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INTERDISCIPLINARY COLLABORATION ACROSS SECONDARY AND PRIMARY CARE TO IMPROVE MEDICATION SAFETY IN THE ELDERLY (The IMMENSE-study) – PROTOCOL FOR A RANDOMIZED CONTROLLED TRIAL

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INTERDISCIPLINARY COLLABORATION ACROSS SECONDARY AND PRIMARY CARE TO IMPROVE MEDICATION SAFETY IN THE ELDERLY (The IMMENSE-study) – STUDY PROTOCOL FOR A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Introduction: Drug related problems (DRPs) are common in the elderly, leading to suboptimal therapy, hospitalizations and increased mortality. The integrated medicines management model (IMM) is a multi-factorial interdisciplinary methodology aiming to optimize individual medication therapy throughout the hospital stay. IMM has shown to reduce hospital visits and drug related hospital readmissions. Using the IMM model as a template, we designed an intervention to improve medication safety in hospitals, and a service to improve communication across the secondary and primary care interface. This paper presents the study protocol to explore the effects of interdisciplinary collaboration with regards to healthcare use, health related quality of life (HRQoL) and medication appropriateness in elderly patients.

Methods and analysis: A total of 500 patients aged 70+ will be included and randomized (1:1) to standard care or the intervention. The intervention comprises five steps mainly performed by pharmacists: i) medication reconciliation at admission, ii) medication review during hospital stay, iii) patient counselling about the use of medicines, iv) comprehensible and patient-friendly medication list with explanations in discharge summary and v) post-discharge phone calls to the primary care level. The primary outcome is the difference in the rate of emergency medical visits (acute rehospitalization + visits to emergency department) 12 months after discharge in intervention and control patients. Secondary outcomes include time to first re-hospitalization, length of hospital stay, mortality, hip fractures, strokes, medication changes, health-related quality of life, and medication appropriateness**.** Patient inclusion started in September 2016.

Ethics and dissemination. The trial was approved by the Norwegian Centre for Research Data and the Norwegian Data Protection Authority.

Trial registration number. ClinicalTrials.gov (NCT02816086).

STRENGTHS AND LIMITAIONS OF THIS STUDY

- No randomized controlled study investigating the effects of implementing an IMM based intervention in the Norwegian health care setting has been published.
- Nationwide health care registers will enable us to collect high quality data for our primary endpoint.
- Collecting outcomes for a period of one year after discharge allows us to measure sustainable effects of our intervention.
- A limitation is that including control and intervention patients from the same wards may introduce education and contamination bias.

- Our intervention is complex, and the study will not answer if there is one specific part of the intervention that is responsible for any observed effects.

INTRODUCTION

Healthcare systems across the world are challenged by an aging population. Aging is frequently accompanied by morbidity which increases the need for pharmacotherapy. The increased complexity of medication regimes combined with frailty, reduced cognitive function and changes in pharmacokinetics and –dynamics, increases the risk of adverse drug effects (ADEs) and other drug-related problems (DRPs) in this population[1 2].

A drug-related problem (DRP) is 'an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes' [3]. DRPs include inappropriate prescribing (drug, dose, dosage frequency, and dosage form), drug-drug interactions, adverse drug reactions, wrong administration, need for monitoring as well as non-adherence to therapy. DRPs occur frequently in elderly [4 5], and are associated with increased risk of hospitalization, morbidity and mortality [6-8]. For instance, adverse drug events alone contribute to 30-40% of acute hospital admissions in the elderly [9 10], many of them being preventable [11-14].

Communication barriers across primary and secondary care, multiple prescribers, fragmentation of care, and frequent transitions across care levels, make hospitalized elderly in particular risk of drug induced harm [15 16]. To improve the medicine management process in hospitals, pharmacist dependent methods like medication reconciliation (MedRec), medication review and patient education have been developed and studied[17-20]. The Integrated Medicines Management (IMM) model is based on interdisciplinary collaboration where clinical pharmacists work together with physicians, nurses and patient seeking to optimize medication therapy by preventing and solving DRP[21 22]. In the IMM model different services like MedRec, medication review, patient counselling and dissemination of correct medication information at transition points are merged together in a systematic way [21 23]. In Northern Ireland, the implementation of the IMM model in hospitals has led to a reduced length of hospitalization and an increased time to re-hospitalization compared to standard care [23 24]. Also in Sweden, implementing IMM in single hospital settings has been associated with a reduction in hospital visits and drug-related re-admissions, improved communication of medication information at transition points and improved quality of drug therapy [21 25 26]. In Norway, hospital pharmacies providing pharmaceutical care services have since 2010 been based on the methods embraced by the IMM methodology [27]. However, no randomized controlled studies investigating the effects of implementing the IMM-model in the Norwegian health care system have been published.

Based on the IMM model, we have designed an interdisciplinary collaboration structure aiming to optimize medication therapy in hospitals and improve the communication of medication-related issues between secondary and primary care. The aim of the study is to explore the effects of this collaboration structure on healthcare use, health related quality of life (HRQoL) and medication appropriateness in elderly patients.

Objectives

The primary objective is to investigate the effects of the interdisciplinary collaboration on rate of emergency medical visits (acute readmissions and visits to emergency departments (ED) 12 months after hospital discharge.

Due to the clinical approach of the study, the complexity of the intervention and the possibility to link with health registers, secondary objectives include to investigate the effects on; self-reported quality of life, acute readmissions, length of index hospital stay, time to first re-hospitalization, rate of visits to general practitioner (GP), mortality rate, medication appropriateness, number of drug-related re-hospitalizations, drug changes, hip fractures and stroke

METHODS AND ANALYSIS

This protocol was developed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 statement [28] (see online supplement for the SPIRIT 2013 checklist).

Study design

This is a non-blinded randomized controlled trial with an intervention group and a control group (1:1 ratio). The intervention group receives the new intervention, while the control group will receive standard care, see Figure 1. Study enrolment started in September 2016.

INSERT FIGURE 1: Flowchart

Settings

The study is carried out at two different locations at the University hospital of North-Norway (UNN); UNN Tromsø and UNN Harstad.

Study population

All acutely admitted patients are screened for eligibility by study pharmacists. Only eligible patients are invited to participate in the study. When written informed consent is obtained from patient or next

of kin, the patient is included. Inclusion is only performed when a pharmacist is present. Readmitted study patients are not re-included, but receive standard care.

Eligibility criteria

Inclusion criteria are: age ≥70 years, acutely admitted and willing to provide written informed consent (patient or next of kin). Exclusion criteria includes: admitted to the study ward more than 72 hours before evaluation for eligibility, moved to and discharged from other wards during the index stay, inability to understand Norwegian (patient or next of kin), considered terminally ill or short life expectancy, planned discharged on the inclusion day, occupying a bed in a study ward but under the care of physicians from a non-study ward, and patients where an intervention from a study pharmacist is considered necessary for ethical reasons (before randomization or in control group).

Randomization and blinding

After collecting baseline data, included patients are randomized into the two study arms using a web-based service supplied by a third party. The randomization blocks sizes will be concealed and permuted. We stratify by study site. As pharmacists are only involved in intervention patients, blinding of group allocation is impossible both to the patients, pharmacists and medical team. However, the primary analysis will be performed by an investigator blinded for group allocation.

Standard care (control group)

Patients assigned to standard care receive treatment from a team consisting of physicians, nurses, nurse assistants, sometimes occupational therapists and physiotherapists. Standard care includes many of the same elements as the intervention, but are less extensive, not standardized and performed by physicians or nurses. Study pharmacists are not involved in any clinical work concerning patients randomised to the control group

Regarding MedRec at admission, this service is currently being implemented in hospitals nationwide as a part of the national patient's safety initiative. The hospital procedure state that MedRec should be performed by a physician at admittance, but local data show that adherence to the procedure is low (data not published). At discharge, the procedures denote that assessments, amendments and recommendations made during hospitalization, together with an updated medication list, should be reported to the GP in an electronical discharge summery. Ward nurses call the home care services or nursing homes to inform about current medication therapy and to investigate the need for prescriptions or medications to be sent home with the patient. The GP is responsible for the follow-up of discharge summary as well as renewal and revision of prescribed medications.

Patients for whom special care is considered necessary at home are referred to a specialized patient care team before or at discharge. These teams may include a pharmacist, which may supply clinical services.

The Intervention

Patients randomized to the intervention group receive a service provided by a pharmacist including 1) MedRec at admission, 2) medication review and monitoring during the hospital stay, 3) patient counselling designed to meet the needs of each individual patient, 4) MedRec at discharge together with an updated and structured medication list given to patients and submitted to primary care at discharge, and 5) study pharmacists call the patient´s GP or nurses in home care service/nursing home to inform about and discuss current drug therapy and recommendations, see Figure 2.

INSERT FIGURE 2: Intervention overview

Step 1: Medication reconciliation (MedRec)

MedRec is performed using a standardized MedRec tool. The tool eases information collection, e.g., documentation of information and information sources, and includes questions about patients' practical handling, knowledge about medications, as well as medication adherence [21 29]. Patients that handle their own medication are, if possible, interviewed. If not, information about medication use is collected from other relevant sources, i.e. medication charts from GP`s, national electronic medical records, local pharmacies, home care services, nursing homes or next of kin. These sources are used to confirm medication information after patient interviews in case of uncertainties. Any adherence or medication information issues registered during MedRec is acted upon during patient counselling or at hospital discharge (Step 3).

During MedRec, the study pharmacists also perform a standardized symptom evaluation to be used in Step 2. The evaluation seeks to answer whether and to what degree patients are experiencing any of the following ten symptoms that may be related to medication therapy: dizziness, general fatigue, memory deficiency, sleeping difficulties, dry mouth, nausea, constipation, micturition difficulties, pain or cough. If patients are not capable of answering the questions, information are obtained from relatives or associated health care workers.

Step 2: Medication review

Medication review is based on gathered information from MedRec, clinical and laboratory data and other relevant information. It is regularly updated during the hospital stay as long as the study

pharmacists are present at the ward. We use a standardized tool to identify DRPs related to the following risk categories: 1) medications requiring therapeutic drug monitoring, 2) medications not appropriate for the elderly, 3) problems related to drug administration/dosage forms, 4) drug-drug interactions, 5) dosing or medications not suitable for the individual patient (e.g. renal and liver failure), 6) no indication for drug therapy, 7) correct length of therapy for temporary use medications, 8) diagnosis or symptoms not optimally treated or untreated, 9) medications giving adverse drug reactions or change in laboratory measurements, and 10) other needs for monitoring of treatments. Identified DRPs are discussed and solved interdisciplinary and with the patient if possible. DRPs not dealt with or solved during hospitalization are in agreement with the hospital physician communicated to the primary care physician as part of the discharge summary together with recommendations and monitoring needs. All identified DRPs are classified according to the validated Norwegian classification system [30].

Step 3: Patient counselling

For patients who will handle their own medication after discharge, a patient counselling session are arranged before discharge. The patient receives an updated medication list which will be discussed and explained. The pharmacist will focus upon changes made during hospitalization and reasons for these changes. The patient is also encouraged to ask questions about their medications. Any medication adherence, handling or information issues identified during the hospital stay are also focused upon. If DRPs are identified during this counselling session, they are discussed with the responsible physician. This step is in addition to the standard discharge meeting between the physician and the patient.

Step 4: Structured and detailed medication list in discharge summaries

The discharge summary normally includes an updated overview of medications to be used after discharge. For intervention patient's pharmacists draft this list in accordance with hospital procedures and the national patient safety program and make sure it is reconciled, structured, correct according to amendments done during hospitalization and contains information and explanations about medication changes made during hospitalization as well as recommendations and follow-up issues. The ward physician uses this draft when preparing the discharge summary.

Step 5: Communication with primary care

Pharmacist make a phone call to the patient`s GP within a week after hospital discharge. The aim is to inform about and discuss current drug therapy and recommendations, so that these are acted upon and implemented. For patients where the home care services or the nursing home administer the medications, in addition to the GP, the responsible nurse is contacted by phone on the day of discharge to inform about medication changes, prescription and monitoring needs and other medication related

recommendations. Changes in multi-dosage dispensed medications are submitted to the local pharmacy responsible for dispensing the patient's medications in agreement with the home care services.

For patient where no change in medications have been made during hospital stay and no need for follow up have been identified, step 5 is not carried out.

Outcomes

Primary outcome

The primary outcome is the rate of the composite endpoint "acute readmissions and ED visits" 12 months after discharge from the index hospital stay. An acute readmission is defined as any subsequent admission following the index admission excluding elective readmissions.

Secondary outcomes

1. Change in self-reported health-related quality of life (HRQoL) from discharge to 1, 6 and 12 months after hospital discharge in the intervention group compared with control group.
2. Length of index hospital stay, difference between intervention or control patients.
3. Time to first acute readmission after discharge from index hospital stay in intervention group compared with control group (up to 12 months follow-up).
4. The proportion of patients readmitted acutely within 30 days (a national quality indicator in Norway).
5. GP visit rate during 12 months' follow-up in intervention group compared with control group.
6. Mortality rate during 12 months' follow-up in intervention group compared with control group.
7. Change in total score from admission to discharge of the Medication appropriateness index (MAI) in intervention compared to control patients.
8. Change in the number of potentially inappropriate drug prescribing identified by The Norwegian General Practice--Nursing Home criteria (NORGEP-NH), Screening Tool of Older Persons' Prescriptions (STOPP) version 2 and Screening Tool to Alert doctors to Right treatment (START) version 2 from admission to discharge in intervention group compared with control group.
9. Change in the number of potentially inappropriate prescribing using START, STOPP and NORGEP-NH from discharge to 3 months and 12 months in intervention compared with control patients.
10. Proportion of medication changes made during hospitalization implemented by the GP/nursing home physician at 3 months and 12 months in intervention patients compared with control patients.

11. Difference in the number of first re-hospitalizations where the reason for hospitalization is possibly, probably or certainly drug-related in intervention and control patients.
12. Hip fracture rate during 12 months' follow-up in intervention patients compared with control patients
13. Stroke rate during 12 months' follow-up in intervention patients compared with control patients.

Sample size calculation

Sample size calculation for the primary outcome is based on a Swedish randomized controlled trial applying the same composite endpoint [12]. The Swedish trial investigated the effectiveness of interventions performed by ward-based pharmacists in reducing morbidity and use of hospital care among patients 80 years and older. They randomized 400 patients in a 1:1 relationship, and found a 16% reduction in all visits to the hospital. If we estimate a rate of unplanned hospital admissions and ED visits of 1.7 per year in our control group, we need to enrol 456 patients (228 in each group) to detect a 16% reduction in hospital visits with a significance level of 5% and a power of 80%. To compensate for dropouts, we aim to include 250 patients in each group.

Data collection and tool application

Baseline data

Baseline data is collected before randomization to avoid collection bias. This include age, gender, smoking status, marital status, level of education, type and amount of help from home care services, and delivery of multi-dosage dispensed medications, medical diagnosis/medical history, weight, blood pressure, heart rate, relevant laboratory values (e.g. blood creatinine, C-reactive protein, haemoglobin and glucose) and medication use at time of hospital admission. The latter is denoted in the handwritten medication chart as standard procedure in our hospitals, while all other information is found in the electronic patient journal. Experience

During hospitalization

For the intervention group only, we collect outcome data from the intervention (e.g. discrepancies identified during MedRec, DRPs, physician agreement with regard to identified discrepancies or DRP, counselling issues etc.) during hospitalization and track communication between pharmacist, patients and health care workers in the ward and in primary care. For all study patients, we collect the

following data from the discharge summary: discharge diagnose(s), laboratory results, medication list including description of changes during hospitalization and recommendations to the next care level.

After discharge

Data collection of outcomes after discharge is identical for all study patients.

National registry data

Data on re-hospitalizations (dates, lengths and reasons), ED visits (dates and reasons), GP visits (dates and reasons), deaths (date and reason), strokes (dates), hip fractures (dates and reasons) and dispensed medications will be collected from the following six Norwegian Health registers, respectively: The Norwegian Patient register (hospitalisations + ED visits), The Norwegian Health Economics Administration register (ED- and GP visits), the National Cause of Death registry, the Norwegian Stroke register, the Norwegian Hip Fracture register and the Norwegian Prescription Database (NorPD) holding information about all pharmacy dispensed medications in Norway. Linking data is possible through the unique personal identification number held by every Norwegian citizen. ED-visits leading to a hospitalization will be counted as a hospitalization. We will collect data from all registers for the period 12 months before and 12 months after index hospitalization to enable adjustment for pre-study patterns.

Medication use

In addition to the data on prescriptions collected from NorPD, updated lists of medications in use is collected from GP offices or nursing homes as appropriate at 3 and 12 months after hospital discharge.

Inappropriate prescribing

The medications list at hospital admission, at discharge and at 3 and 12 months after discharge will retrospectively be subject for application of the following scoring tools to identify possible inappropriate prescribing by an investigator blinded for group allocation: NORGEP-NH [31], STOPP and START [32]. The medication lists at admission and at discharge will be scored in accordance with the medication appropriateness index (MAI) by an experience pharmacist blinded to group allocation [33 34].

Health-related quality of life (HRQoL)

We use EQ-5D and EQ-VAS to measure HRQoL [35]. This is performed by a study nurse blinded to group allocation. The measurement is performed at the end of the hospital stay and 1, 6 and 12 months' post discharge. The study nurse call patients and perform the interview by phone. Patients

where next of kin provide informed consent is excluded from this measure. We collect information about need for home care services/nursing home at 1, 6 and 12 months to adjust for in our HRQoL analysis.

Drug-related re-hospitalizations

An interdisciplinary group of physicians and pharmacists will retrospectively assess whether the patients first re-hospitalization was related to his/her medications and whether it could have been prevented. This will be performed blinded to group allocation.

Data management

All data except registry data is entered manually into a Microsoft Access© database. A random sample of patients will be drawn for control of data quality. Patient-ID is removed from all paper records and given consecutive study numbers. A list linking patient-IDs to study numbers is stored electronically in the hospital research server, separate from the Microsoft Access database. Only study personnel have access to the research server. Study papers used during work are kept at the hospital in accordance with hospital patient protection routines.

Statistical analysis

We will use IBM SPSS Statistics for data analysis. Data will be analysed according to intention-to-treat (ITT) principles, and the report of results will follow the CONSORT guidelines[36]. All participants will be included in the analysis, regardless of whether they completed the intervention or not. A per protocol analysis will also be performed. Descriptive statistics for both study arms, and the total study population will be provided.

The primary analysis will be a Poisson regression of the rate of the composite end-point during 12 months' post discharge between the two study groups taking into account censoring of study participants. Adjustment for study site will be conducted. A two-sided alpha level of 5% will be used. We also plan to perform a secondary analysis of the primary endpoint using the proportion of patients fulfilling the composite endpoint and a survival analysis of the time to reach the composite end-point. In all analyses, adjustment for baseline variables will be conducted if appropriate.

We will analyse secondary outcomes applying appropriate statistical tests, e.g., comparison between study arms by logistic regression analysis for binary responses and using Cox proportional hazards models for survival data. Continuous responses will be analysed using linear regression. A two-sided 5% significance level will be applied, with no adjustments for multiplicity.

The amount of data collected allows different subgroup analyses and include; to assess whether the effect of the intervention varies by; 1. number of medications at admittance or discharge; 0-5, 6-10, >10, 2. age groups 70-80, 80-90 and >90, 3. responsible for their own medication at discharge, 4. number and type of comorbidities at discharge, 5. number of hospital visits prior to inclusion, 6. length of hospital stay, 7. referred from home, home-care or nursing home, and 8. able to self-provide informed consent or not.

ETHICS AND DISSEMINATION

The trial will be conducted in compliance with the protocol, the principles of Good Clinical Practice and the Helsinki declaration. The study has approval from the Norwegian Centre for Research data and the Norwegian Data Protection Authority to collect, store and link research data. Only patients who supply a written informed consent are included in the study. If patients are not able to consent, the next of kin is asked. If a patient is in delirium at hospital admission, the next of kin is contacted for a written consent. When the patient is out of delirium, he/she is asked to give the written consent themselves. Those who refuse is excluded from the study.

We will not expose the patient for any new clinical intervention that may put the patient at risk. In fact, some of the elements/procedures included in the intervention have already been shown to reduce drug-related hospitalizations, and visits to emergency departments [19 20]. Nevertheless, our intervention brings a new health-care profession, the pharmacist, into the team for whom the patient will have to relate to. We anticipate that patients feeling uncomfortable with this will deny study participation.

We aim to publish study results in international peer-reviewed open access journals.

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COMPETING INTERESTS

None of the authors have any competing interests to be declared.

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DISCLOSURE

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

AUTHOR CONTRIBUTION

JSJ, KH, KHH, BGH, SH, EK, LSW, KV, LM and AGG have all been involved in study design. JSJ, KH, KHH and BGH have drafted the manuscript. SH, EK, LSW, KV, LM and AGG have read and commented on the draft. JSJ, KH, KHH, BGH, SH, EK, LSW, KV, LM and AGG have all read and approved the final manuscript.

LIST OF ABBREVIATIONS

DRP; drug related problem, ED; emergency department, GP; general practitioner, HRQoL; Health related quality of life, IMM; integrated medicines management; MAI; medication assessment index, MedRec; medication reconciliation, the Norwegian Prescription Database (NorPD), NORGEP-NH; The Norwegian general practice- Nursing Home criteria, NPR; Norwegian patient registry, START; Screening Tool to Alert doctors to Right treatment, STOPP; Screening Tool of Older Persons' Prescriptions, UNN; University hospital of North Norway, UiT; University of Tromsø.

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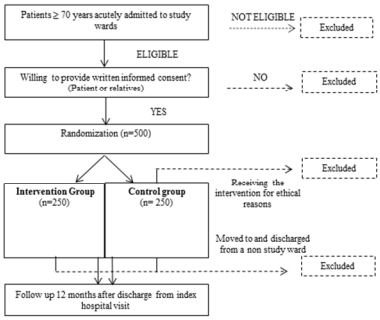

Figure 1: Flow chart of the study and study participants

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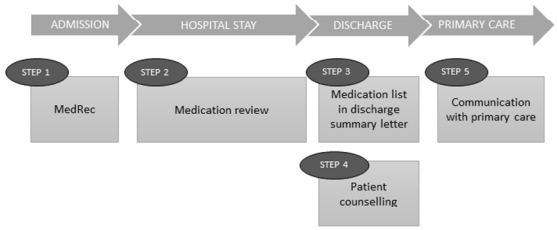

Figure 2: The intervention based on the Integrated Medicines Management (IMM) model (Step 1-4). Step 5 is added to the original model. ‼ ┼

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

Section/item	Item No	Description	Addressed on 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
	2b	All items from the World Health Organization Trial Registration Data Set	1-12
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,12
	5b	Name and contact information for the trial sponsor	12
	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	12
	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)	N/A

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
	6b	Explanation for choice of comparators	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, noninferiority, 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
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	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-7
	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)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5
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	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)	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	10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	NA
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5
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	5
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5
	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 methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9-10
	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

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	10-11
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
	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)	11
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
	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	N/A
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	11
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)	N/A

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	4
	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	10-11
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	12
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	N/A
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	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	12
	31b	Authorship eligibility guidelines and any intended use of professional writers	12
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	In Norwegian only
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

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

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INTERDISCIPLINARY COLLABORATION ACROSS SECONDARY AND PRIMARY CARE TO IMPROVE MEDICATION SAFETY IN THE ELDERLY (The IMMENSE-study) – STUDY PROTOCOL FOR A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Introduction: Drug related problems (DRPs) are common in the elderly, leading to suboptimal therapy, hospitalizations and increased mortality. The integrated medicines management model (IMM) is a multi-factorial interdisciplinary methodology aiming to optimize individual medication therapy throughout the hospital stay. IMM has been shown to reduce readmissions and drug-related hospital readmissions. Using the IMM model as a template, we have designed an intervention aiming both to improve medication safety in hospitals, and communication across the secondary and primary care interface. This paper presents the study protocol to explore the effects of the intervention with regards to healthcare use, health related quality of life (HRQoL) and medication appropriateness in elderly patients.

Methods and analysis: A total of 500 patients aged ≥70 years will be included and randomized to standard care or intervention group (1:1). The intervention comprises five steps mainly performed by pharmacists: i) medication reconciliation at admission, ii) medication review during hospital stay, iii) patient counselling about the use of medicines, iv) comprehensible and patient-friendly medication list with explanations in discharge summary and v) post-discharge phone calls to the primary care level. The primary outcome is the difference between intervention and control patients in the rate of emergency medical visits (acute readmissions + visits to emergency department) 12 months after discharge. Secondary outcomes include length of index hospital stay, time to first readmission, mortality, hip fractures, strokes, medication changes, HRQoL, and medication appropriateness**.** Patient inclusion started in September 2016.

Ethics and dissemination. The trial was approved by the Norwegian Centre for Research Data and the Norwegian Data Protection Authority. We aim to publish the results in international peer-reviewed open access journals, at national and international conferences and as part of two PhD theses

Trial registration number: ClinicalTrials.gov (NCT02816086).

STRENGTHS AND LIMITAIONS OF THIS STUDY

- No randomized controlled trial investigating the effects of implementing an IMM based intervention in the Norwegian health care setting has yet been published.
- National health care registries will enable us to collect high quality data for several outcomes including the primary.
- Collecting outcomes for a one-year period after discharge allows us to measure sustainable effects of our intervention.

- By including control and intervention patients from the same wards we may introduce education and contamination bias, which is a limitation.
- We are implementing a complex intervention, and this study will not allow for studying whether any of the specific steps are more of less responsible for any observed effects.

INTRODUCTION

Healthcare systems across the world are challenged by an aging population. Aging is frequently accompanied by morbidity, which increases the need for pharmacotherapy. The increased complexity of medication regimes combined with frailty, reduced cognitive function and changes in pharmacokinetics and –dynamics, increases the risk of adverse drug events and other drug-related problems (DRPs) in this population[1 2].

A DRP is ”an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes”[3]. DRPs include inappropriate prescribing (drug, dose, dosage frequency, and dosage form), drug interactions, adverse drug reactions, wrong administration, need for monitoring as well as non-adherence to medication therapy. DRPs occur frequently in the elderly[4 5], and are associated with an increased risk of hospitalization, morbidity and mortality[6-8]. For instance, adverse drug events alone contribute to 30-40% of acute hospital admissions in the elderly[9 10], many of them being preventable[11-14].

Communication barriers across primary and secondary care, multiple prescribers, fragmentation of care, and frequent transitions across care levels make hospitalized elderly in particular risk of drug-induced harm[15 16]. To improve the medicines management process in hospitals, pharmacist dependent methods like medication reconciliation (MedRec), medication review and patient education have been developed and studied[17-20]. The Integrated Medicines Management (IMM) model is based on interdisciplinary collaboration where clinical pharmacists work together with physicians, nurses and patients aiming to optimize medication therapy by preventing and solving DRPs[21 22]. In the IMM model different services like MedRec, medication review, patient counselling and dissemination of correct medication information at transition points are merged together in a systematic way[21 23]. In Northern Ireland, the implementation of the IMM model in hospitals has led to a reduced length of hospital stay and an increased time to re-admission compared to standard care[23 24]. Also in Sweden, implementing IMM in single hospital settings has been associated with a reduction in readmissions and drug-related re-admissions, improved communication of medication information at transition points and improved quality of medication therapy[21 25 26]. In Norway, pharmaceutical care services in hospitals have since 2010 been based on the methodology embraced by the IMM model[27]. However, no randomized controlled trail investigating the effects of implementing the IMM model in the Norwegian health care system has been published.

Based on the IMM model, we have designed an interdisciplinary collaboration structure aiming to optimize medication therapy in hospitals and to improve communication of medication-related issues between secondary and primary care. The aim of the study is to explore the effects of the intervention on healthcare use, health related quality of life (HRQoL) and medication appropriateness in elderly patients.

Objectives

The primary objective is to investigate the effects of the intervention on rate of emergency medical visits (acute readmissions and visits to emergency departments (EDs)) 12 months after hospital discharge.

Secondary objectives include to investigate the effects on; self-reported HRQoL, acute readmissions, length of index hospital stay, time to first readmission, General practitioner (GP) visit rate, mortality rate, medication appropriateness, medication-related readmissions, medication changes, hip fracture rate and stroke rate.

METHODS AND ANALYSIS

This protocol is developed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 statement [28] (see online supplement for the SPIRIT 2013 checklist).

Study design

This is a non-blinded randomized controlled trial with an intervention group and a control group (1:1 ratio). The intervention group receives the intervention, while the control group receives standard care, see Figure 1. Study enrolment started in September 2016.

INSERT FIGURE 1: Study Flowchart

Settings

The study is carried out at two acute internal medicine wards at the University Hospital of North-Norway (UNN); a geriatric internal medicine ward at UNN Tromsø and a general acute internal medicine ward at UNN Harstad. The geriatric ward cares for older patients with complex acute medical needs and has consultants specialized in geriatric medicine. The general medicine ward treats patients admitted for stroke, pulmonary-, kidney- and endocrine diseases as well as patients with geriatric concerns.

Study population

All acutely admitted patients are screened for eligibility and recruited by study pharmacists. Only eligible patients are invited to participate in the study. When written informed consent is obtained from patient or next of kin, the patient is included. Inclusion is only performed when a pharmacist is present. Readmitted study patients are not re-included, but receive standard care.

Eligibility criteria

Inclusion criteria: age ≥70 years, acutely admitted and willing to provide written informed consent (patient or next of kin). Exclusion criteria: admitted to the study ward more than 72 hours before evaluation of eligibility, moved to and discharged from other wards during the index stay, inability to understand Norwegian (patient or next of kin), considered terminally ill or with a short life expectancy, planned discharged on the inclusion day, occupying a bed in a study ward but under the care of physicians from a non-study ward, or if an intervention from a study pharmacist is considered necessary for ethical reasons (before randomization or in control group).

Randomization and blinding

After collecting baseline data, patients are randomized into the two study arms using a web-based service supplied by a third party. The randomization block sizes are concealed and permuted. We stratify by study site. As pharmacists are only involved in intervention patients, blinding of group allocation is impossible for both the patients, pharmacists and medical team. However, the primary analysis will be performed by an investigator blinded for group allocation.

Standard care (control group)

Patients assigned to standard care receive treatment from a team consisting of physicians, nurses, nurse assistants, sometimes occupational therapists and physiotherapists. Standard care may include elements as MedRec, medication review and patient counselling performed by physicians or nurses during the hospital stay. However, it is not standardized, structured or involving pharmacists. Study pharmacists are not involved in any clinical work concerning patients randomised to the control group.

Regarding MedRec at admission, this service is currently being implemented in hospitals nationwide as a part of the national patient safety program. The local hospital procedure at UNN states that MedRec should be performed by a physician at admittance, but local data show that adherence to the procedure is low (data not published). Local procedures for communication of medication information at hospital discharge requires that a discharge summary, including an updated medication list in addition to assessments, amendment and recommendations made during the hospital stay, is submitted

electronically to the GP at discharge. For patients living in nursing homes or are cared for by the home care service, ward nurses call the home care services or nursing homes to inform about current medication therapy and to investigate the need for prescriptions or medications to be sent home with the patient. The GP is responsible for the follow-up of discharge summary recommendations as well as renewal and revision of prescribed medications.

Patients, for whom special home care is considered necessary, may be referred to a specialized patient care team before or at discharge. This team may include a pharmacist, which may supply pharmaceutical care services.

The Intervention

Patients randomized to the intervention group receive the IMM-based intervention including: 1) MedRec at admission, 2) medication review and monitoring during the hospital stay, 3) patient counselling designed to meet the needs of each individual patient, 4) MedRec at discharge together with an updated and structured medication list given to patients and submitted to primary care at discharge, and 5) a follow up phone call to the patients GP and nurses in home care service/nursing home to inform about and discuss current medication therapy and recommendations, see Figure 2. Step 5 is in addition to the original IMM model. The study pharmacist is performing all steps in close collaboration with the hospital physician who has the medical responsibility for the patients.

INSERT FIGURE 2: Intervention overview

Step 1: Medication reconciliation (MedRec)

MedRec is performed using a standardized MedRec tool developed in Sweden and adapted to Norwegian circumstances/conditions[21 29]. The tool facilitates information collection about the patient`s medication use and serves as documentation of information and information sources. It also includes questions about the patients practical handling and knowledge about medications, as well as medication adherence[21 29]. Patients that handle their own medication are interviewed if possible. If not, information about medication use is collected from other relevant sources, i.e. medication lists from GPs, national electronic medical records, local pharmacies, home care services, nursing homes or next of kin. These sources are also used to confirm medication information after patient interviews in case of uncertainties. Any adherence or medication information issues identified during MedRec is acted upon during patient counselling or at hospital discharge (Step 3).

During MedRec, the study pharmacists also perform a standardized symptom assessment to be used in Step 2. This is done to identify possible adverse drug reactions, or possible targets for medication therapy improvements from a patient perspective. The assessment is performed to reveal if a patient

recently has experienced any of the following ten symptoms potentially related to medication therapy: dizziness, general fatigue, memory deficiency, sleeping difficulties, dry mouth, nausea, constipation, micturition difficulties, pain or cough. If the patient is incapable of answering the questions, information is obtained from relatives or associated health care workers.

Step 2: Medication review

Medication review is based on information collected during MedRec, clinical and laboratory data and other relevant information. It is regularly updated during the hospital stay as long as the study pharmacists are present at the ward. A standardized tool, developed in Sweden and adapted to Norwegian circumstances, is applied to identify DRPs related to the following risk categories[21]: 1) medications requiring therapeutic drug monitoring, 2) potential inappropriate medications for elderly, 3) problems related to drug administration/dosage forms, 4) drug interactions, 5) dose or medications not suitable for the individual patient (e.g. renal or liver failure), 6) lack of indication for drug therapy, 7) appropriate length of therapy for temporarily used medications, 8) suboptimal treated or untreated diagnosis or symptoms, 9) medications causing adverse drug reactions or change in laboratory measurements and 10) other needs for monitoring of treatments. Identified DRPs are discussed and solved in the interdisciplinary team and with the patient if possible. DRPs not dealt with or solved during the hospital stay are communicated to the GP as part of the discharge summary together with recommendations and monitoring needs. Identified DRPs are classified according to the validated Norwegian classification system[30].

Step 3: Patient counselling

For patients who will handle their own medication after discharge, a patient counselling session is arranged before discharge. The patients receive an updated medication list, which is discussed and explained. The pharmacists focuses upon changes made during the hospital stay and reasons for these changes. Patients are also encouraged to ask questions about their medications. Any medication adherence, handling or information issues identified during the hospital stay is also focused upon. If DRPs are identified during this counselling session, they are discussed with the responsible physician. This step does not replace the standard discharge meeting between the physician and the patient.

Step 4: Structured and detailed medication list in discharge summaries

The discharge summary normally includes an updated overview of medications to be used after discharge. For intervention patients the study pharmacists draft this list in accordance with hospital procedures and the national patient safety program. They make sure it is reconciled, structured, and correct according to amendments done and contains information and explanations about medication

changes made during the hospital stay as well as recommendations and follow-up issues. The responsible ward physician uses this draft when preparing the discharge summary.

Step 5: Communication with primary care

Within a week after discharge, the pharmacists calls the patient`s GP to inform about and discuss current medication therapy changes and recommendations stated in the discharge summary. The aim is to ensure that the changes and recommendations are implemented and acted upon

One the day of discharge, for patients where the home care services or the nursing home administer the patient`s medications, the pharmacists calls the responsible nurse to inform about medication changes, prescription and monitoring needs and other medication-related recommendations. Changes in multi-dosage dispensed medications are submitted to the local pharmacy responsible for dispensing the patient's medications in agreement with the home care services.

This step is not carried out for patients with no change in medications during the hospital stay and/or no identified need for follow up.

Outcomes

Primary outcome

The primary outcome is the rate of the composite endpoint "acute readmissions and ED visits" 12 months after discharge from the index hospital stay in the intervention group compared with control group. An acute readmission is defined as any subsequent admission following the index admission excluding elective readmissions.

Secondary outcomes (intervention group compared with control group)

1. Change in self-reported health-related quality of life (HRQoL) from discharge to 1, 6 and 12 months after hospital discharge.
2. Length of index hospital stays.
3. Time to first acute readmission after discharge from index hospital stay (up to 12 months follow-up).
4. The proportion of patients readmitted acutely within 30 days (a national quality indicator in Norway).
5. GP visit rate during 12 months' follow-up.
6. Mortality rate during 12 months' follow-up.
7. Change in total score from admission to discharge of the Medication appropriateness index (MAI)

8. Change in the number of potentially inappropriate medications prescribed identified by The Norwegian General Practice-Nursing Home criteria (NORGEP-NH), Screening Tool of Older Persons' Prescriptions (STOPP) version 2 and Screening Tool to Alert doctors to Right treatment (START) version 2 from admission to discharge.
9. Change in the number of potentially inappropriate medications prescribed using START version 2, STOPP version 2 and NORGEP-NH from discharge to 3 and 12 months.
10. Medication changes made during index hospital stay implemented by the GP at 3 and 12 months.
11. Number of medication-related first readmissions after index hospital stay.
12. Hip fracture rate during 12 months' follow-up.
13. Stroke rate during 12 months' follow-up

Sample size calculation

Sample size calculation for the primary outcome is based on a Swedish randomized controlled trial applying the same composite endpoint[12]. The Swedish trial investigated the effectiveness of interventions performed by ward-based pharmacists in reducing morbidity and use of hospital care among patients 80 years and older. They randomized 400 patients in a 1:1 relationship, and found a 16% reduction in all-cause visits to the hospital in the intervention group. If we estimate a rate of acute hospital admissions and ED visits of 1.7 per year in our control group, we need to enrol 456 patients (228 in each group) to detect a 16% reduction in hospital visits with a significance level of 5% and a power of 80%. To compensate for dropouts, we aim to include 250 patients in each group.

Data collection and tool application

Baseline

Baseline data for all study patients is collected before randomization to avoid collection bias. This include age, gender, smoking status, marital status, level of education, type and amount of help from home care services, and delivery of multi-dosage dispensed medications, medical diagnosis/medical history, weight, blood pressure, heart rate, relevant laboratory values (e.g. blood creatinine, C-reactive protein, haemoglobin and glucose) and medication use at time of hospital admission. The latter is denoted in the handwritten medication chart as standard procedure in our hospitals, while all other information is found in the electronic patient journal.

Hospital stay

For the intervention group only, we collect outcome data from the intervention (e.g. discrepancies identified during MedRec, DRPs, physician agreement with regard to identified discrepancies or DRP, counselling issues etc.) during hospitalization and track communication between pharmacist, patients and health care workers in the ward and in primary care. For all study patients, we collect the following data from the discharge summary: discharge diagnose(s), laboratory results, medication list including description of changes during the hospital stay and recommendations to the next care level.

After discharge

Data collection of outcomes after discharge is identical for all study patients.

National registries

Data on readmissions (dates, lengths and reasons), ED visits (dates and reasons), GP visits (dates and reasons), deaths (date and reason), strokes (dates), hip fractures (dates and reasons) and dispensed medications will be collected from six Norwegian Health registries. These registries are, respectively: The Norwegian Patient Registry (hospitalizations + ED visits), The Norwegian Health Economics Administration Registry (ED- and GP visits), the National Cause of Death Registry, the Norwegian Stroke Registry, the Norwegian Hip Fracture Registry and the Norwegian Prescription Database (NorPD) holding information about all pharmacy dispensed medications in Norway. Linking data is possible through the unique personal identification number held by every Norwegian citizen. ED visits leading to a hospital stay will be counted as a hospital stay. We will collect data from all registries for the period 12 months before and 12 months after index hospital stay to enable adjustment for pre-study patterns.

Medication use

In addition to the data on prescriptions collected from NorPD, updated lists of medications in use are collected from GP offices or nursing homes as appropriate at 3 and 12 months after hospital discharge.

Inappropriate prescribing

The medications lists at hospital admission, at discharge and at 3 and 12 months after discharge will retrospectively be subjected to application of the following scoring tools to identify possible inappropriate prescribing by an investigator blinded for group allocation: NORGEP-NH [31], STOPP and START [32]. The medication lists at admission and at discharge will be scored in accordance with the medication appropriateness index (MAI) by an experience pharmacist blinded to group allocation [33 34].

Health-related quality of life (HRQoL)

We use EQ-5D and EQ-VAS to measure HRQoL[35]. This is performed by a study nurse blinded to group allocation. The measurement is performed at the end of the hospital stay and 1, 6 and 12 months after discharge. The study nurse call patients and perform the interview by phone. Patients, where next of kin provide informed consent, is excluded from this measure. We collect information about need for home care services/nursing home at 1, 6 and 12 months to adjust for in the HRQoL analysis.

Medication-related readmissions

An interdisciplinary group of physicians and pharmacists will retrospectively assess whether the patient's first readmission was related to his/her medications and whether it could have been prevented. This will be performed blinded to group allocation.

Data management

All data, except registry data, is entered manually into a Microsoft Access© database. A random sample of patients will be drawn for control of data quality. Patient-ID is removed from all paper records and given consecutive study numbers. A list linking patient-IDs to study numbers is stored electronically on the hospital research server, separate from the Microsoft Access database. Only study personnel have access to the research server. Study papers used during work are kept at the hospital in accordance with hospital's patient protection routines.

Statistical analysis

We will use IBM SPSS Statistics for data analysis. Data will be analysed according to intention-to-treat principles, and the reporting of results will follow the CONSORT guidelines[36]. All participants will be included in the analysis, regardless of whether the intervention was completed or not. A per protocol analysis will also be performed. Descriptive statistics for both study arms, and the total study population will be provided.

The primary analysis will be a Poisson regression of the rate of the composite end-point during 12 months after discharge between the two study groups. Censoring of study participants will be accounted for, and an adjustment for study site will be conducted. A two-sided alpha level of 5% will be used. We also plan to perform a secondary analysis of the primary endpoint using the proportion of patients fulfilling the composite endpoint and a survival analysis of the time to reach the composite end-point. In all analyses, adjustment for baseline variables will be conducted if appropriate.

We will analyse secondary outcomes applying appropriate statistical tests, e.g. comparison between study arms by logistic regression analysis for binary responses and using Cox proportional hazards

models for survival data. Continuous responses will be analysed using linear regression. A two-sided 5% significance level will be applied, with no adjustments for multiplicity.

The amount of data collected allows for different subgroup analyses and include: to assess whether the effect of the intervention varies by: 1) number of medications at admission or discharge; 0-5, 6-10, >10, 2) age groups 70-80, 80-90 and >90, 3) patient responsibility for their own medication at discharge, 4) number and type of comorbidities at discharge, 5) number of hospital visits prior to inclusion, 6) length of hospital stay, 7) referred from home, home-care or nursing home, or 8) able to self-provide informed consent or not.

ETHICS AND DISSEMINATION

The trial will be conducted in compliance with the protocol, the principles of Good Clinical Practice and the Helsinki declaration. The study has approval from the Norwegian Centre for Research Data and the Norwegian Data Protection Authority to collect, store and link research data. Only patients who supply a written informed consent are included in the study. If patients are not able to consent, the next of kin is asked. If a patient is temporarily incapable of giving consent, for instance in the case of delirium, consent is first sought from the next of kin. If and when the patient is again considered able to consent he/she is asked to give the written consent themselves. Patients who refuse participation is excluded from the study.

We will not expose the patient for any new clinical intervention that may put the patient at risk. In fact, some of the elements/procedures included in the intervention have already been shown to reduce drug-related readmissions, and visits to the ED[19 20]. Nevertheless, our intervention brings a new health-care profession, the pharmacist, into the interdisciplinary team for whom the patient will have to relate to. We anticipate that patients feeling uncomfortable with this will refuse study participation.

We aim to publish study results in international peer-reviewed open access journals, at national and international conferences and as part of two PhD theses.

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COMPETING INTERESTS

None of the authors has any competing interests to declare.

FUNDING

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DISCLOSURE

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

AUTHOR CONTRIBUTION

JSJ, KH, KHH, BHG, SH, EK, LSW, KKV, LM and AGG have all been involved in study design. JSJ, KH, KHH and BHG have drafted the manuscript. SH, EK, LSW, KKV, LM and AGG have read and commented on the draft. All authors have read and approved the final manuscript.

LIST OF ABBREVIATIONS

DRP: drug related problem, ED: emergency department, GP: general practitioner, HRQoL: Health related quality of life, IMM: integrated medicines management, MAI: medication assessment index, MedRec: medication reconciliation, NORGEP-NH: The Norwegian general practice-Nursing Home criteria, NorPD; the Norwegian Prescription Database NPR: Norwegian patient registry, START: Screening Tool to Alert doctors to Right treatment, STOPP: Screening Tool of Older Persons' Prescriptions, UiT: University of Tromsø, UNN: University hospital of North Norway.

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Figure 1: Flow chart of the study and study participants.

Figure 2: The intervention based on the Integrated Medicines Management (IMM) model (Step 1-4). Step 5 is added to the original model.

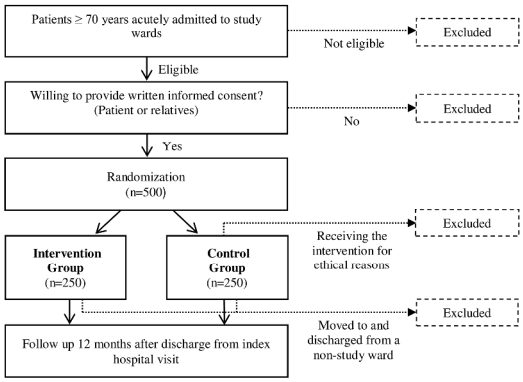

Figure 1: Flow chart of the study and study participants

297x420mm (600 x 600 DPI)

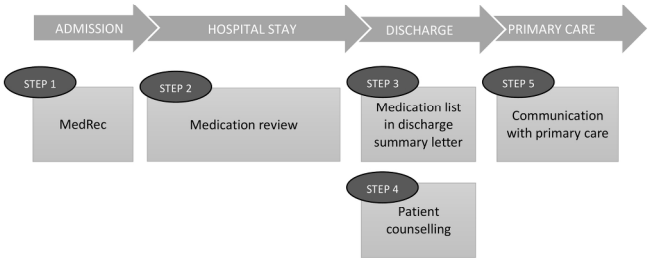

Figure 2: The intervention based on the Integrated Medicines Management (IMM) model (Step 1-4). Step 5 is added to the original model.

210x148mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Addressed on 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
	2b	All items from the World Health Organization Trial Registration Data Set	1-12
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	13
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,13
	5b	Name and contact information for the trial sponsor	13
	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	13
	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)	N/A

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
	6b	Explanation for choice of comparators	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, noninferiority, 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
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	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-8
	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)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5-6
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	8-9
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)	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	NA
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5
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	5
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5
	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 methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9-11
	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

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	11
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
	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)	11
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
	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	N/A
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	12
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)	N/A

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	4
	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	10-11
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	12
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	N/A
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	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	12
	31b	Authorship eligibility guidelines and any intended use of professional writers	13
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	In Norwegian only
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

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