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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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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

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

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

The eligibility criteria for participants are:

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

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

Interventions

Participants will be randomly assigned to receive either a medication optimization intervention or the usual care. Both groups will be subjected to a medication review by ward-based pharmacists, along with the usual care from their attending physicians. For those assigned to the intervention group, the multidisciplinary deprescribing team, which will consist of a physician and a pharmacist, will conduct the medication optimization intervention within 48 h of allocation. Ward-based nurses will be consulted by the deprescribing team, as required, to collect any information necessary for the medication optimization proposal. All members of the deprescribing team will receive standardized instruction and guidance in advance. In addition, monthly deprescribing-team meetings will be held for monitoring and quality control of interventions.

Overall, the intervention will consist of a medication review, followed by the development of a medication optimization proposal based on the STOPP/START criteria[5] and a medication

optimization protocol (**Figure 2**). First, the study participant's baseline data (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) will be collected via a chart review and entered into a computer-based medication optimization support system, developed specifically for the trial. The medication optimization support system will automatically generate a draft of proposal according to the STOPP/START criteria.[5] After reviewing the draft proposal, the deprescribing team will conduct a step-by-step discussion based on the medication optimization protocol **(Figure 3)**, involving the following steps per the algorithm proposed by Scott et al.[8]

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

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

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

   Study participants' symptoms and laboratory results will be reviewed to determine any adverse effect that outweighs the expected benefits of the prescribed drug.

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

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

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

   Medications aimed to prevent the occurrence of disease (e.g. statins and glucose-lowering drugs) will be considered for their benefits, the length of time required for the expected benefit, and the participant's preference and estimated life expectancy.

The rationale for medication optimization proposal will be explained and discussed in detail with each participant or next of kin (NOK). Upon participant's agreement, the team will recommend the medication optimization plan, including its rationale, to the participant's attending physician. Whether the proposal would be accepted or not will be left to the discretion of the participant and his/her attending physician, as a part of clinical judgment. The details of each medication optimization proposal and the list of medications at discharge will be recorded to track adherence to the proposal.

Medication optimization summary, including the reason for prescription modification and relevant precautions, will be sent to the study participant's primary care physician and community pharmacists upon discharge.

Outcomes

Primary outcome

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

Secondary outcomes

The following endpoints at the baseline, 24 weeks, and 48 weeks post-randomization, will be assessed as secondary outcomes.

1. **Number of regular and potentially inappropriate medications**

   The number of prescribed medications listed in participant's medical record handbook, referral letter, or electronic medical record over a duration of 28 days or longer at the baseline, 24 weeks, and 48 weeks post-randomization will be considered as "regular medication." Any prescribed

regular medication listed in the STOPP criteria[5] will be indicated as PIM, whose number at the baseline, 24 weeks, and 48 weeks post-randomization will be recorded simultaneously.

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

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

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

   Self-reported general health status will be recorded at three time points using EQ5D-3L.[16] We will use the Japanese version of EQ5D-3L and a Japanese scoring system that have been found to be valid and reliable.[17]

In addition to the above-listed outcomes, the ones listed below, occurring within 48 weeks after randomization, will be assessed including the event dates.

- All-cause death
- All-cause death during initial hospitalization
- Unscheduled hospital visits
- Rehospitalization
- Drug adverse events

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

- Injury due to falls

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

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

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

Blinding

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

Data collection and management

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

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
Time point (week)	0	0	8 ± 2	16 ± 2	24 ± 2	32 ± 2	40 ± 2	48 ± 2
Enrollment								
Informed consent	x							
Sociodemographic characteristics	x							
Allocation		x						
Intervention		x						
Assessments								
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

monitoring report. There is no predetermined interim analysis for the current study. All study results will be analyzed by a statistician in a de-identified form.

Harms

For the current trial, medication modification in the intervention group will be at the discretion of the participant and his/her attending physician, as a part of clinical practice. Thus, the risk of adverse events related to the intervention is not expected to significantly deviate from the usual care. However, any adverse event during the study period will be recorded according to the Japanese version of PRO-CTCAE.[18] Investigators will report to the president (chairman of the ethics committee) and I-DSMB on all serious adverse events during the study period.

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

1) All-cause death;

2) All-cause rehospitalization;

3) Disability.

Patient and public involvement

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

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. If a study

candidate is unable to provide consent due to a lack of capacity (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, because an oral consent is acceptable for study enrollment, provided that a written consent can be obtained at a later date. If there is any revision to study protocol that could affect the participants' decision to participate, the principle 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 author upon reasonable request.

DISCUSSION

Herein, we describe the detailed methodology of the MPEG trial, a single center, open-label, randomized controlled trial with a two-arm parallel design. The main goal of this study is to demonstrate the efficacy and feasibility of multidisciplinary team-based intervention using both explicit and implicit

criteria for medication optimization. While the benefits of deprescribing have been increasingly highlighted and appear promising in terms of reducing inappropriate prescription, controversy regarding whether the deprescribing approach actually improves clinically significant outcomes remains unanswered.[10-12] Furthermore, the definition of deprescribing varies across studies, ranging from the use of explicit criteria, such as the STOPP/START criteria[5] and Beers criteria,[25] to the more implicit "deprescribing protocol" approach proposed by Scott et al.[8] Considering the strength and weakness of explicit and implicit criteria, the complimentary use of both in the current study is expected to enhance the efficacy of medication optimization process in elderly individuals.

Other methodological limitations that potentially affected the non-significant results of previous deprescribing trials are the relatively shorter follow-up period and a lack of sufficient power to detect the true effect of intervention on clinically important outcomes.[10-13] In this study, we will collect longitudinal data of approximately 500 patients for up to 48 weeks, allowing sufficient power and follow-up period to detect clinically important effects of the medication optimization intervention. 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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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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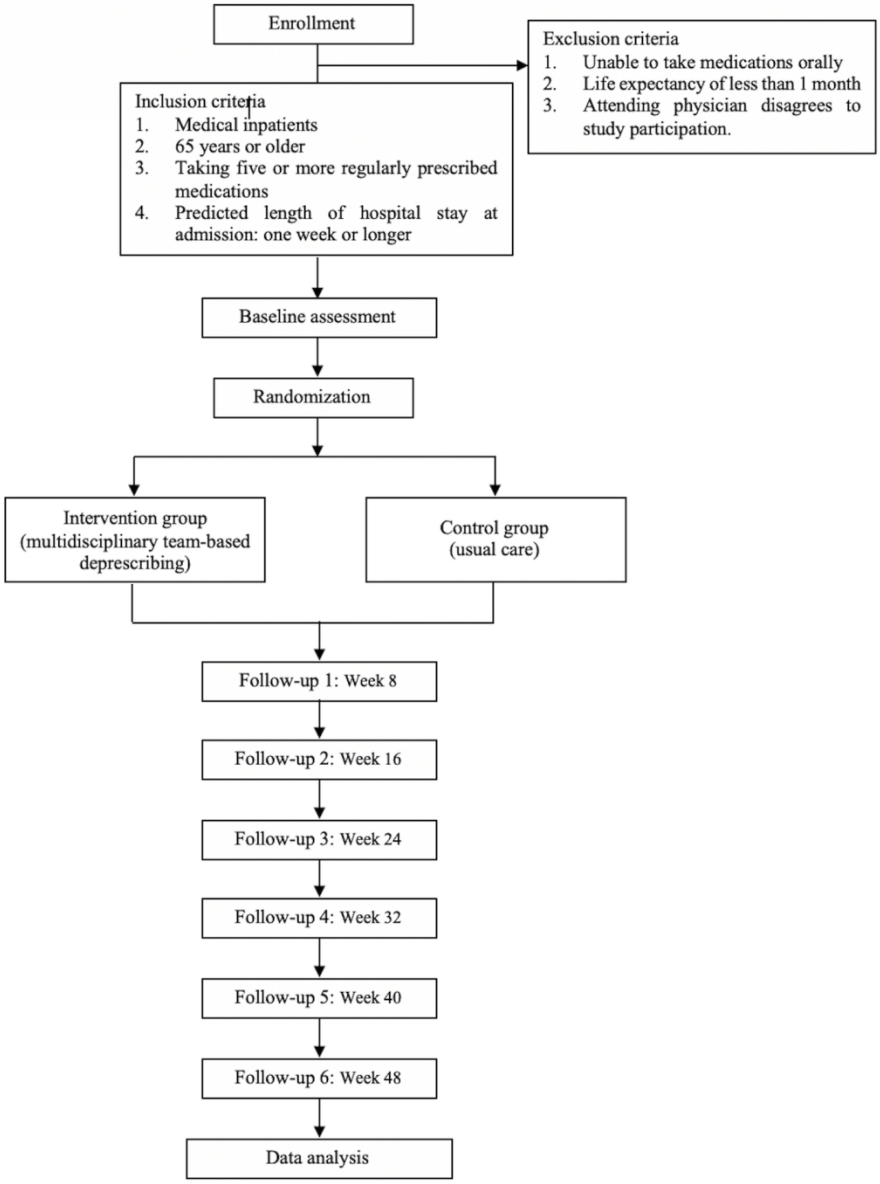
Figure legends

Figure 1. Flowchart summarizing the MPEG trial procedure

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.



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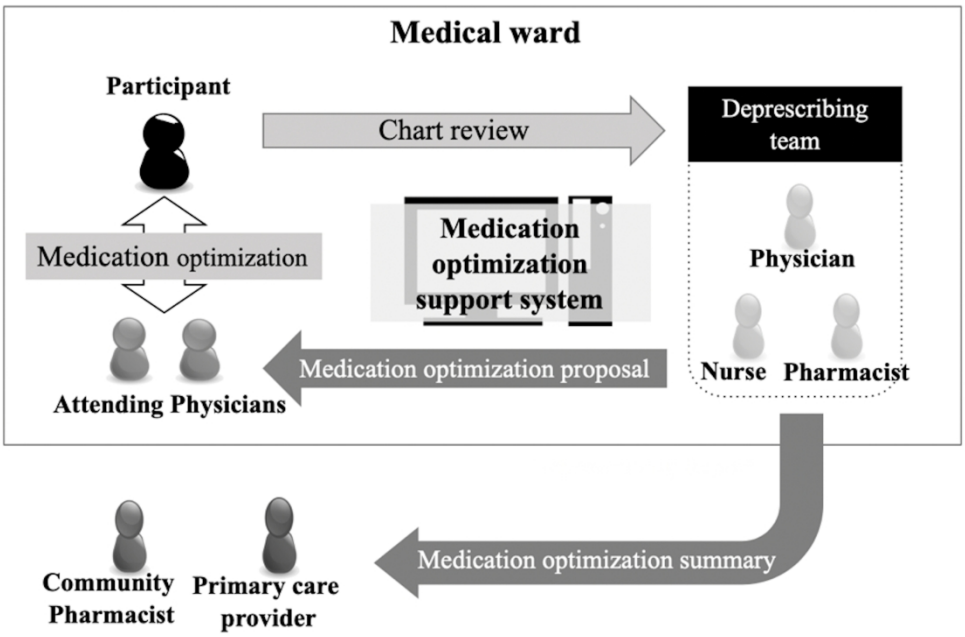

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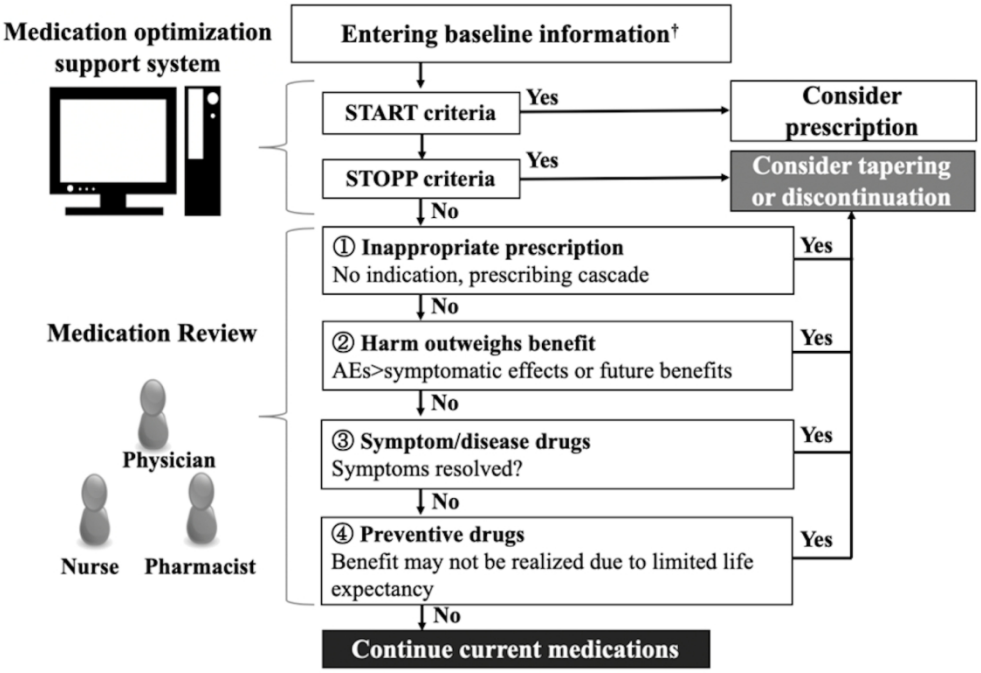

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

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

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

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	N/A
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	12-13
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Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3-4
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4-5
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will	5

		perform the interventions (eg, surgeons, psychotherapists)	
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Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	14
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-8
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	4,10-12, Figure 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	9
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Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9-10

Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
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Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10-12
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10-12
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10-13
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	12-13
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
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Ethics and dissemination			
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Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	14
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Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect	14

		confidentiality before, during, and after the trial	
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	14
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Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

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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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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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, quality of life score, level of long-term care required, drug-related adverse events, death during hospitalization, and 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 the 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 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 readmission 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 the deprescribing protocol, has been expected to improve patient outcomes. Scott et al. defined it as “the systematic process of identifying 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 pointed out that studies that 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

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

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

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

Interventions

Participants will be randomly assigned to receive either a medication optimization intervention or the usual care. Both groups will be subjected to medication reconciliation by ward-based pharmacists using data provided by the medical record handbook, patient/family, or a referral letter, along with the usual care from their attending physicians. For those assigned to the intervention group, the multidisciplinary deprescribing team, which will consist of a physician and a pharmacist, will conduct the medication optimization intervention within 48 h of allocation. Ward-based nurses will be consulted by the deprescribing team, as required, to collect any information necessary for the medication optimization proposal, including patient preference and medication adherence. All members of the deprescribing team will receive standardized instruction and guidance in advance. In addition, monthly deprescribing-team meetings and case-based reflection for selected cases during the previous month will be held for monitoring and quality control of interventions.

Overall, the intervention will consist of a medication review, followed by the development of a medication optimization proposal based on the STOPP/START criteria[5] and a medication optimization protocol (**Figure 2**). First, the study participant's baseline data (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) will be collected via a chart review and entered into a computer-based medication optimization support system, developed specifically for the trial. The medication optimization support system will automatically generate a draft proposal according to the STOPP/START criteria.[5] After reviewing the draft proposal, the deprescribing team will conduct a step-by-step discussion based on the medication optimization protocol **(Figure 3)**, involving the following steps per the algorithm proposed by Scott et al.[8]

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

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

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

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

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

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

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

Medications aimed to prevent the occurrence of disease (e.g., statins and glucose-lowering drugs) will be considered for their benefits, the length of time required for the expected benefit, and the participant's preference and estimated life expectancy.

The rationale for the medication optimization proposal will be explained and discussed in detail with each participant or next of kin (NOK). Upon the participant's agreement, the team will recommend the medication optimization plan, including its rationale, to the participant's attending physician. Whether the proposal would be accepted or not will be left to the discretion of the participant and his/her attending physician, as a part of clinical judgment. The details of each medication optimization proposal and the list of medications at discharge will be recorded to track adherence to the proposal.

Medication optimization summary, including the reason for prescription modification and relevant precautions, will be sent to the study participant's primary care physician and community pharmacists upon discharge.

Outcomes

Primary outcome

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

Secondary outcomes

The following endpoints at the baseline, 24 weeks, and 48 weeks post-randomization will be assessed as secondary outcomes.

1. Number of regular and potentially inappropriate medications

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

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

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

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

Self-reported general health status will be recorded at three time points using EQ5D-3L.[16] We will use the Japanese version of EQ5D-3L and a Japanese scoring system that have been found to be valid and reliable.[17]

In addition to the above-listed outcomes, the ones listed below, occurring within 48 weeks after randomization, will be assessed including the event dates.

- All-cause death
- All-cause death during initial hospitalization
- Unscheduled hospital visits
- Re-hospitalization
- Drug adverse events

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

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

- Falls

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

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 the participants' 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 healthcare 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

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

Blinding

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

Data collection and management

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

findings (eGFR, serum sodium level, and serum potassium level) will also be assessed by reviewing the participants' medical record handbook, referral letter, and electronic medical record. Participants will be followed-up by a telephone interview every 8 weeks, through 48 weeks, to assess any incidence of primary and secondary outcomes. The follow-up telephone interview will be performed by a trained research assistant blinded to group allocation. If the study candidate is unable to respond to the telephone interview due to lack of capacity, a predetermined NOK will be contacted. The 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
Time point (week)	0	0	8 ± 2	16 ± 2	24 ± 2	32 ± 2	40 ± 2	48 ± 2
Enrollment								
Informed consent	x							
Sociodemographic characteristics	x							
Allocation		x						
Intervention		x						
Assessments								
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,

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 monitoring report. There is no predetermined interim analysis for the current study. All study results will be analyzed by a statistician in a de-identified form.

Harms

For the current trial, medication modification in the intervention group will be at the discretion of the participant and his/her attending physician, as a part of clinical practice. Thus, the risk of adverse events related to the intervention is not expected to significantly deviate from the usual care. However, any adverse event during the study period will be recorded according to the Japanese version of PRO-CTCAE.[18] Investigators will report to the president (chairman of the ethics committee) and I-DSMB on all serious adverse events during the study period.

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

1) All-cause death;

2) All-cause re-hospitalization;

3) Disability.

Patient and public involvement

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

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

author upon reasonable request.

DISCUSSION

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

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

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

evidence regarding the effect of medication optimization that may enhance the safety and efficient care of elderly multimorbid medical inpatients. In addition, the MPEG trial results will provide a rationale for future multicenter confirmatory studies.

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Authors' contributions:

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

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Competing interests statement: Authors declare no conflict of interests.

Figure legends

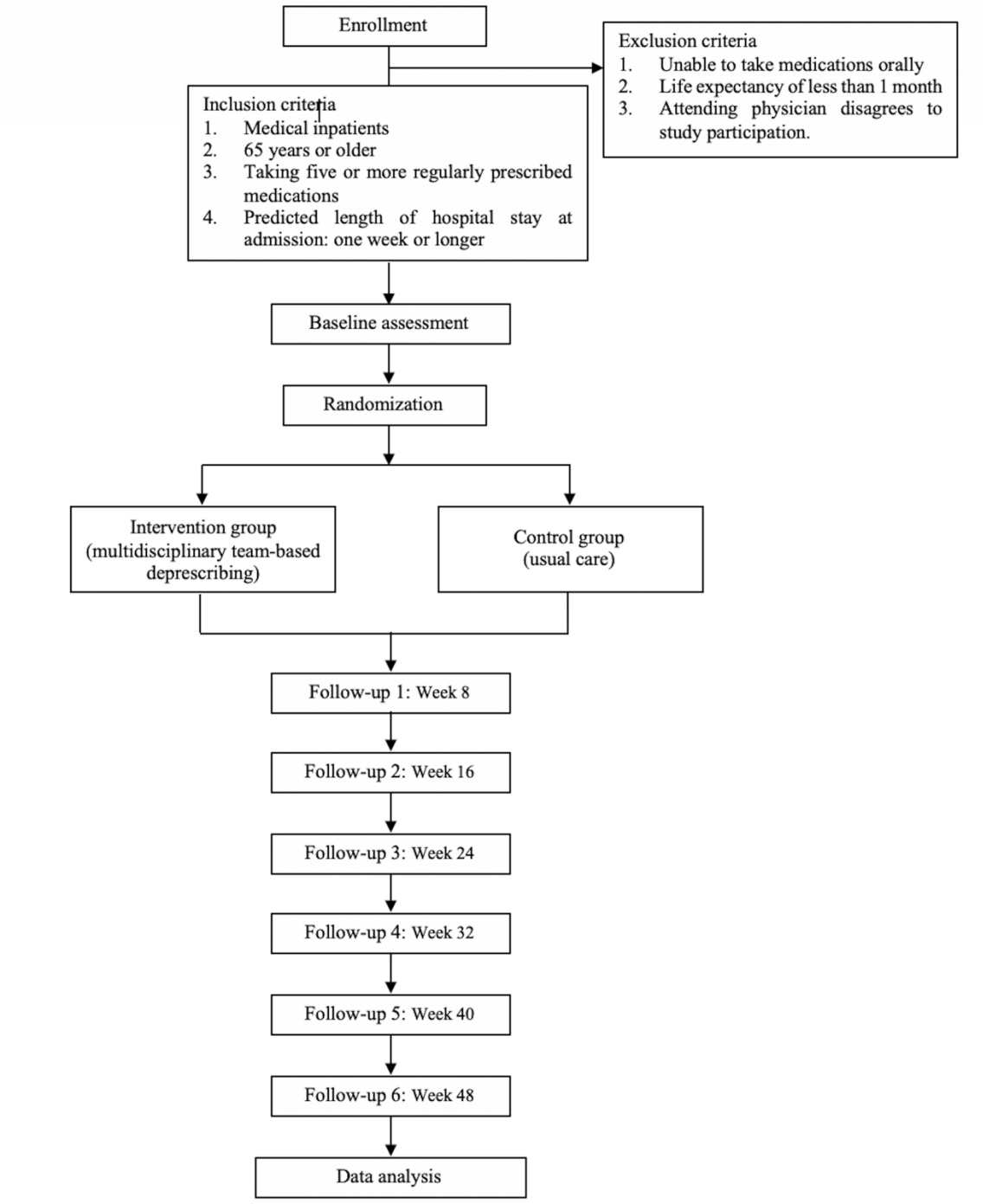
Figure 1. Flowchart summarizing the MPEG trial procedure

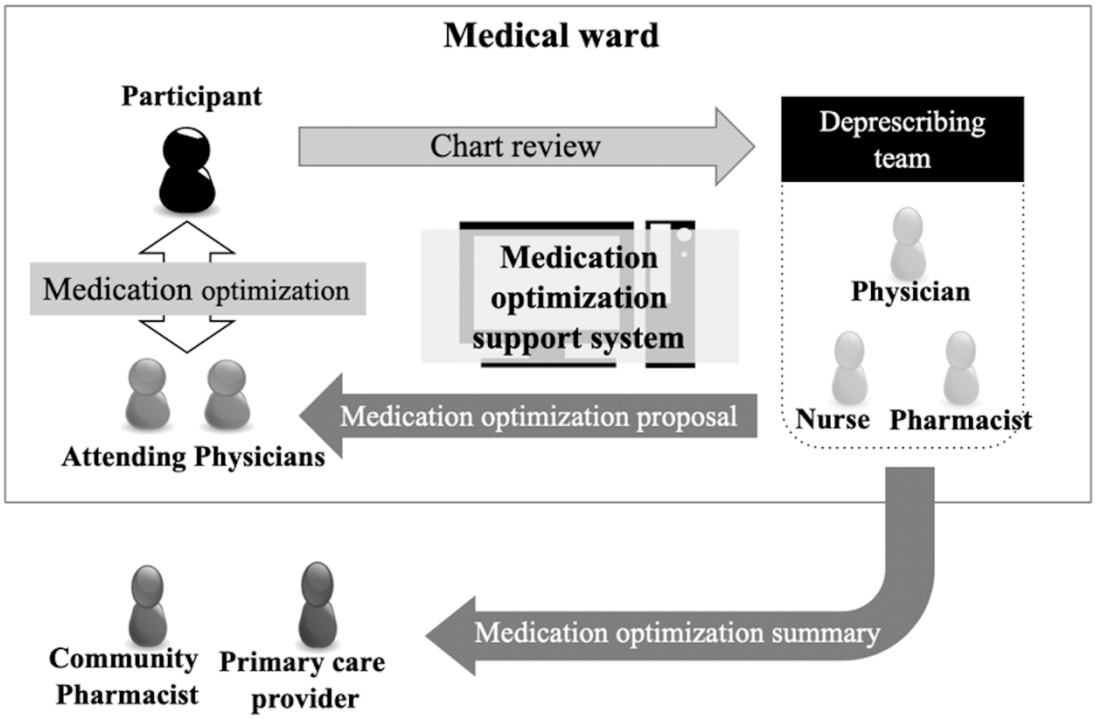
Figure 2. Scheme of multidisciplinary team-based medication optimization intervention

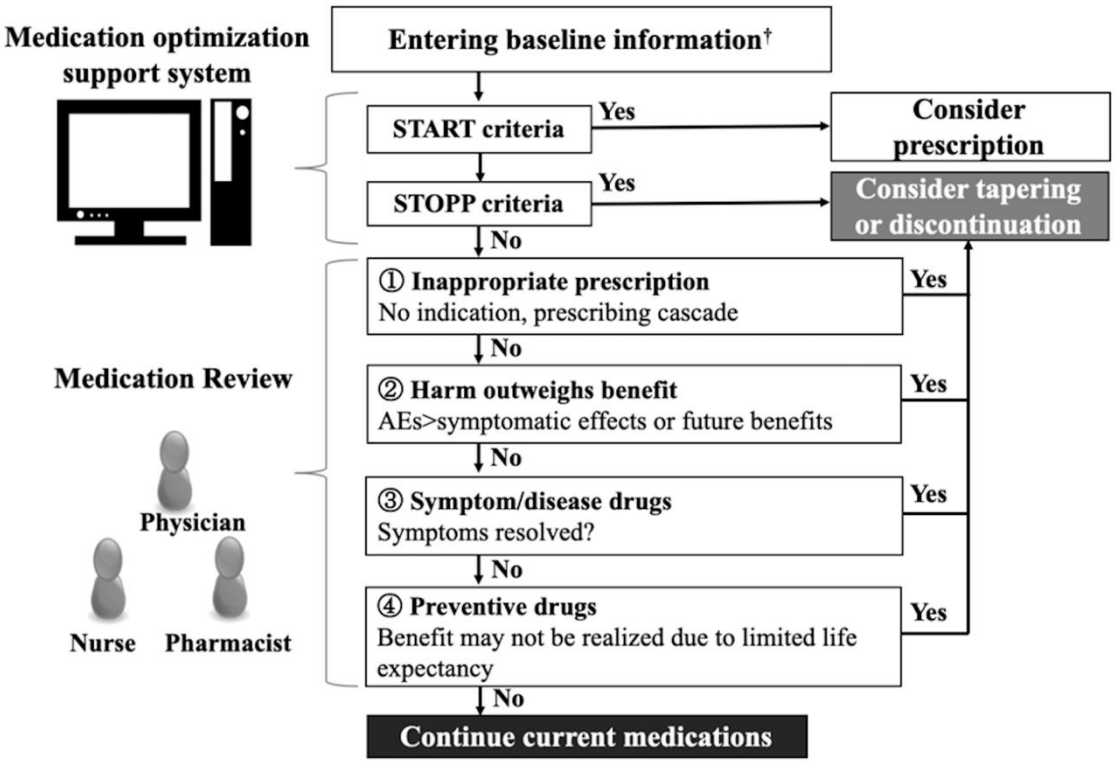
Figure 3. Medication optimization protocol for the MPEG trial

† 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.

Supplementary file. Model consent form


Enrollment
Exclusion criteria
1. Unable to take medications orally
2. Life expectancy of less than 1 month
3. Attending physician disagrees to study participation.
Inclusion criteria
1. Medical inpatients
2. 65 years or older
3. Taking five or more regularly prescribed medications
4. Predicted length of hospital stay at admission: one week or longer
Baseline assessment
Randomization
Intervention group (multidisciplinary team-based deprescribing)
Control group (usual care)
Follow-up 1: Week 8
Follow-up 2: Week 16
Follow-up 3: Week 24
Follow-up 4: Week 32
Follow-up 5: Week 40
Follow-up 6: Week 48
Data analysis


Medical ward
Participant
Chart review
Deprescribing team
Medication optimization
Medication optimization support system
Physician
Nurse
Pharmacist
Attending Physicians
Medication optimization proposal
Community Pharmacist
Primary care provider
Medication optimization summary



Ver.No.1（2018/8/18）

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

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	N/A
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	12-13
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3-4
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4-5

Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-7
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	14
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-8
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	4,10-12, Figure 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be	9-10

		provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10-12
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10-12
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10-13
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12

Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	12-13
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12-13
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	13
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	14
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13-14

Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	14
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	13-14
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A