DSMB on all serious adverse events during the study period.

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37 17 Serious adverse events in the MPEG trial are defined as follows:

- 38  
39 18 1) All-cause death;  
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41 19 2) All-cause re-hospitalization;  
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43 20 3) Disability.  
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49 **22 Patient and public involvement**

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51 23 The current trial will be conducted without direct patient involvement. The Institutional Ethics  
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53 24 Committee of St. Marianna University School of Medicine includes patient representatives, charged  
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55 25 with the responsibility to protect patient rights; thus, the MPEG trial protocol was reviewed by a  
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57 26 patient representative. Besides the above review process, patients will not be invited to comment on  
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59 27 the study design and interpretation of the study results. Patients were not involved in the writing of  
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60 28 this manuscript.



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## **ETHICS AND DISSEMINATION**

### **Ethics approval and consent to participate**

The current study protocol was approved by the Institutional Ethical Committee of St. Marianna University School of Medicine (No. 4129). Before study participation, oral and written explanations will be provided to all study candidates, and then written consent will be obtained (Supplementary file: patient consent form). If a study candidate is unable to provide consent due to a lack of capacity (i.e., the researcher deems it inappropriate to obtain informed consent from the study candidate), the same will be obtained from the candidate's NOK. For this trial, a candidate's NOK is defined as the candidate's closest blood relative or one who is eligible to provide consent on behalf of the subject based on their mutual relationship. If the NOK cannot visit the hospital on that day, he/she will be contacted via telephone; oral consent is acceptable for study enrollment, provided that written consent can be obtained at a later date. If there is any revision to the study protocol that could affect the participants' decision to participate, the principal investigator will inform the participants and confirm their intent to continue their participation.

### **Confidentiality**

The data obtained will be managed by the personal information manager, in accordance with the Act on the Protection of Personal Information, until five years after publication of the study results. Personal information, such as participants' name, date of birth, and hospital ID will be stored in a secure database (HOPE eACReSS) with password protection. All hard copies of data will be maintained in a locked cabinet. Data included in the HOPE eACReSS will be completely de-identified at the time of data entry to the web-based clinical research data management system.

### **Dissemination plan and availability of data**

The results of the current study will be disseminated to healthcare providers, policy makers, and patients via presentations at local and national meetings, as well as by publication in a peer-reviewed journal. The datasets used and analyzed during the current study are available from the corresponding

1 author upon reasonable request.

2

### 3 **DISCUSSION**

4       Herein, we describe the detailed methodology of the MPEG trial, a single center, open-label,  
5 randomized controlled trial with a two-arm parallel design. The main goal of this study is to demonstrate  
6 the efficacy and feasibility of multidisciplinary team-based intervention using both explicit and implicit  
7 criteria for medication optimization. While the benefits of deprescribing have been increasingly  
8 highlighted and appear promising in terms of reducing inappropriate prescription, controversy  
9 regarding whether the deprescribing approach actually improves patient outcomes remains  
10 unresolved.[10-12] In particular, there is a lack of evidence regarding the comparative effect of  
11 medication optimization on clinically important outcomes such as survival, hospital admission, and  
12 emergency department visits. Thus, the MPEG trial will primarily examine the effects of medication  
13 optimization on these clinically important outcomes, as well as the number of prescribed medications,  
14 quality of life score, level of long-term care required, drug-related adverse events, death during  
15 hospitalization, and falls.

16       Furthermore, the definition of deprescribing varies across studies, ranging from the use of  
17 explicit criteria, such as the STOPP/START criteria[5] and Beers criteria,[25] to the more implicit  
18 “deprescribing protocol” approach proposed by Scott et al.[8] Considering the strengths and weaknesses  
19 of explicit and implicit criteria, the complimentary use of both in the current study is expected to  
20 enhance the efficacy of the medication optimization process in elderly individuals. Other  
21 methodological strengths of the MPEG trial include a relatively longer follow-up period and sufficient  
22 power to detect the true effect of intervention on clinically important outcomes. Previous deprescribing  
23 trials that failed to reveal the effects of deprescribing were suggested to be limited by a shorter follow-up  
24 and a lack of sufficient power to detect the true effect.[10-13] In this study, we will collect longitudinal  
25 data of approximately 500 patients for up to 48 weeks, allowing sufficient power and follow-up period  
26 to detect clinically important effects of the medication optimization intervention.

27       Potential limitations of the current trial include the single center design and the potential of  
28 contamination due to its open-label nature; however, the results of this study will provide critical

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3 1 evidence regarding the effect of medication optimization that may enhance the safety and efficient care  
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5 2 of elderly multimorbid medical inpatients. In addition, the MPEG trial results will provide a rationale  
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7 3 for future multicenter confirmatory studies.  
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3 recruitment and enrollment. We thank Junko Mita, Miyuki Kondo, and Satomi Tsuchiya for their  
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## 8 **Authors' contributions:**

9 Each author has contributed significantly to the study. KI, MH, AT, HM, EI, EKo, YI, and TM  
10 participated integrally in the study design. KI, EI, and MT contributed primarily to statistical analyses.  
11 KI, MH, TS, IM, MA, TO, AT, HM, HH, EKo, YI, TT, EKu, and SMA contributed to study protocol  
12 implementation, data acquisition, and study data interpretation. KI and SMA drafted the initial  
13 manuscript, and all other authors, including CO and TM, read and approved the final manuscript.

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16 Culture, Grant-in-Aid for Young Scientists, 2018-2021 (grant number 18K15434, Kenya Ie).

18 **Competing interests statement:** Authors declare no conflict of interests.

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3 **1 Figure legends**  
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9 **4 Figure 1. Flowchart summarizing the MPEG trial procedure**  
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13 **6 Figure 2. Scheme of multidisciplinary team-based medication optimization intervention**  
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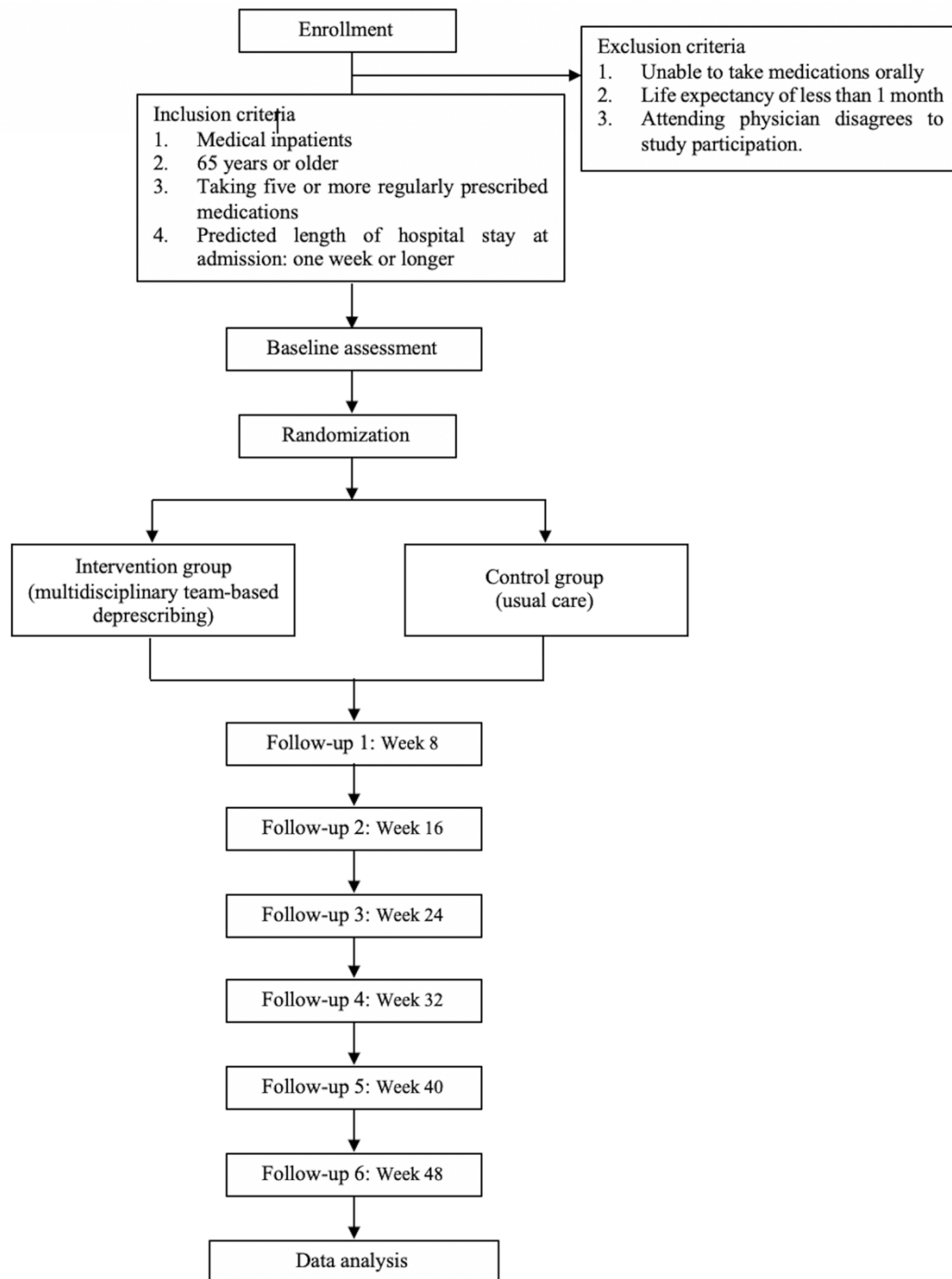
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17 **8 Figure 3. Medication optimization protocol for the MPEG trial**  
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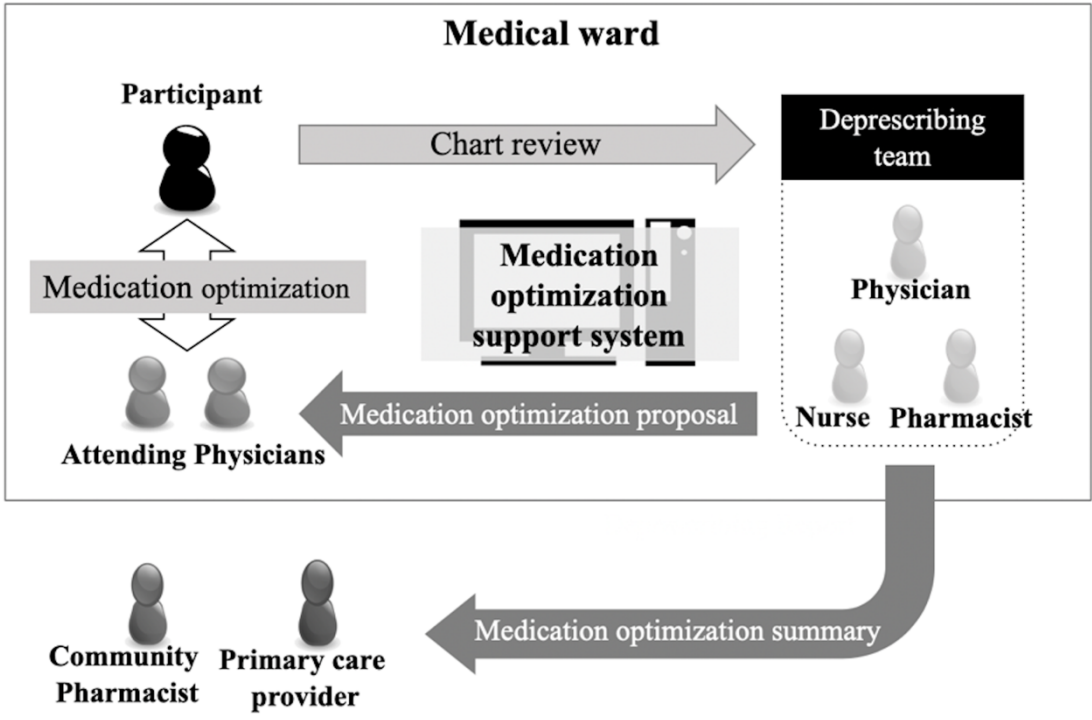
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20 **9** † Baseline information includes study participants' age, sex, past medical history, comorbid  
21 **10** conditions, height, weight, blood pressure, pulse rate, oxygen saturation, body temperature, eGFR,  
22 **11** serum sodium level, serum potassium level, and regularly prescribed medications.  
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25 **13 Supplementary file. Model consent form**  
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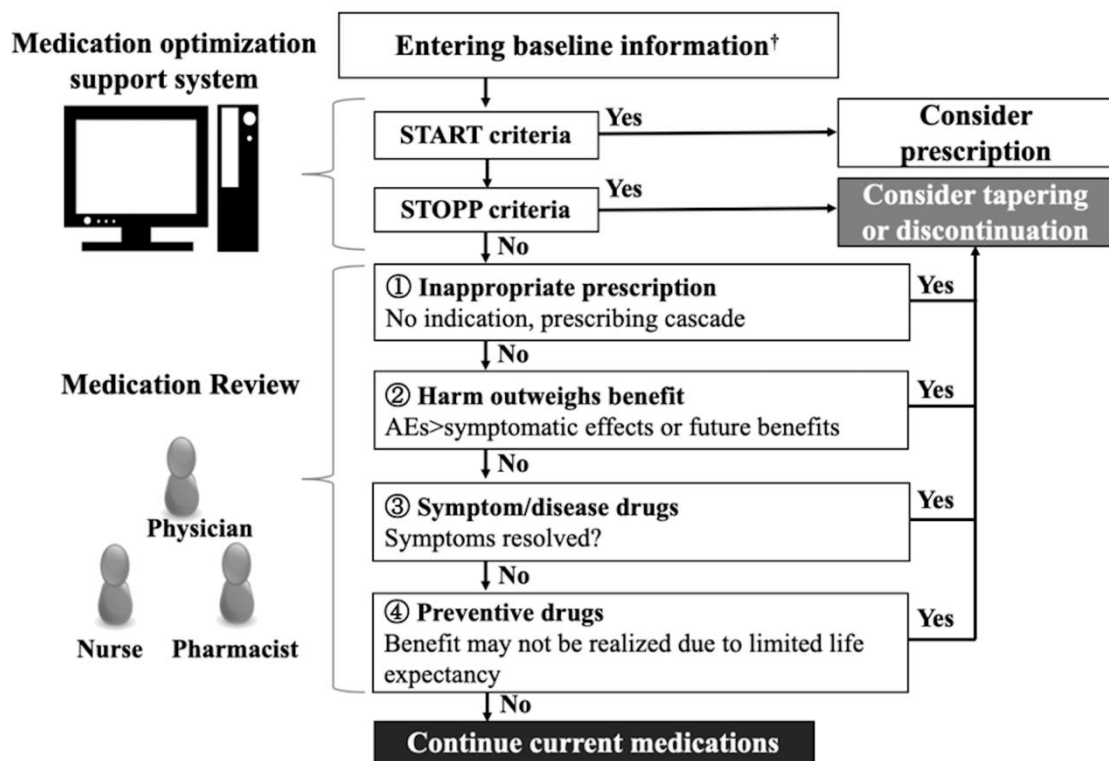




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# Informed Consent Form

Study name :

**Medication optimization Protocol Efficacy for Geriatric inpatients (MPEG) trial**

<Description>

1. Introduction: About clinical trials.
2. Purpose of this trial.
3. Method of this trial.
4. Planned participation period and planned number of participants.
5. Expected effects of medication optimization protocol and possible adverse effects.
6. Participation in this trial is at the discretion of the patient.
7. We may discontinue intervention in this study.
8. Even if the results of this trial are published, your personal information will not be revealed.
9. What to do if you agree to participate in this trial.
10. About your expenses.
11. Doctor in charge.

Please mark the left checkbox only if you do not agree to the future secondary use of your anonymous information obtained from this trial.

**【Patient】**

I agree to participate in this trial and have understood the above listed contents.

Date : \_\_\_\_\_

Signature : \_\_\_\_\_

**【Patient's next of kin】**

I agree with Mr/Ms. \_\_\_\_\_'s participation in this trial and have understood the above listed contents.

Date : \_\_\_\_\_

Signature : \_\_\_\_\_

Relationship with the patient : \_\_\_\_\_

**【Explainer】**

I fully explained the contents of the above clinical trial to the patient.

Date : \_\_\_\_\_

Signature : \_\_\_\_\_

Affiliation : \_\_\_\_\_

# Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. *Ann Intern Med.* 2013;158(3):200-207

		Reporting Item	Page Number
<b>Administrative information</b>			
Title	<a href="#">#1</a>	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	<a href="#">#2a</a>	Trial identifier and registry name. If not yet registered, name of intended registry	2, 4
Trial registration: data set	<a href="#">#2b</a>	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	<a href="#">#3</a>	Date and version identifier	2
Funding	<a href="#">#4</a>	Sources and types of financial, material, and other support	19
Roles and responsibilities: contributorship	<a href="#">#5a</a>	Names, affiliations, and roles of protocol contributors	19

1	Roles and	<a href="#">#5b</a>	Name and contact information for the trial sponsor	N/A
2	responsibilities:			
3	sponsor contact			
4	information			
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8	Roles and	<a href="#">#5c</a>	Role of study sponsor and funders, if any, in study design;	N/A
9	responsibilities:		collection, management, analysis, and interpretation of data;	
10	sponsor and funder		writing of the report; and the decision to submit the report for	
11			publication, including whether they will have ultimate authority	
12			over any of these activities	
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16	Roles and	<a href="#">#5d</a>	Composition, roles, and responsibilities of the coordinating	12-13
17	responsibilities:		centre, steering committee, endpoint adjudication committee,	
18	committees		data management team, and other individuals or groups	
19			overseeing the trial, if applicable (see Item 21a for data	
20			monitoring committee)	
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24	<b>Introduction</b>			
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26	Background and	<a href="#">#6a</a>	Description of research question and justification for undertaking	3-4
27	rationale		the trial, including summary of relevant studies (published and	
28			unpublished) examining benefits and harms for each intervention	
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32	Background and	<a href="#">#6b</a>	Explanation for choice of comparators	3-4
33	rationale: choice of			
34	comparators			
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37	Objectives	<a href="#">#7</a>	Specific objectives or hypotheses	4
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40	Trial design	<a href="#">#8</a>	Description of trial design including type of trial (eg, parallel	4
41			group, crossover, factorial, single group), allocation ratio, and	
42			framework (eg, superiority, equivalence, non-inferiority,	
43			exploratory)	
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46	<b>Methods:</b>			
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48	<b>interventions, and</b>			
49	<b>outcomes</b>			
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53	Study setting	<a href="#">#9</a>	Description of study settings (eg, community clinic, academic	4-5
54			hospital) and list of countries where data will be collected.	
55			Reference to where list of study sites can be obtained	
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1	Eligibility criteria	<a href="#">#10</a>	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
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6	Interventions:	<a href="#">#11a</a>	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-7
7	description			
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10	Interventions:	<a href="#">#11b</a>	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)	14
11	modifications			
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15	Interventions:	<a href="#">#11c</a>	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7
16	adherence			
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21	Interventions:	<a href="#">#11d</a>	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
22	concomitant care			
23				
24				
25	Outcomes	<a href="#">#12</a>	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	7-8
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34	Participant timeline	<a href="#">#13</a>	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	4,10-12, Figure 1
35				
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40	Sample size	<a href="#">#14</a>	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
41				
42				
43				
44				
45	Recruitment	<a href="#">#15</a>	Strategies for achieving adequate participant enrolment to reach target sample size	9
46				
47				
48				
49	<b>Methods: Assignment</b>			
50	<b>of interventions (for</b>			
51	<b>controlled trials)</b>			
52				
53				
54	Allocation: sequence	<a href="#">#16a</a>	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	9-10
55	generation			
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provided in a separate document that is unavailable to those who enrol participants or assign interventions

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3			
4	Allocation	<a href="#">#16b</a>	Mechanism of implementing the allocation sequence (eg, central 10
5	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
6			describing any steps to conceal the sequence until interventions
7	mechanism		are assigned
8			
9			
10			
11	Allocation:	<a href="#">#16c</a>	Who will generate the allocation sequence, who will enrol 10
12	implementation		participants, and who will assign participants to interventions
13			
14			
15	Blinding (masking)	<a href="#">#17a</a>	Who will be blinded after assignment to interventions (eg, trial 10
16			participants, care providers, outcome assessors, data analysts),
17			and how
18			
19			
20	Blinding (masking):	<a href="#">#17b</a>	If blinded, circumstances under which unblinding is permissible, N/A
21	emergency unblinding		and procedure for revealing a participant's allocated intervention
22			during the trial
23			
24			
25	<b>Methods: Data</b>		
26	<b>collection,</b>		
27	<b>management, and</b>		
28	<b>analysis</b>		
29			
30			
31			
32	Data collection plan	<a href="#">#18a</a>	Plans for assessment and collection of outcome, baseline, and 10-12
33			other trial data, including any related processes to promote data
34			quality (eg, duplicate measurements, training of assessors) and a
35			description of study instruments (eg, questionnaires, laboratory
36			tests) along with their reliability and validity, if known.
37			Reference to where data collection forms can be found, if not in
38			the protocol
39			
40			
41			
42			
43	Data collection plan:	<a href="#">#18b</a>	Plans to promote participant retention and complete follow-up, 10-12
44	retention		including list of any outcome data to be collected for participants
45			who discontinue or deviate from intervention protocols
46			
47			
48			
49	Data management	<a href="#">#19</a>	Plans for data entry, coding, security, and storage, including any 10-13
50			related processes to promote data quality (eg, double data entry;
51			range checks for data values). Reference to where details of data
52			management procedures can be found, if not in the protocol
53			
54			
55	Statistics: outcomes	<a href="#">#20a</a>	Statistical methods for analysing primary and secondary 12
56			outcomes. Reference to where other details of the statistical
57			analysis plan can be found, if not in the protocol
58			
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1	Statistics: additional	<a href="#">#20b</a>	Methods for any additional analyses (eg, subgroup and adjusted	12
2	analyses		analyses)	
3				
4	Statistics: analysis	<a href="#">#20c</a>	Definition of analysis population relating to protocol non-	12
5	population and missing		adherence (eg, as randomised analysis), and any statistical	
6	data		methods to handle missing data (eg, multiple imputation)	
7				
8				
9				
10	<b>Methods: Monitoring</b>			
11				
12	Data monitoring:	<a href="#">#21a</a>	Composition of data monitoring committee (DMC); summary of	12-13
13	formal committee		its role and reporting structure; statement of whether it is	
14			independent from the sponsor and competing interests; and	
15			reference to where further details about its charter can be found,	
16			if not in the protocol. Alternatively, an explanation of why a	
17			DMC is not needed	
18				
19				
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21				
22	Data monitoring:	<a href="#">#21b</a>	Description of any interim analyses and stopping guidelines,	N/A
23	interim analysis		including who will have access to these interim results and make	
24			the final decision to terminate the trial	
25				
26				
27	Harms	<a href="#">#22</a>	Plans for collecting, assessing, reporting, and managing solicited	13
28			and spontaneously reported adverse events and other unintended	
29			effects of trial interventions or trial conduct	
30				
31				
32				
33	Auditing	<a href="#">#23</a>	Frequency and procedures for auditing trial conduct, if any, and	12-13
34			whether the process will be independent from investigators and	
35			the sponsor	
36				
37				
38	<b>Ethics and</b>			
39	<b>dissemination</b>			
40				
41				
42	Research ethics	<a href="#">#24</a>	Plans for seeking research ethics committee / institutional review	13
43	approval		board (REC / IRB) approval	
44				
45				
46	Protocol amendments	<a href="#">#25</a>	Plans for communicating important protocol modifications (eg,	14
47			changes to eligibility criteria, outcomes, analyses) to relevant	
48			parties (eg, investigators, REC / IRBs, trial participants, trial	
49			registries, journals, regulators)	
50				
51				
52				
53	Consent or assent	<a href="#">#26a</a>	Who will obtain informed consent or assent from potential trial	13-14
54			participants or authorised surrogates, and how (see Item 32)	
55				
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1	Consent or assent:	<a href="#">#26b</a>	Additional consent provisions for collection and use of	N/A
2	ancillary studies		participant data and biological specimens in ancillary studies, if	
3			applicable	
4				
5				
6	Confidentiality	<a href="#">#27</a>	How personal information about potential and enrolled	14
7			participants will be collected, shared, and maintained in order to	
8			protect confidentiality before, during, and after the trial	
9				
10				
11	Declaration of interests	<a href="#">#28</a>	Financial and other competing interests for principal	19
12			investigators for the overall trial and each study site	
13				
14				
15	Data access	<a href="#">#29</a>	Statement of who will have access to the final trial dataset, and	14
16			disclosure of contractual agreements that limit such access for	
17			investigators	
18				
19				
20	Ancillary and post trial	<a href="#">#30</a>	Provisions, if any, for ancillary and post-trial care, and for	N/A
21	care		compensation to those who suffer harm from trial participation	
22				
23				
24	Dissemination policy:	<a href="#">#31a</a>	Plans for investigators and sponsor to communicate trial results	14
25	trial results		to participants, healthcare professionals, the public, and other	
26			relevant groups (eg, via publication, reporting in results	
27			databases, or other data sharing arrangements), including any	
28			publication restrictions	
29				
30				
31				
32				
33	Dissemination policy:	<a href="#">#31b</a>	Authorship eligibility guidelines and any intended use of	N/A
34	authorship		professional writers	
35				
36				
37	Dissemination policy:	<a href="#">#31c</a>	Plans, if any, for granting public access to the full protocol,	14
38	reproducible research		participant-level dataset, and statistical code	
39				
40				
41	<b>Appendices</b>			
42				
43	Informed consent	<a href="#">#32</a>	Model consent form and other related documentation given to	13-14
44	materials		participants and authorised surrogates	
45				
46				
47	Biological specimens	<a href="#">#33</a>	Plans for collection, laboratory evaluation, and storage of	N/A
48			biological specimens for genetic or molecular analysis in the	
49			current trial and for future use in ancillary studies, if applicable	
50				
51				

52 None The SPIRIT checklist is distributed under the terms of the Creative Commons Attribution License CC-  
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