UiT The Arctic University of Norway

Department of Pharmacy

Optimizing medication therapy in older hospitalized patients

Identifying potentially inappropriate medications and testing an interdisciplinary intervention

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A dissertation for the degree of Philosophiae Doctor – April 2022

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Acknowledgements

This Ph.D. project has been a long, educational but strenuous process, and I would have never been able to finish without the support of so many wonderful people.

First and foremost, my supervisors, **Beate Hennie Garcia** and **Kjell H. Halvorsen**. You had the idea for this Ph.D. project and have been with me through this entire process.

Beate, you have been my number one cheerleader, giving me constructive feedback and encouragement when I have needed it. Your enthusiasm for research, skills as a writer, and organized mind are inspiring, but what I value most about you is how understanding and caring you are, always making sure I am not overworked or stressed. You are also a nice person to be around, and I always enjoy your company.

Kjell, you have been a part of my professional journey since the beginning in 1999. You have always made me look at the broader picture when I see details. Your diplomatic skills, analytical mind, and in-depth knowledge of medication use in older adults have been much appreciated. I also value the friendships and out-of-office time our families share.

Further, I would like to thank the following for their valuable contribution to this project and for making writing this thesis possible for me:

Kristian Svendsen, for helping me understand statistical analysis, being a Co-author on three of the papers in this thesis, and contributing to the data analysis. You have always found time for me when I have a problem to discuss, and I have learned a lot from you.

Lars Småbrekke, for your kindness, sharing your knowledge in statistical analysis and academic writing with me, contributing to Paper IV and proofreading my thesis and articles.

All the members of The IPSUM research group for creating such a great work environment. Thanks for all the moring coffees, lunch breaks, and social gatherings. I will miss being around you every day and hope we can continue collaborating on projects.

Frode Skjold, for all the help with data management and helping me with SPSS syntax.

Elena Kamycheva, for enabling us to collaborate with the geriatric ward at UNN initially and contribute to the study design and as a co-author in Paper I and IV.

To all **patients who were willing to participate** in the IMMENSE study, and the **personnel at the two study wards** for welcoming the pharmacists into the ward teams.

Stine Haustreis, Kjerstin Havnes, Hilde Ljones Wetting, Lillann Skaue Wilsgård and **Anne Synnøve Rian** for your amazing efforts as study pharmacists in the project, and **Kjerstin** also for sharing the PhD journey on this project with me.

My **CoAuthors** who have contributed to the papers for your constructive imputes and valuable perspectives.

All the master students who have been involved in the IMMENSE study**, Elise Naklin, Charlotte Røsnes, Hans-Alte Laiti, Marie Eline Charlotte Valstad, Maren Eidsmo, Anngisha Arungumar, Tript Kaur** and **Siri Pharm** for letting me be a part of your projects and learning from your work and for your help with data management and validation**.**

Birthe Angermo, for the excellent support with data collection, and **Inger Spestad Køller** for help with designing the study database.

The hospital pharmacy in Tromsø, for being the best employer I could ask for, allowing me to adjust my position when I have needed to spend more (or less) time on research. My wonderful **colleagues at the hospital pharmacy and the antibiotic stewardship team at UNN** for making my workdays every other week so educational, meaningful, and fun.

June Utnes Høgli, for changing employer for six months, taking over my responsibilities in the antibiotic stewardship team so I could finish this thesis.

My nabors and friends in “lykliga gatan”, for all the walks, tea breaks, laughs, taking care of our kids and logistic support, and **Marita** for proofreading the thesis.

My parents in low, **Maud and Kjell-Bjørn** for always being there for us, and washing all our clothes the last months of this project. You are amazing!

My **childhood friends** from Harstad and **family** for support and mental breaks.

To the love of my life **Terje,** you have been the foundation in my life for over 20 years. You have been super supportive through all the years I have spent on this thesis, always motivating me to keep working and giving me advice and new perspectives. I haven't contributed as much to family life as I would have liked to the last year, but you are a super dad with full control of the family logistics. **Malin and Miriam**, you are the best daughters a mother could ask for, and I love you endlessly.

And last, I dedicate this thesis to my **mother** and **late father**. You have given me the greatest gift any parent could give their child, unconditional love and affection. I am forever grateful for your love and support.

Jeanette Schultz Johansen

Tromsø, April 2022

Scientific environment

This work has been performed as part of the IPSUM (identify and Prevent Suboptimal Medication Use) research group at the Department of pharmacy, UiT The Arctic University of Norway. Paper II was planned in collaboration with the University Hospital of North Norway, where Elena Kamycheva was involved as a supervisor for a period.

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Funding

Department of Pharmacy, Faculty of Health Sciences, UiT The Arctic University of Norway.

Abbreviations

ADE	Adverse drug events
ADR	Adverse drug reactions
CI	Confidence interval
DOACs	Direct oral anticoagulants
ED-visits	Emergency department visits
GP	General practitioner
IMM	Integrated medicined management
IQR	Interquartile range
ITT	Intention to Treat analysis
ME	Medication Error
MRP	Medication-related problems
NORGEP	The Norwegian General Practice criteria
NORGEP-NH	The Norwegian General Practice - Nursing Home criteria
NorPD	The Norwegian Prescription Database
NPR	Norwegian Patient Registry
PIM	Potentially inappropriate medication
PIP	Potentially inappropriate prescribing
PP	Per protocol
PPO	Potentially prescribing omission
RCT	Randomized controlled trial
SD	Standard deviation
START	Screening tool to alert to right treatment
STOPP	Screening tool of older people’s prescriptions
WHO	World Health Organization

Definitions of terms used in this thesis

Adverse drug reaction (1)

‘A response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.’

Adverse drug events (1)

‘Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.’ An adverse drug event is generally viewed as a broader term than adverse drug reactions (2).

Medication error (3)

‘A mediation error is an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient.’

Medication-related problem or drug-related problem (4)

‘A medication-related problem is an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes.’

Clinical Pharmacy (5)

‘A health specialty that describes the activities and services of the clinical pharmacist in developing and promoting the rational and appropriate use of medicinal products and devices’

Medication optimization (6)

‘A person-centred approach to safe and effective medicines use, to ensure people obtain the best possible outcomes from their medicines’.

Medication reconciliation (7)

‘Medication reconciliation is the process of creating the most accurate list possible of all medications a patient is taking — including drug name, dosage, frequency, and route — and comparing that list against the physician’s admission, transfer, and/or discharge orders, with the goal of providing correct medications to the patient at all transition points within the hospital.’

Medication review (8)

‘Medication review is a structured evaluation of a patient’s medicines with the aim of optimizing medicines use and improving health outcomes. This entails detecting drug-related problems and recommending interventions.’ Medication reviews can be classified according to the information source available:

Medication review	*Information source*
Type 1 (simple)	Only medication history available
Type 2 (intermediate)	Medication history and patient interview or clinical data available
Type 3 (advances)	Medication history, patient interview and clinical data available

Older adults

In medical literature, older adults or elderly is often used to describe persons over the age of 65-70 years (after retirement), but no clear definitions of older adults exist. This thesis uses an age limit of 65 years in Paper I and 70 years in Paper II-IV, to describe older adults.

Transition of care (9)

‘Transitional care is defined as a set of actions designed to ensure the coordination and continuity of healthcare as patients transfer between different locations or different levels of care within the same location’List of papers

List of papers

Paper I: Johansen JS, Halvorsen KH, Svendsen K, Havnes K, Garcia BH. The impact of hospitalisation to geriatric wards on the use of medications and potentially inappropriate medications - a health register study. BMC geriatrics. 2020;20(1):190. doi: 10.1186/s12877-020-01585-w.

Paper II: Johansen JS, Havnes K, Halvorsen KH, Haustreis S, Skaue LW, Kamycheva E, et al. Interdisciplinary collaboration across secondary and primary care to improve medication safety in the elderly (IMMENSE study): study protocol for a randomised controlled trial. BMJ Open. 2018;8(1):e020106. doi: 10.1136/bmjopen-2017-020106

Paper III: Johansen JS, Halvorsen KH, Havnes K, Wetting HL, Svendsen K, Garcia BH. Intervention fidelity and process outcomes of the IMMENSE study, a pharmacist-led interdisciplinary intervention to improve medication safety in older hospitalized patients. Journal of clinical pharmacy and therapeutics. 2021**.** doi: 10.1111/jcpt.13581

Paper IV: Johansen JS, Halvorsen KH, Svendsen K, Havnes K, Robinson EG et al. Interdisciplinary collaboration across secondary and primary care to improve medication safety in the elderly (IMMENSE study): a randomized controlled trial. (Manuscript submitted 08.04.22)

Abstract

Background:

Suboptimal use of medications is an important contributor to hospitalizations and adverse events in older adults. Increased awareness of the role of medication-related problems (MRPs) in preventing patients from reaching their health outcomes has led to initiatives to optimize medication use. One type of MRP is potentially inappropriate medications (PIMs). Numerous tools aim to identify PIMs in older adults. These tools help identify areas for improvement and can be part of interventions to optimize medication therapy in different care settings. Among the most vulnerable patients to MRPs are older patients admitted to hospitals, and especially those admitted to specialized geriatric wards. Introducing clinical pharmacist services for older hospitalized patients may enable the identification and prevention of MRPs. Yet it is unknown how clinical pharmacist services should be provided to impact patient outcomes.

Aim:

The overall aim of this thesis is to provide knowledge on PIM use in hospitalized older patients and to investigate how clinical pharmacist services in an interdisciplinary setting can contribute to medication optimization and improve patient outcomes.

Methods:

We used Norwegian national health registers to identify geriatric ward patients and their medication use before and after hospitalization. To identify the magnitude of PIM prescribing and to identify post discharge changes, we used two explicit PIM lists, The European Union (EU)(7)-PIM list and the Norwegian General Practice – Nursing Home criteria (NORGEP-NH) list. We designed a 5-step intervention, introducing clinical pharmacists in the ward teams working by the integrated medicines management (IMM) model to optimize medication use and improve communication with primary care. The intervention was tested in a non-blinded randomized controlled trial (RCT) conducted in two internal medicines wards at the University Hospital of North Norway. Acutely admitted patients ≥70 years were randomized 1:1 to standard care or to intervention. The primary outcome was the rate of emergency medical visits (readmissions and emergency department visits) 12 months after discharge.

Results:

PIMs were frequent and affected over half of the 715 hospitalized patients included in the study. A geriatric hospital stay did not reduce PIM use, and the two PIM lists gave conflicting results as to whether PIM use was increased after discharge. In the RCT, 480 patients with a mean age of 83.1 years (SD: 6.3) were included in the modified intention to treat analysis. An evaluation of the process outcomes and intervention fidelity in 221 intervention patients showed that a total of 437 medication discrepancies were identified in 159 (71.9%) patients, and 1042 MRPs were identified in 209 (94.6%) patients, of which 67% were communicated to and solved by the interdisciplinary team during the hospital stay. A total of 121 (54.8%) patients received all intervention steps if appropriate. The intervention had no significant effect on the rate of emergency medical visits in intervention patients versus control patients after 12 months with an adjusted incidence rate ratio of 1.02 (95% CI: 0.82-1.27), nor did we observe any significant effects on time to the first emergency medical visit, 30-days readmissions rate, length of index hospital stay or mortality.

Conclusions:

Our findings demonstrate that PIMs are frequent in older hospitalized patients and were not reduced post-discharge in a geriatric patient group. Including clinical pharmacists services into wards teams may, through identification and prevention of MRPs, contribute to optimizing medication use, but we did not find that a five-step intervention including enhanced communication with primary care significantly reduced the rate of emergency medical visits in the year after discharge. There is a need for further studies to identify interventions that optimize medication use and simultaneously produce meaningful improvements in patient outcomes. More patient-focused interventions and interventions that follow patients over time may be considered.

1 Introduction

1.1 Older adults and health care use

Norway has an aging population (10). In 2020, 12.5% of the Norwegian population was ≥70 years, which is estimated to increase to 20% by 2060 (11). The need for health care services increases with age, and older adults ≥70 years are responsible for 40% of all acute hospital admissions (12, 13). The expected increase in older adults in the coming years will challenge our health care system's capacity and stimulate initiatives to prevent unnecessary health care use and effectively utilize all available health care personnel (14).

1.2 Medication use in older adults

Medication use increases with age as multimorbidity, and the coexistence of multiple chronic diseases, becomes more prevalent (15). In 2017, data from the Norwegian prescription database (NorPD) showed that 57% of the Norwegian population ≥65 years were dispensed more than five different prescription medications (16). The use of many medications (often more than five) is defined as polypharmacy (17). The prevalence of polypharmacy is rising in high-income countries worldwide (17). Polypharmacy in older adults with multimorbidity is often a consequence of applying single disease evidence-based guidelines to prevent future morbidity and mortality (18). This despite multimorbid older patients often being excluded from the randomized controlled trials (RCT) that guidelines are founded upon (19, 20). Polypharmacy may be viewed as a ‘necessary evil’ (21). Necessary because polypharmacy is often appropriate and beneficial in specific diseases (22). Evil because observational studies have linked polypharmacy to numerous adverse outcomes like drug interactions, hospitalizations, falls, reduced adherence, and adverse drug reactions (ADR) (23). One reason polypharmacy may be of particular concern in older adults is age-related changes in pharmacokinetics and dynamics of medications. These changes make older adults more vulnerable to ADR (24). Age-related factors like multimorbidity, frailty, and geriatric syndromes also add to the risk of ADR (25).

1.3 Medication safety

Medications are one of the most influential and effective interventions in health care, enabling a better and longer life. However, medications also represent one of the leading causes of avoidable

harm in health care (26, 27). Medications are an important factor causing hospitalizations and emergency department (ED) - visits, where between 9-20% are estimated to be medication-related (28-34). Furthermore, medication-related harm is among the most frequent types of patient harm in hospitals (28, 35). In hospitalized older adults, the prevalence of ADRs is estimated to be 11.5-22% (31, 36-38). Serious ADRs are reported to occur in 4-9.2% of hospitalized patients (36, 39). The majority of ADRs occurring in older hospitalized patients are found to be preventable (37, 38).

Medication harm is also frequent after hospitalization, estimated to affect one in three older adults after hospital discharge, causes being both adverse drug events and non-adherence (40). In the USA, it is estimated that in 5% of older adults annually seek medical care for adverse drug events(41). Consequently, medication-related harm and misuse put a significant burden on both the patients and health care budgets (27, 40, 42, 43). Globally, the annual costs associated with medication errors alone have been estimated to be 42 billion US dollars (44).

In 2017, the World health organisation's (WHO) Third Global Patient Safety Challenge was dedicated to medication safety (27). WHO highlighted transition of care as a particular concern to medication safety. Transitions of care occur when a patient moves between facilities, care levels or health providers. These transitions increase the possibility of communication errors related to medications. Poor quality in the transfer of medication information has been highlighted as an important area for health care improvement nationally and internationally (43, 45). Medication errors in the form of unintended medication discrepancies are frequent, affecting nearly every patient at one point during the transition in or out of hospital (45). Discrepancies that are unidentified and unsolved may lead to patient harm (46). Medication reconciliation is proposed as one of the key strategies to reduce medication discrepancies in the WHO campaign “Global Patient Safety Challenge, medication without harm” (45). In Norway, The National Patient Safety Program “In Safe Hands” has included work packages on medication reconciliation at care transitions since 2011 (43). Still, studies performed after 2011 have found medication discrepancies in 50-84% of patients admitted to Norwegian hospitals (47-53).

1.4 Potentially inappropriate prescribing in older adults, definitions and ways to measure it.

Appropriate prescribing relates to the quality of prescribing (54). Evaluating the appropriateness of a prescription involves several elements, i.e., respecting patients' choices, minimizing risks/maximizing benefits, and minimizing cost (55). Prescribing not meeting established quality standards for prescribing in older adults is labeled potentially inappropriate prescribing (PIP). PIP includes under-prescribing (i.e., potentially prescribing omissions, failure to prescribe medication when indicated and no contraindications), mis-prescribing (i.e., incorrect medication, dose, duration, or drug interactions), and over-prescribing (i.e., no valid indication) (56). Related to medication safety, different terms and terminologies in use may be confusing. With regards to this thesis, Figure 1 illustrates how terminology is used and relates to each other and how PIP could be fitted into this context.

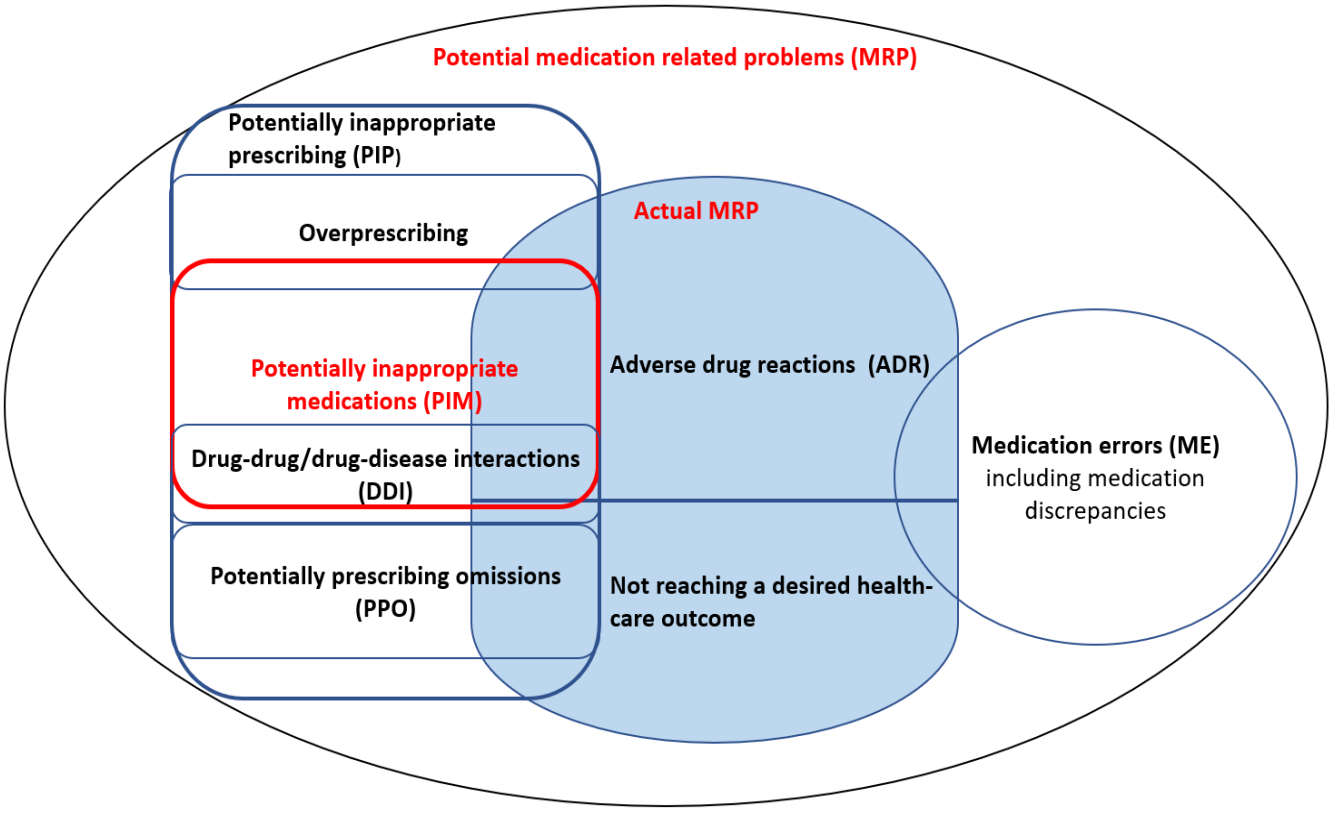

Figure 1 *Illustration on how different terminology concerning medication safety and potentially inappropriate prescribing (2, 54) relate to each other and are viewed in this thesis. The terms in red are in focus in this thesis.*

Inappropriate prescribing measures can be explicit (criterion-based - medication focused), implicit (judgment-based - patients focus), or a combination of both. The concept of PIP focusing on prescribing is often simplified only to assess pharmacological appropriateness, i.e., whether a medication is judged to have a greater risk than effect in an older population (54). This is the case with many explicit criteria lists of potentially inappropriate medications (PIMs) in older adults. These criteria comprise lists of medications, medication classes, or dosages to be avoided or used with caution in older people in general or with specific diseases and represent an essential part of the broader concept of PIP (see Figure 1). Explicit PIM – criteria lists are usually developed by consensus techniques, using trial evidence and experts on pharmacotherapy in older adults (56). The advantage of explicit criteria of PIMs (called PIM lists in this thesis) is the straightforward application, often requiring little or no clinical judgment. In the clinical setting, they alert prescribers to PIMs that should be considered in individual patients (57).

In 1991, the first explicit criteria list for identifying PIM in people over 65 years was published by Beers et al. (58). Ancestor to many other criteria lists, the Beers list is still the most widely used and cited. It has been updated on several occasions, the last in 2019 by the American Geriatrics Society (58-61). As therapy traditions and the availability of medications vary, transferring PIM lists from one country to another often requires modification and revalidation (54). Consequently, many different tools to identify PIMs have been developed. A systematic review by Motter et al. identified 36 explicit criteria lists for PIM identification published from 1991 to 2017 (62). Surprisingly, the authors found limited overlap between the PIM lists presented. The authors explain the heterogeneity in PIM lists by the complexity of medication management in older adults, limited evidence base, and different approaches and attitudes of the health professionals involved in developing the lists. Nevertheless, there is some consensus between PIM lists; benzodiazepines, NSAIDs and anticholinergic medications like amitriptyline are defined as PIMs in most lists (62, 63).

Next to the Beers list, the STOPP/START list (screening tool of older people's prescriptions/screening tool to alert doctors to right treatment) is the most cited and investigated list and is relevant for European countries (56, 64, 65). The tool was first published in 2008 and revised in 2015 (64, 65). One strength with the STOPP/START list is the broader evaluation of

PIPs, including under-prescribing by identifying potentially prescribing omissions (PPO), and over-prescribing by addressing medication without a valid indication. While the STOPP/START list is often regarded as an explicit tool, it requires access to clinical information, like medication history, laboratory values, and disease severity, to be applied in full (66, 67). It also includes some implicit criteria, like stopping medications without a valid indication (65).

PIM criteria lists are valuable in health service research investigating trends in prescribing quality or targets for prescribing improvement. When prescription registries are used to assess PIM prevalence, explicit lists that require a minimum of clinical information are often the best choice. The European Union (EU)(7)-PIM list, The Norwegian General Practice (NORGEP) criteria, and the Norwegian General Practice – Nursing Home criteria (NORGEP-NH) are relevant examples.

The EU(7)-PIM list initiative is an explicit tool developed to identify and compare PIM use between European countries (68). It is based on PIM lists from Germany, France, the US, and Canada and suggestions from drug experts from seven European countries (69-73). The list defines 282 medications/medication classes as potentially inappropriate.

There are two PIM lists developed for older adults in Norway. The NORGEP list was developed by a group of geriatricians, clinical pharmacologists, and general practitioners applying a Delphi consensus method (74). The aim was to identify pharmacological inappropriate prescriptions for the elderly (≥70 years). The criteria include 36 statements, 21 single drugs and 15 drug-drug interactions. The NORGEP list is based partly on the Beers criteria, general evidence from literature and experts' opinions (74). To remain clinically valid, explicit criteria lists require regular updating as evidence evolves, and new therapies are introduced. In 2015, the NORGEP-NH list was published. The list was based on the NORGEP list (75). The authors of NORGEP-NH aimed to establish a clinically relevant tool for assessing medication use in nursing home residents, although it may be applicable for older adults outside institutions. The list consists of three parts a) 11 single substance criteria of medications to avoid b) 15 medication combinations to avoid c) 8 medication groups for which continued use in nursing home patients should be reassessed.

1.5 PIM – consequences and prevalence

We are concerned with PIMs due to their link to adverse events and outcomes. Observational studies have demonstrated associations between PIMs and numerous adverse outcomes like ADRs, hospitalizations, ED visits and increased health care costs (76-79). Consequently, identifying the prevalence of PIMs and finding ways to improve prescribing is important.

The population prevalence of PIMs depends on the criteria list applied, whether the list has been fully applied or modified, and the data collection methods (62, 80). Among older adults in different health care settings in Norway, the prevalence of PIMs range between 14-55%, and even higher when including "as needed medications", see Table 1 for an overview of Norwegian studies estimating the prevalence of PIMs in older adults.

Older hospitalized patients have a high prevalence of PIMs. A recent systematic review found a pooled PIM prevalence of 47%, 46%, and 65% if the Beers criteria, the STOPP criteria, or study/country-specific criteria were applied (81). A hospitalization often leads to changes in medications, but the literature is conflicting about the impact of hospitalization on PIM use after discharge (82-88). Whether hospitalizations in Norway affect PIM use has only been explored in single-center studies, where either increasing prevalence or a non-significant reduction from admission to discharge have been observed (86, 89, 90). Knowledge of the impact of hospitalizations on PIM use and the prevalence in Norway is important to identify areas of improvement.

Table 1 *Overview of Norwegian studies estimating the prevalence of PIMs with a published criteria list in older adults.*

AUTHOR, PUBLICATION YEAR	POPULATION	DATASOURCE MEDICATIONS	NUMBER INCLUDED IN STUDY	CRITERIA OF PIM IDENTIFICATION	PREVALENCE OF PIM
HOSPITAL SETTING					
BAKKEN MS ET AL. 2012**(89)**	IC-NH, hospital	Medical records	290	NORGEP	35% (at discharge)
KERSTEN H ET AL. 2015 **(86)**	Hospital	Medical records	323	NORGEP + Beers 2012	38% (at discharge)
BJØRNESTAD EØ ET AL. 2013**(91)**	Hospital	Medical records	49	STOPP	29%
NURSING HOMS SETTING					
HALVORSEN KH ET AL. 2017 **(92)**	NH	Medical records	4373	NORGEP-NH	40% (Part A) 27% (Part B)
HALVORSEN KH ET AL 2019**(93)**	NH	Medical records	103	NORGEP-NH	28% (Part A) 16% (part B)
NYBORG G ET AL. 2017 **(94)**	NH	Medical records	881	NORGEP-NH	44% (part A + B) 70% (PRN drugs)
HOME CARE AND MDD					
HALVORSEN KH ET AL 2012**(95)**	MDD-users	MDD- supplier	11254	NORGEP	26%
JOSENDAL AV ET AL. 2020**(96)**	MDD-users	MDD-supplier	45593	NORGEP	27%
FIALOVÁ D ET AL. 2005**(97)**	Home care patients	Medical records, interview	388	Beers 2003[b]	15%
GENERAL OLDER POPULATION					
NYBORG G ET AL 2012 **(98)**	Adults over 70	NorPD	445900	NORGEP	35%
OTHER POPULATIONS					
OESTERHUS R ET AL. 2017**(99)**	Home dwelling with mild dementia	Medical records	251	NORGEP	14%
PARKER K ET AL 2019**(100)**	Advanced CKD patients	Medical records	180	STOPP vs 2	54-55%[a]

a) RCT prevalence in the control and intervention groups

b) Other tools also applied, only showing the results for Beers 2003

Abbreviations: CKD; chronic kidney disease, IC-NH; intermediate care nursing home, MDD; multidose dispensed drugs, NH; nursing home, NorPD; Norwegian Prescription Database, PIM; potentially inappropriate medications, PRN; pro re nata (as needed)

1.6 Optimizing medication therapy in older adults

Optimizing medication therapy in older adults is a complex endeavor as reaching the desired outcome of medication use is influenced by many factors. Events or circumstances involving medication therapy that actually or potentially interferes with desired health outcomes are called medication-related problems (MRPs). MRPs may arise from the prescribing (i.e., the prescribing not being appropriate for the individual patient), the medication itself (i.e, PIMs resulting in adverse drug reactions), from health-system challenges (i.e., medication monitoring, fragmentation of care, and communication issues) and patient challenges when it comes to administering and adhering to medication regimens. Optimizing medications so that each medication alone and the medication regime in total provide a benefit to patients grows exceedingly challenging with age, multimorbidity and polypharmacy, see Figure 2 (6, 101, 102). The Government white paper nr 28 from 2015 ‘Medical products- Correct use- better health’ called for more research on medication use among older adults in Norway and the development of innovative solutions that can reduce MRPs (43).

There exist several measures that may optimize and increase the safety of medication use for older adults. These include educational interventions, medication reconciliation, medication reviews, computerized support systems incorporating PIM criteria lists, and comprehensive geriatric assessment (103-105). Medication reconciliation and review are the most widely spread and evaluated interventions (104). Medication reconciliation is effective in reducing medication errors, but there is limited evidence that medication reconciliation alone is associated with improvements in clinical outcomes (106-109). However, an updated and correct list of medications is a prerequisite for conducting a medication review (104). A medication review is a structured ‘evaluation of a patient’s medicines with the aim of optimizing medicines use and improving health outcomes’ (8). How medication reviews are performed in practice differs from simple prescription reviews to comprehensive medication reviews with full access to clinical patient information and incorporation of the patients’ views and preferences (104). The different levels of medication reviews performed in trials could be one reason why meta-analysis and systematic reviews have failed to find a general effect of medication reviews on clinical outcomes (110). For medication reviews to be effective in improving patient outcomes, evidence suggests they need to be performed in combination with co-interventions like patient education and transitional care elements (111).

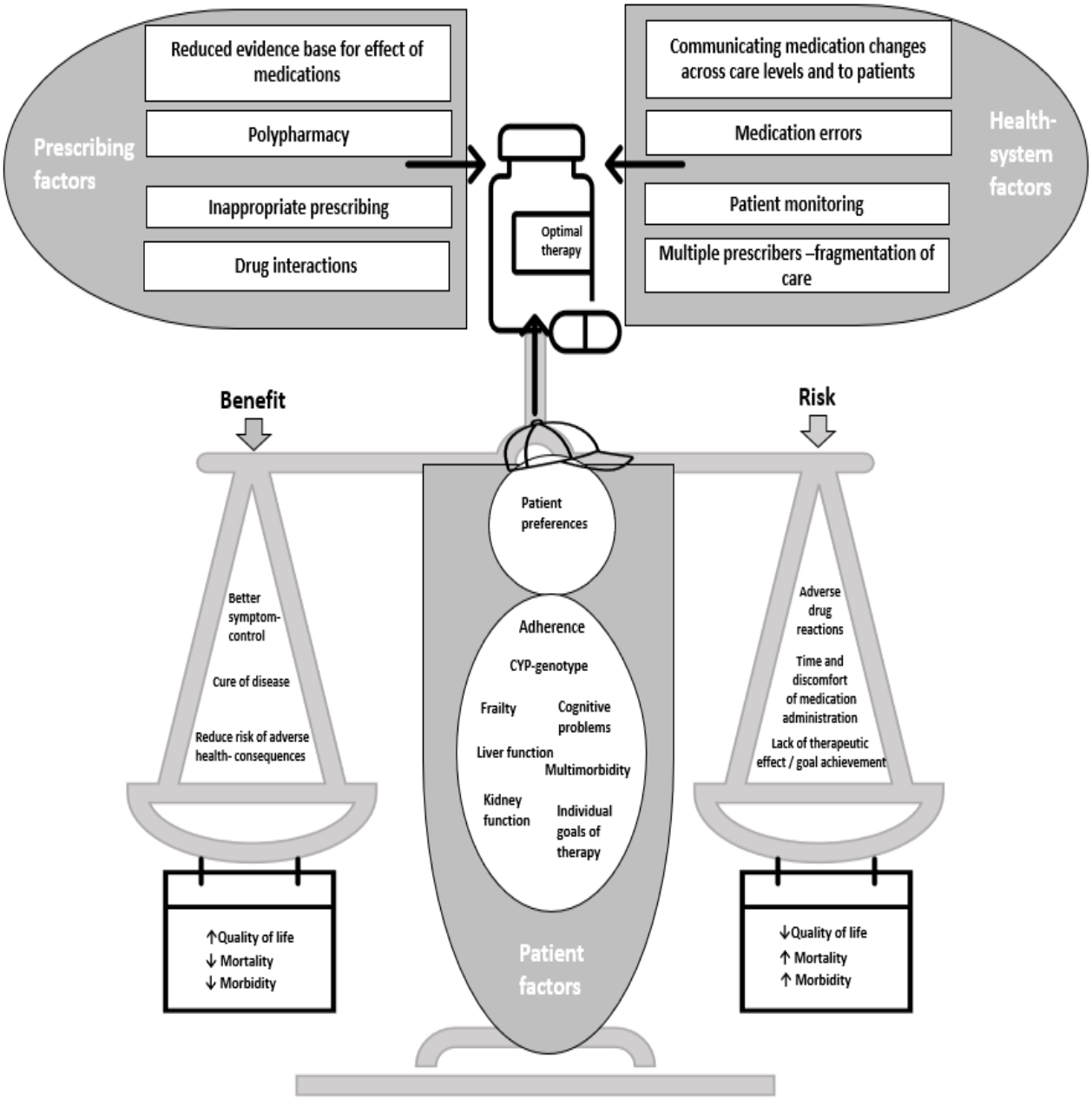

Figure 2 *"The balance of optimal medication therapy". Illustrating some patient-, prescribing-, and health system- challenges adding to the complexity of adapting and maintaining an optimal medication regime in older adults.*

Hospitalized patients are vulnerable to MRPs (112). However, hospitalization may also be an opportunity to improve medication use. In hospitals, there are highly qualified professionals to review the patients' medical needs. The patients are available for constant monitoring of changes, and there is easy access to clinical and diagnostic data. Geriatric wards are specialized to care for older multimorbid and often frail patients. A core feature is the presence of an interdisciplinary health care team and the use of comprehensive geriatric assessments. Standard care at these wards typically includes reviewing and optimizing medications (113, 114), but its effects on optimizing medications in a Norwegian context have not been explored.

1.7 The pharmacist's role in optimizing medication use and improving medication safety in hospitals

Clinical pharmacists are increasingly recognized as important members of interdisciplinary ward teams with their specialized knowledge of medications. Clinical pharmacy has been defined by the European Society of Clinical Pharmacy (ESCP) as 'a health speciality that describes the activities and services of the clinical pharmacist in developing and promoting the rational and appropriate use of medicinal products and devices'(5). The role of the clinical pharmacist, identifying and solving MRPs through patient-centered activities in hospitals, began evolving in the US in the 1960s (115). In Norway, clinical pharmacist services started to expand in the late 1990s (115). In the last 15 years, there has been a significant development in the role of clinical pharmacists in Norwegian hospitals, alongside and perhaps fueled by increased awareness and focus on patient- and medication safety in society (43, 116). The clinical pharmacist typically performs patient-oriented tasks like medication reconciliation, medication review, and patient counseling.

Working in interdisciplinary teams in hospitals, clinical pharmacist services has been shown to reduce the number of medication discrepancies, identify, and solve MRPs, improve medication appropriateness, and improve adherence (117-121). However, to maximize the benefits for all patients, rational and responsible use of resources is necessary. We need evidence of how pharmacist resources can be most appropriately applied to affect patient outcomes like ADRs, health care use, and health-related quality of life. Unfortunately, the literature does not provide a clear answer to how clinical pharmacist services should be delivered to best affect patient outcomes. Summarizing the effect of clinical pharmacist services in hospitals is challenging,

mainly because of a lack of standardized terminology to describe interventions and the heterogeneity of intervention contents, populations studied, and outcomes assessed (121). In Table 2, an overview of systematic reviews and meta-analyses published in the last ten years to investigate the effect of clinical pharmacist interventions in hospitalized patients is summarized. The heterogeneity of study findings adds additional complexity, and the conclusions reached in systematic reviews and meta-analyses are sensitive to which studies are included. Nevertheless, the evidence so far points to multifaceted interventions that includes transition of care elements as being more successful with regards to reducing health care contacts (122-124). Collaboration with other health care professionals by integrating pharmacists in hospital ward teams also seems to be essential in improving patients' clinical outcomes like readmissions and ED visits (121, 125-127).

Table 2 *Overview of reviews, systematic reviews and meta-analysis published over the last ten years aiming to synthesize the evidence of hospital clinical pharmacist services on clinical outcomes. Studies focusing on single diseases are not included.*

AUTHOR /YEAR	STUDY TYPE	INTERVENTIONS STUDIED	POPULATION	OUTCOMES INCLUDED	NUMBER OF STUDIES/ TYPES	RESULTS / CONCLUSIONS
DELGADO-SILVERIA ET AL. 2021(121)	Scoping review	Interventions made by hospital pharmacists in hospital and transition of care	Over 65 years, in hospital, taking more than five drugs	Mortality, QoL, Health care resources	N = 26, RCT = 21, Quasi RCT= 4, Pre-post design= 2	No hard evidence demonstrating the effectiveness of hospital pharmacist interventions in older polymedicated patients Mortality does not show as a relevant outcome. Including a pharmacist in multidisciplinary geriatric teams seems more promising than isolated pharmacist interventions.
VAN DER LINDEN ET AL. 2020(127)	Evidence based review	Clinical pharmacy services	Over 65 years (mean age), in hospital	Health care utilization, mortality	N = 35, RCT= 26, QE = 9	A positive effect of a clinical pharmacy intervention on post-discharge hospital visits was reported in 7 individual studies. Of the studies powered to assess hospital visits after discharge 3 of 9 studies were positive. Large, multi-center RCT should be performed.
DAWOUD DM ET AL. 2019(126)	Systematic review and meta-analysis	Ward-based pharmacists interventions	All ages, acute hospitalizations	Mortality, economic evaluation, ADE, QoL, Readmissions, medication errors, patient satisfaction and more	N = 25, RCT=18, Economic studies= 7	Regular pharmacist input was most cost-effective. It reduced length-of-stay (mean = −1.74 days [95% CI: 2.76, −0.72], and increased patient and/or carer satisfaction (Relative Risk = 1.49 [1.09, 2.03] at discharge. At £20,000 per quality-adjusted life-year-gained cost-effectiveness threshold, it was either cost-saving or cost-effective.

BONETTI AF ET AL. 2019(128)	Systematic review and meta-analysis	Pharmacist-led discharge counselling	Hospitalized patients	Readmissions, ED-visits	N = 21	Insufficient evidence regarding the effect of pharmacists-led discharge counselling on hospital readmission and emergency department visits. Moderate-to-high heterogeneity among trials prevented drawing further conclusions
SKJØT-ARKIL H ET AL. 2018(124)	Systematic review	Multifaceted pharmacist-led interventions	Hospitalized patients	All outcomes included	N = 28, 16 RCT, 12 QE	May improve the quality of medication use and reduce hospital visits, length of stay, and time to revisits. No effects were seen on mortality, patient-reported outcomes and cost-effectiveness.
KIESEL E ET AL. 2017(120)	Systematic review	Pharmacist intervention in the hospital setting	Hospitalized, over 65 years (geriatric patients), in Europe	Outcomes relating to the patients, medications, and costs	N = 18, 5 RCT, 1 cluster RCT, 12 other controlled studies	May improve the appropriateness of medications, seamless care and drug safety for geriatric inpatients while being cost-effective. Outcomes such as quality of life, mortality, compliance and readmissions presented variable results
MEKONNEN AB ET AL. 2016(123)	Systematic review and meta-analysis	Pharmacist-led medication reconciliation programs with the aim of improving care transitions to and from hospitals	Hospitalized	Health care utilization, mortality, ADE	N = 17, 8 RCT,3 QE, 6 Before and after studies	Significant reduction in ADE-related hospital revisits (RR 0.33; 95% CI 0.20 to 0.53), ED-visits (RR 0.72; 95% CI 0.57 to 0.92) and hospital readmissions (RR 0.81; 95% CI 0.70 to 0.95). The pooled data on mortality and composite readmission and/ or ED visit did not differ among the groups
RENAUDIN P ET AL. 2016(129)	Systematic review and meta-analysis	Pharmacist-led medication reviews	Hospitalized patients	All-cause readmission, ED-visits, drug-related readmission mortality, LOS, adherence, QoL	N = 19, 19 RCT	No significant reduction in the rate of all-cause readmission and/or ED visits RR 0.97 (CI,0.89-1.05). Secondary outcomes did not differ except for drug-related readmission RR 0.25 (CI: 0.14-0.45) and all-cause ED-visits RR 0.70 (CI, 0.59-0.85).

WALSH KA ET AL. 2016(119)	Systematic review and meta-analysis	Pharmacist interventions	Older hospitalized patients	Potentially inappropriate prescribing by a validated tool	N = 5, 3 RCT, 2 controlled trials	Multidisciplinary teams involving pharmacists may improve the appropriateness of prescribing in older hospitalised patients
HAMMAD EA ET AL. 2016(130)	Systematic review	Pharmacy led medicine reconciliation continued through the hospital stay until discharge (not involving telephone helpline and post-discharge follow-up calls)	Hospitalized patients	Process outcomes, clinical outcomes and costs	N = 13, 3 RCT, 3 before and after, 2 QE, 4 prospective uncontrolled, 1 not stated	Continuity of care was improved, but unknown if this precludes actual patient harm. The composite of optimum MedRec practice is not widely standardized and requires discussion among health professions and key organizations.
GRAABÆK T ET AL. 2013(131)	Systematic (mini) review	Pharmacist-led medication reviews	Hospitalized patients	Process or outcome data	N = 31, 6 RCT, 4 other controlled studies, 21 descriptive studies	Positive effects on medication use, health service use, and costs, despite large variability in design, methodologies, and outcome measures.

Abbreviations: ADE; Adverse drug events, CI; confidence interval, ED; Emergency department, LOS; Length of hospital stay, MedRec; medication reconciliation, RCT; randomized controlled trial; RR; relative risk, QoL; Quality of life; QE; Quasi-experimental

1.8 The Integrated Medicines Management model

One well-known multifaceted and inter-disciplinary approach to providing clinical pharmacist services is the Integrated Medicines Management (IMM) model. It was developed in Northern Ireland and further developed in Lund, Sweden (118, 132). One of the model's key features is the seamless transfer of medication information between health care levels. It is based on systematic training and includes well-defined activities and standard operating procedures, and responsibilities for the different team members (118). The clinical pharmacist performs most interventions, but collaboration with physicians and nurses is fundamental for success (118). Patient cooperation is also necessary, ensuring that the patient understands and engages in their health situation and medication use. Figure 3 presents the four interventions steps included in the IMM model (115, 118). Inspired by the work in Lund, Norwegian hospital pharmacies started to introduce the model in 2009 (53). The procedures were translated and adapted to a Norwegian setting while also incorporating elements from Northern Ireland (115). In Norway, the hospital pharmacies have collectively decided to develop clinical pharmacy services based on the IMM model(115). In the Government white paper nr 28 from 2015, 'Medical products- Correct use- better health,' Clinical pharmacist working by the IMM model was presented as a promising intervention to improve medication safety in hospitals (43).

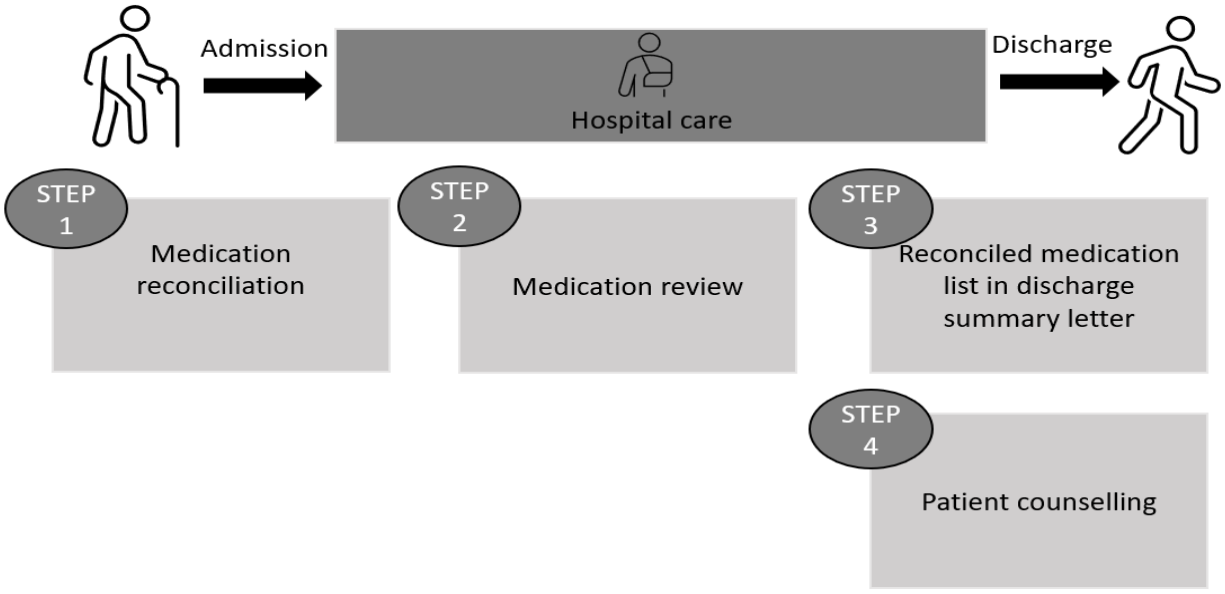

Figure 3 *The Integrated Medicines Management model (115, 118).*

One reason for choosing IMM as the template for developing clinical pharmacist services in Norway was its evidence base. In Northern Ireland, a randomized clinical trial by Scullin et al. found that patients receiving clinical pharmacist services following the IMM model had reduced length of hospital stay, decreased rate of readmissions and increased time to first readmission over 12 months after index stay (133). The effect on length of stay seemed to uphold in routine implementation (134). In Sweden, implementing IMM in hospital settings has in controlled studies been associated with reduced drug-related readmissions (135), readmissions (136), reductions in medication errors at transition points (137-139), and improved medication appropriateness (118, 135, 140). In 2009, a Swedish RCT including steps similar to the IMM model was published(141). Gillespie et al. found that a comprehensive pharmacist intervention in hospitalized patients over the age of 80, including a post-discharge follow-up call to patients after discharge, resulted in a 16% reduction in visits to the hospital (141) and an 80% reduction in drug-related readmissions (104). The authors show that multifaceted interventions, including a pharmacist in ward care, can affect patient-specific outcomes. In recent years, after the work on this thesis was started, studies have challenged the findings from Gillespie et al., and this is elaborated on in the discussion.

Data suggests that clinical pharmacist interventions may potentially affect patient health outcomes but does not provide definite answers to how interventions should be tailored to produce the best results (121, 124, 142). Also, health care systems in different countries have different challenges when it comes to medication management. A complex health intervention like the IMM model, being effective in Sweden and North Ireland, does not necessarily produce the same effects in the context of a Norwegian hospital ward. When starting the work on this thesis in 2014, the effects of implementing IMM-based interventions on health outcomes in older inpatients in Norway had not been investigated, despite being the basis for clinical pharmacy services in Norwegian hospitals. Both in a Norwegian and international perceptive, there was a need for high-quality studies on the effect of integrating clinical pharmacists services in wards teams caring for older hospitalized patients (124, 127).

2 Aims

The overall aim of this thesis is to provide knowledge on PIM use in hospitalized older patients and investigate how clinical pharmacist services in an interdisciplinary setting can contribute to medication optimization and improve patient outcomes. The specific objectives addressed in the papers were the following:

Paper I

To investigate how hospitalization in a Norwegian geriatric ward impacts the use of medications and PIMs among older adults, comparing two different tools of PIM identification.

Paper II

To describe an interdisciplinary collaboration structure aiming to optimize medication therapy and improve communication of medication-related issues between secondary and primary care. Describe how a study (the IMMENSE study) testing the effects of the intervention will be performed (study protocol).

Paper III

To describe how the interventions in the IMMENSE study were delivered (interventions fidelity) and the process outcomes of the intervention.

Paper IV

To investigate the effects of the IMMENSE study on its primary outcome, the rate of emergency medical visits 12 months after discharge, and the secondary outcomes related to health care use and mortality.

3 Methods

3.1 Study design and setting

The four papers included in this thesis are based on two main studies, mainly focusing on patients admitted to geriatric wards.

Paper I is a health register study linking data from two national health registries; the Norwegian patient registry (NPR) and the Norwegian Prescription Database (NorPD). The application of national prescribing registries to explore medication and PIM use related to hospitalizations in geriatric wards is a novel approach that allowed us to investigate the changes in dispensed PIMs at a national level.

Specialized Geriatric wards were identified by manual screening of the national register for units in secondary care ("register for enheter i spesialisthelsetjenesten" (RESH)) (143) and dialogue with NPR. NPR subsequently tagged hospital wards in ten Norwegian hospitals as geriatric wards.

Paper II - IV is based on a non-blinded parallel-group randomized controlled study; The IMprove MEdicatioN Safety in the Elderly (IMMENSE) study. A randomized trial is considered the best design for evaluating the effect of interventions (144).

The study was conducted at the University hospital of North-Norway (UNN), a 581-bed hospital located in three cities in Northern Norway (Tromsø, Harstad and Narvik), serving as the local hospital for approximately 200000 inhabitants (145). The largest hospital site in Tromsø also holds a regional function. The IMMENSE study mainly recruited patients from a 14-bed geriatric ward at UNN Tromsø. A second study site, a 16-bed general internal medicine ward at UNN Harstad also receiving geriatric patients, was added to enhance the patient recruitment and the generalizability of the findings.

3.2 Patient selection

3.2.1 The effect of a geriatric hospital stay on medication use and PIM-use (Paper I)

In Paper I, we used the NPR to identify all patients ≥65 years admitted to geriatric wards in Norway in 2013. The first hospitalization to a geriatric ward in 2013 was their index hospital stay. We excluded all patients with hospital admissions 120 days before or after the index hospital stay because we wanted to measure the effect on medication use of a single hospitalization. Furthermore, as we were interested in medication users, we excluded patients if no medications were dispensed according to NorPD 120 days before or after the index hospitalization. We excluded patients discharged to an institution or nursing home (missing data from NorPD) and patients who died in 2013 as they could have died in the 120 days following the index stay (date of death unknown).

3.2.2 Participants in the IMMENSE study (Paper III and IV)

The IMMENSE study was initially planned to be conducted exclusively in a geriatric ward and include patients ≥ 65 years, the same age group as in Paper I. When we decided to add a second study site, the age limit was increased as patients in the general medicine ward were thought to be healthier than the selected population admitted to a specialized geriatric ward.

Patients eligible for inclusion in the IMMENSE study were ≥70 years, acutely admitted to one of the two study wards, and willing to provide written informed consent (patient or next of kin). Not eligible for inclusion where patients admitted to the study ward more than 72 hours before evaluation of eligibility, 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. Patients were excluded after randomization if moved to and discharged from other wards during the index stay as we would be unable to perform the discharge steps of the intervention in other wards. Patients were also excluded if an intervention from a study pharmacist was considered necessary for ethical reasons in the control group. To avoid biased enrollment, the order in which patients were approached to participate was based on the time of admittance, not the pharmacist's choice. The most recent admitted patients approached first.

3.3 Randomization and blinding (Paper II and IV)

With randomization, we aim to prevent biases introduced by the pharmacist influencing or predicting the group assignment. Randomization also aims to create comparable groups in the covariates that we recognize and can measure and in covariates that are not recognized and measurable (144).

In the IMMENSE study, patients were allocated to intervention or control in a 1:1 ratio by a web-based service supplied by the department of applied clinical research at the Norwegian University of Science and Technology. The randomization block sizes were concealed, varied in size, and permuted. As the two study sites were different in terms of the study population, pharmacist resources, and physician working procedures, we stratified randomization for the study site. The nature of the intervention meant it was impossible to blind the patients or ward personnel to group allocation, and patients were informed about the outcome of the randomization. However, the primary outcome analysis (**Paper IV**) was conducted on a blinded dataset by researchers not involved in performing or planning the intervention. Also, the study nurse collecting the health-related quality of life measures for participants was blinded to group allocation (results not part of this thesis).

3.4 The IMMENSE study – preparation and intervention (Paper II-IV)

3.4.1 IMMENSE study preparation

Planning of the IMMENSE study started in 2014 with the start of this Ph.D. project and was a collaboration between the UiT The arctic university of Norway, and the geriatric ward at UNN Tromsø. To design a feasible intervention with relevant outcomes, we first searched medical literature on how pharmacists could best work in an interdisciplinary ward setting. The intervention steps and design of the study were further developed in 2014-2016. We held network seminars with researchers from Norway and Sweden, discussing the intervention components, data collection, and outcomes. A meeting with leading GPs from the municipality of Tromsø was held to discuss how GPs and hospital wards could improve information exchange at care transitions. Physicians and other wards personnel were informed about the study and asked for feedback in the design phase. We also visited hospital pharmacies in Norway where clinical pharmacists were working by the IMM model to learn how the model was adapted and implemented in different ward settings.

Study procedures for both the administrative part of running the RCT and conducting the clinical work of the intervention were developed. The clinical IMM working procedures and forms were adopted from "Sykehusapotekene HF" and were also used in a parallel RCT run in Oslo (146). Furthermore, we developed study-specific working procedures for steps 4 and 5 of the intervention. A flowchart with an overview of the study procedures and forms used in the clinical intervention and data collection is presented in Appendix A.

Before starting the study, inclusion procedures and data collection were tested in the geriatric ward. Several meetings with the study pharmacists were held and procedures adjusted; however, no formal feasibility study or pilot study was conducted.

3.4.2 The IMMENSE intervention.

The intervention was based on the four-step IMM methodology adding a fifth step, phone-based follow-up with primary care. The choice to add a fifth step was based on evidence that despite discharge summaries with medication reports, medication changes at hospital discharge may not be adhered to in primary care (147-149). The study pharmacists performed the intervention steps in close collaboration with nurses and the hospital physicians, the latter holding the medical responsibility for the patients. All pharmacists received training in performing the intervention according to the IMM procedures. However, this did not follow a structured education program due to differences in knowledge, skills, and competencies between study pharmacists.

Table 3 *Description of interventions steps in the IMMENSE study*

Intervention step	When performed	Description
Step 1: Medication reconciliation	At study inclusion, no later than 72 hours after admittance to the ward.	If possible, patients were interviewed about medication use at home by applying a standardized IMM Medication reconciliation interview. The interview included questions about practical handling, knowledge, and medication adherence. Information from patient interviews was cross-checked with other sources like national summary care records, local pharmacies, GPs, home care services, nursing homes or next of kind until a complete list of the patients' medications in use was confirmed. This pharmacist compiled medication list was then compared to the medication list in use in the hospital at study inclusion and identified medication discrepancies discussed with the physicians.

Step 2: Medication review	At study inclusion and repeated while admitted to hospital.	A standardized IMM procedure for identifying MRPs was applied. The structured and comprehensive medication review identifies MRPs in the following risk categories (1) medications requiring therapeutic drug monitoring (2) potential inappropriate medications for older adults (the START/STOPP list and the NORGEP-NH list (65, 75)) (3) Problems related to drug administration/dosage form or adherence (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 changes in laboratory measurements (10) other needs for monitoring of treatments. Identified MRPs were discussed and solved in the interdisciplinary team and with the patient if possible.
Step 3: Medication list in discharge summary letter	At discharge	The study pharmacists drafted a discharge medication list in the electronic medical journal that was reconciled, structured and correct. The medication list included information and explanations about mediation changes made during the hospital stay and unsolved MRPs with suggested solutions to the GP and the need for monitoring of medication therapy. The responsible ward physician used this draft when preparing the final discharge summary.
Step 4: Patient counseling	At discharge	Before discharge, a patient counseling session was arranged with the study pharmacist for patients who handled their medication after discharge. The patients should receive an updated patient-friendly medication list, which was discussed and explained. In the counseling, the pharmacists focused on changes made during the hospital stay and the reasons for these changes. Patients were also encouraged to ask questions about their medications.
Step 5: Communication with primary care	At discharge and within a week after discharge	a) <u>Call to GP</u> Within a week after discharge, the pharmacists called the patient's GP to discuss current medication therapy changes, recommendations, and monitoring needs stated in the discharge summary (if relevant). The aim was to ensure that the changes and recommendations were implemented and acted upon. b) <u>Call to primary care nurses</u> At discharge, the pharmacist or ward nurse called home care services or nursing homes if these are responsible for administering the patient's medications. Changes in medications were explained with suggested monitoring of effects or side effects if relevant. Multi-dose dispensed medication was changed if requested by home care services.

3.5 Data sources, collection, and management

3.5.1 Paper I

Two Norwegian health registries constitute the data source of **Paper I**. NPR holds information on all consultations with secondary care in Norway (150), while NorPD contains information on all

medications prescribed (reimbursed or not) and dispensed at Norwegian pharmacies to individual patients living outside institutions, i.e., ambulant care (151). Variables that were available from the two registries are found in Appendix B. Linking of registry data was possible through unique personal identification numbers held by every Norwegian citizen. NorPD performed the linking of the datasets by generating study-specific ID numbers for all included patients.

3.5.2 Paper II-IV

Baseline information for all study participants was collected before randomization from patients or next of kin, handwritten medication charts, and the hospital medical records. Baseline information included age, level of education, type and amount of help from home care services, medical history, laboratory values, and medication use at hospital admission. Comorbidity was calculated by applying the Charlson comorbidity index (152) retrospectively to admissions and discharge diagnoses.

A Microsoft Access® database was developed with help from the clinical research unit at UNN to aid in data collection and management. Patients were given a unique study number, and all patient information and intervention steps performed were documented anonymously in the database. Information was mainly entered into the database by the study pharmacists, with pharmacist students entering and validating some baseline information like medication use. Detailed study procedures for data registration were developed. Information from the database was transferred to SPSS (Statistical Program for Social Sciences) version 28.0 (IBM Corp. NY) for data management and quality control. If a patient was missing data for any of the variables included in **Paper III and IV**, study paper files and patient records were checked for missed registrations.

3.6 Outcome assessment

3.6.1 Medication use (Paper I)

NorPD was the source of medication use in **Paper I**. We applied a fixed time window approach to identify medication use before and after the index hospital stay (153, 154). We counted medications in use as the number of Anatomical Therapeutic Chemical (ATC)-codes dispensed within 120 days before or after the index hospital stay (155). We chose 120 days because reimbursed medications in Norway (i.e., all medications used for chronic diseases) can only be dispensed for a maximum

of 90 days. Consequently, medications dispensed 120 days before and after hospitalization should represent regular use for chronic conditions, leaving a 30-day window to account for non-adherence and stockpiling. A 120-day fixed-time window was also used in a Danish registry study investigating changes in medication use after geriatric stay (156). Sensitivity analysis where the fixed time window was set to 90 days or 150 days was performed but did not change the findings in **Paper I**.

3.6.2 PIM identification (Paper I)

We used two explicit criteria lists to identify PIM in **Paper I**, the NORGEP-NH list (75) and the EU(7)-PIM list (68). This allowed us to investigate if our findings would change according to the PIM list applied. Furthermore, it enabled us to compare a Norwegian developed list to a list created to compare PIM prescribing patterns across European countries. The NORGEP-NH list was preferred over the NORGEP list, as the NORGEP-NH list represents the most updated Norwegian PIM list. Because data from NorPD does not include the prescribed dose of medications and our population being hospitalized and not residing in nursing homes, we had to make some adaptions to the lists. We applied 263 criteria of the 282 criteria in the EU(7)-PIM list. From the NORGEP-NH list, we applied all the 26 criteria in parts A and B. We excluded the de-prescribing criteria in part C as these criteria are most relevant for a nursing home population. We used a Syntax approach in the statistical program SPSS when applying the PIM criteria lists. The syntax identified ATC-codes or Nordic article numbers (in cases with only specific strength or formulations were defined as PIM) corresponding to the different PIM criteria's from the medications dispensed in NorPD 120 days before or after the index hospital stay. See **Appendix C** for NORGEP-NH syntax not included in **Paper I**.

3.6.3 Intervention fidelity and process outcomes of the IMMENSE study (Paper III)

While performing the intervention, study pharmacist documented their everyday work in the study database. All intervention steps were recorded as well as reasons for not performing one of the five intervention steps. For **Paper III**, step 5 of the intervention was dichotomized as follows; a) call to general practitioners and b) call to primary care nurses, as these could be viewed as separate steps. The full intervention coverage was calculated as the number of patients where the study pharmacist had self-declared delivering intervention steps, also including steps not delivered when

not relevant to patients according to the study protocol, i.e., a call to the GP not needed when no medication follow-up issues where identified at discharge.

The medication reconciliation performed at admission (step 1), and medication reviews (step 2) resulted in process outcomes in the form of Medication discrepancies and MRPs. While medication discrepancies are an MRP by the definition deployed in this thesis (4), we decided to separate them as they result from different processes. Discrepancies and MRP were recorded in the study database, as well as their proposed solutions and implementation. MRP was categorized by applying a Norwegian classification system developed by Ruths et al. (157). Medication discrepancies by categories in the Norwegian IMM procedure with local adaptions and recommendations to solve MRPs were classified into 15 categories developed by the research team.

3.6.4 Primary and secondary outcomes of the IMMENSE study (Paper II and IV)

The choice of primary outcome measure is challenging when the intervention is complex and aims to optimize medications. A literature review including 37 studies in secondary care found that 135 different outcome measures had been used to evaluate the effect of clinical pharmacy interventions (158). Core outcome sets of interventions like the IMMENSE study had not been published when planning the study (158). We choose to investigate the effect of the intervention on both health care use, patient-related outcomes, and outcomes related to their medication use. The primary outcome was selected based on a study by Gillespie et al. (141) and was the rate of emergency medical visits 12 months after discharge from the index hospital stay. This composite endpoint consisted of acute hospital readmissions, hospital visits not leading to readmissions, and municipality-run emergency departments (ED) visits. The rate of the primary endpoint was based on information from two Norwegian health registries, NPR and The Norwegian Health Economics Administration Registry (in Norwegian “kontroll of utbetaling av helserefusjoner (KURH)-databasen”). NPR holds information on all hospital visits, while The Norwegian Health Economics Administration Registry provides information on visits to municipality run EDs (159). We excluded all ED visits occurring within 6 hours of an admission to a hospital to avoid double counting events. It was assumed that 6 hours would give the patients enough time to transport from the ED to the hospital.

In addition to the primary outcome, we chose 13 secondary outcomes for the complete evaluation of the IMMENSE study (**Paper II**). The EuroQol 5 dimension (EQ-5D) and EuroQol visual

analogue Scale (EQ-VAS) were used to measure health-related quality of life (160). EQ-5D was chosen as it is relatively fast to apply, can be used in economic evaluations, and has some data supporting the use in patients with cognitive impairment (161, 162). To investigate the effect on the appropriateness of prescribing, we planned to apply three different tools; The Medication appropriateness index (MAI), an implicit tool (163), the NORGEP-NH list, and the STOPP/START list measuring both PIMs and PPOs (65, 75). Medication lists were collected from GPs and nursing homes at three and twelve months post-discharge to investigate possible sustained effects on the appropriateness of prescribing.

3.7 Statistical analysis

3.7.1 Paper I

We compared the mean number of medications before and after hospitalization with a dependent paired sample t-test. The proportion of patients with PIMs was compared using the related samples McNemar test. Change in the number of identified PIMs before and after hospitalization was examined by applying the related samples Wilcoxon signed-rank test.

3.7.2 Paper II and IV

The rate of the primary outcome (emergency medical visits) in control and intervention patients was analyzed using a multilevel poison regression, where “days under risk” were used as an offset (log-transformed). “Days under risk” was 365 days or until the day of death, also subtracting days admitted to hospital, as no new event was possible when hospitalized. A multilevel Poisson regression was not stipulated in the protocol or statistical analysis plan but was decided to be the most appropriate test to account for clustering of events in patients and between study wards. We performed both an unadjusted and an adjusted analysis where we adjusted for the number of emergency medical visits in the 365 days before index hospitalization and study site in single-level models. The choice of covariates in the analysis was based on guidance on adjustment for baseline covariates in clinical trials from the European medicines agency (164). A prespecified subgroup analysis was performed on the primary outcome.

Kaplan-Meier plots were compiled to visualize the time to first readmission or emergency medical visit, and a log-rank test was applied to compare the survival curves of the control and intervention

groups. As Kaplan-Meier curves and log-rank tests are univariate analyses, we performed a *Cox* proportional hazards regression to generate the Hazard rate and adjust the estimates for covariates (study site and the number of emergency medical visits in the year before index hospital stay). Differences in length of stay between groups were assessed with an independent sample Mann-Whitney test. The differences in proportions of patients alive at 12 months and patients readmitted within 30 days were compared with Logistic regression (unadjusted and adjusted). A two-sided alpha level of 5% was used with no adjustments for multiplicity.

No data was available on the rate of emergency medical visits in our population. The sample size calculation for the primary outcome was therefore based on a Swedish RCT from Gillespie et al. applying the same composite outcome as the IMMENSE study (141). Gillespie et al. randomized 400 patients ≥ 80 years in a 1:1 relationship to a ward-based clinical pharmacist intervention and found a 16% reduction in all-cause visits to the hospital in the intervention group. We estimated the same rate of acute hospital admissions and ED visits of 1.7 per year in our patient population and found we need to enroll 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 aimed to include 250 patients in each group. The increased number of drop-outs made us extend inclusion by one month.

4 Ethical considerations

Both trials were conducted in compliance with the principles of Good Clinical Practice and the Declaration of Helsinki (165).

4.1 Ethical approvals

In **Paper I**, The regional ethics committee (REC) and the Norwegian Data Protection Authority approved the study before we got access to the relevant data from NPR and NorPD. Norwegian health registers are regulated by Norwegian law (166), and no consent to participate is needed from the individuals contributing with data in the dataset.

For the IMMENSE study (**Paper II-IV**), an application for ethical approval was first sent to REC. REC replied that the study did not require a permit from them according to Norwegian health research legislation as the primary outcome of the IMMENSE study was not to give new knowledge about health or diseases but to evaluate a work method and collaboration structure (167). Thus, the Norwegian Centre for Research Data recommended the study, and the Norwegian Data Protection Authority gave permission to collect, store and link research data. A data protection impact assessment (DPIA) was also developed in collaboration with the Norwegian Center for Research data. The data protection officer at UNN also approved the study. The trial was registered at clinical trials.gov: NCT02816086, before recruiting patients.

4.2 Research on patients without the ability to provide informed consent

An important principle in medical research is that all participation in trials should be based on informed consent that is voluntary, explicit and documented (165). In the IMMENSE study, all patients or their next of kin were given oral and written information about the study and subsequently signed written informed consent to enter the trial (see Appendix D). The study included patients who were unable to give informed consent. Ethical committees consider several aspects before deciding to allow the inclusion of patients without the capacity to consent in clinical trials. The risk associated with study inclusion should be minimal. The patient should not oppose inclusion, and there should be a reason to believe that the research results could be helpful for the person or other person with similar diseases/conditions (167). These prerequisites were fulfilled in the IMMENSE study. The risks associated with the intervention were judged to be low, as similar

interventions in other health care settings had led to improvements in prescribing quality or patient outcomes without reporting adverse effects (118, 133, 168). Patients with cognitive challenges or dementia are also vulnerable to medication-related harm (169). One could argue that excluding them from a trial aiming to gain knowledge of how we best can collaborate around medication optimization will not be in their best interest.

It was challenging to assess some patients' ability to consent to trial participation as some degree of cognitive impairment was frequent, especially in the geriatric study ward. If uncertain, the study pharmacist discussed the ability to consent with the ward team and physicians and sometimes the patients' next of kin. If a patient was temporarily incapable of giving consent, for instance, in delirium, consent is first sought from the next of kin. When/if the patient was again considered able to consent, they were asked to supply the written consent themselves, and if they refused, they were excluded from the study. For patients unable to consent and where the next of kin was not present on the ward within that working day, we included and randomized patients after oral consent from the next of kin, pending the written informant consent to be signed when visiting the ward or returned by mail. In cases where the written informed consent was not obtained from the next of kin after one reminder, the patients were excluded.

5 Results

This chapter summarized the main results of the papers. Please refer to the individual articles for more details about the results.

5.1 Paper I

In **Paper I,** we investigated how hospitalization in geriatric wards affected medication use and PIM use by comparing the two explicit PIM lists, the NORGEP-NH list and the EU(7)-PIM list. We identified 2242 patients over the age of 65 hospitalized in a geriatric ward in Norway in 2013 and included 715 in the analysis. We identified the following:

Regarding overall medication use

The mean number of medications increased significantly from 6.5 (SD: 3.5) before hospitalization to 7.5 (SD: 3.5) after hospitalization (95% CI: 1.2-0.8. $p<0.001$). The number of users of the following medications increased the most after discharge: paracetamol (+70), atorvastatin (+61), calcium and vitamin D (+53), pantoprazole (+33), metoprolol (+33), dipyridamole (+32) and vitamin B (+32). The combination of paracetamol and codeine (-11) and ethylmorphine (-11) had the largest drop in the number of patients dispensed the medication.

Regarding PIM use

Using the EU (7)-PIM list, the proportion of patients with PIMs increased from 62.4% before to 69.2% after hospitalization ($p<0.001$). The median number of PIMs also increased significantly post-discharge ($p<0.001$). The increase in PIMs by the EU(7)-PIM list after hospitalization was primarily driven by the increased use of dipyridamole and direct oral anticoagulants (DOACs). Dipyridamol and DOACs are defined as PIMs by EU (7)-PIM but not by the NORGEP-NH list.

According to the NORGEP-NH list, PIM use did not change significantly after discharge (49.9% to 50.6%, $p=0.73$), nor did the median number of PIMs per patient.

Regarding agreements between tools

The two tools for identifying PIM use agreed on the classification of patients as PIM users or non-PIM users in 71.9% after hospitalization. Hypnotics and sedatives were responsible for most PIMs in both tools, zopiclone being the single medication responsible for most PIMs.

5.2 Paper II

The results of the IMMENSE study planned and outlined in **Paper II** are presented in **Paper III** and **IV.** Future research and publications from Paper II are described in section 7, Future research and perspectives.

5.3 Patient flow in the IMMENSE study (Paper III and IV)

While the IMMENSE study where recruiting, study wards had 3742 admissions of patients over 70 years, 516 patients were randomized, and 221 and 480 patients were included in the main analysis in Paper III and IV, respectively. An outline of the patient flow is presented in Figure 4.

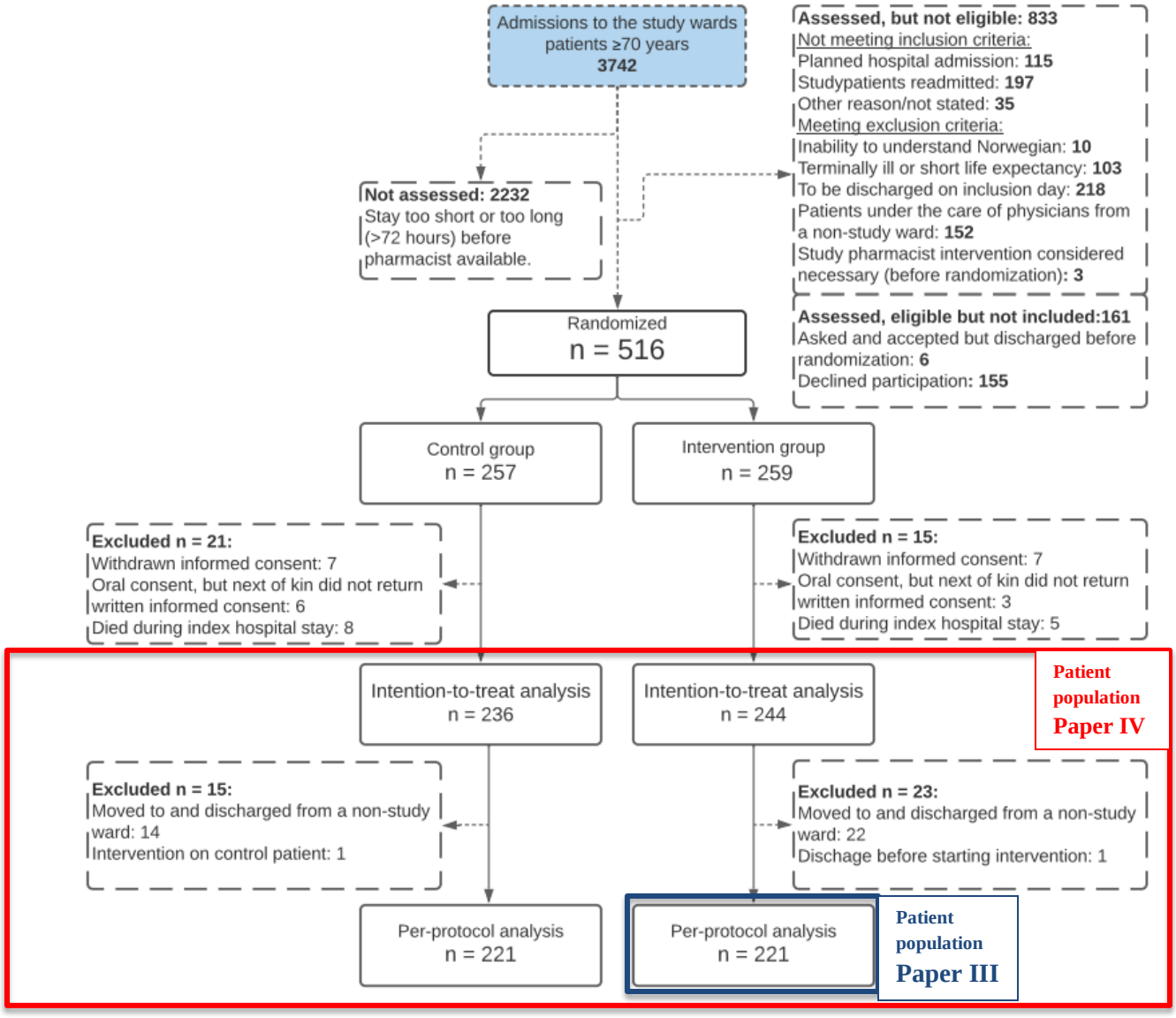

Figure 4 *Outline of the patient flow in the IMMENSE study and the patients included in the results section of Paper III and IV*

5.4 Paper III

In **Paper III,** we report on how the interventions planned in **Paper II** were delivered to intervention patients included in the per-protocol analysis (not excluded after randomization) and the number and types of medication discrepancies and MRPs identified and solved in hospital (process outcomes).

Regarding intervention fidelity

Of the 221 intervention patients in the per-protocol analysis, 121 (54.8%) received all the intervention steps. More patients in the geriatric ward (58.6%) received all intervention steps than in the general internal medicine ward (37.5%). Most patients (34.8%) not receiving the full intervention missed only one step.

Regarding identified medication discrepancies and MRPs

The pharmacists identified 437 medication discrepancies (median 1, IQR 0-3, range 0-10) in 159 patients (71.9%). Of the discrepancies, 92.9% were presented to and discussed with the physician, and changes were made in the medication charts for 292 discrepancies (66.8%).

A total of 1042 MRPs (median 4, IQR 2-6, range 0-28) were identified in 209 patients (94.6%). The most prevalent MRPs were related to medication choice, identified in 181 patients (81.9%) and dosage, identified in 124 (56.1%) patients. A total of 700 MRPs (67.2%) were solved in the inter-disciplinary team in the hospital as recommended by the pharmacist. 239 MRPs (22.9%) were communicated to primary care because the GP was in a better position to initiate and follow up on changes. The medications most frequently involved in MRPs included zopiclone (37 MRPs), paracetamol (35 MRPs), pantoprazole (35 MRPs), polyethylene glycol (30 MRPs) and iron-preparations (30 MRPs).

5.5 Paper IV

In **Paper IV**, we present the main results of the IMM-based intervention with enhanced communication with primary care on the outcomes related to health care use and mortality.

The 480 patients included in the ITT analysis had a mean age of 83.1 years (SD 6.4), used a median of 7 regular medications at admission (IQR: 4-10), and had a median Charlson comorbidity index score of 2 (IQR: 1-4).

The intervention did not lead to statistically significant changes in the rate of the composite primary outcome of emergency medical visits after 12 months with an adjusted incidence rate ratio of 1.02 (95% CI: 0.82-1.27). This result was consistent across prespecified subgroups. There was a slight but non-significant difference between the groups in median time to first emergency medical visit, with 137 days (95% CI: 92-182) for the intervention group and 110 (95% CI: 74-146) in the control group, adjusted hazard rate of 0.96 (95% CI: 0.78-1.19). When visualizing the daily risk of emergency medical visits over one year, the intervention seems to have a positive effect during the first 60 days (Paper IV, Figure 3). However, differences between the groups are not significant and perish over time.

No significant differences between groups were identified on the secondary outcomes median length of index hospital stay, time to first rehospitalization, number of patients with readmission within 30 days of all-cause mortality within one year.

The per-protocol analysis did not change the conclusions from the ITT analysis, but effect estimates moved slightly towards the intervention.

6 Discussion

For a discussion of all the findings, please see the individual papers. This section presents a discussion on the main findings in the context of medication optimization in older adults, the role of clinical pharmacist services, and the overall methodological considerations of the thesis.

This thesis provides knowledge on PIM use in hospitalized older adults and investigates how clinical pharmacist services in an interdisciplinary setting can contribute to medication optimization. We found that PIM use was frequent, affecting over half of all geriatric hospitalized patients in Norway in 2013. Geriatric hospital stays did not with reduced PIM use 120 days after discharge, but the two tools used to identify PIM did not agree on whether PIM use was increased after discharge. A geriatric hospital stay could be viewed as an opportunity to optimize medication use. However, the results in **Paper I**, suggest the need for further interventions to improve prescribing quality in this vulnerable patient group. In **Paper II,** we designed a multistep intervention based on the IMM model to optimize medication use in older hospitalized adults and describe an RCT to test the intervention. In **Paper III,** we show that the intervention did identify and solve many medication discrepancies and MRPs, but not all patients received all intervention steps. Despite the IMMENSE intervention identifying and solving many MRPs, **Paper IV** showed that the intervention had no significant effects on the primary and secondary outcomes related to healthcare use or mortality.

6.1 Optimizing medication use in older adults - the role of PIMs and MRPs.

When aiming to optimize medication use, the first step is to assess whether the ongoing therapy is suboptimal, whether the suboptimal therapy is because of PIMs or MRPs. In **Paper I,** we used national health registers to identify geriatric ward patients and their medication use before and after a hospitalization. We used two explicit PIM lists, the EU (7)-PIM list and the NORGEP-NH list, to identify the magnitude of PIM prescribing and identify changes post-discharge. Explicit PIM lists applied to information from prescription databases are valuable in providing a crude estimate of prescribing quality in a population and assessing how prescribing changes over time (170). Using national prescription data to assess how hospitalization affects medication use and PIM use in a Norwegian setting is a novel approach, and we show that this is feasible in **Paper I**.

We observed that the diversity of medications defined as PIMs in the two PIM lists applied in **Paper I** resulted in different prevalence in the same population, as seen in several studies comparing PIM lists (171-173). The different medications defined as PIMs raise the question of which tool alerts of PIMs where changing prescribing will be of the most benefit to patients? For most explicit PIM lists, like the NORGEP-NH list and the EU (7)-PIM list, there is limited evidence on the clinical implications for patients being exposed to PIMs (174). For example, a study of 232 hospitalized patients ≥75 years did not find an association with the number of PIMs identified by a modified NORGEP list on clinical outcomes, like cognitive status, activities of daily living and physical function (86). Furthermore, a Norwegian cross-sectional study in older multimorbid patients found that strict adherence to the NORGEP list could have prevented only 15% of serious adverse drug events in the hospital (175). Some criteria lists, like the STOPP/START list, focus not only on PIMs but also include potential under-prescribing and overprescribing. There is more evidence for an association with adverse patient outcomes for the STOPP/START list than with the NORGEP- NH list or the EU(7)-PIM list (174). Applying recommendations from the STOPP/START list to hospitalized patients has been investigated in several RCTs. Some have found routine applications to reduce ADRs, PIPs, falls, and medication costs in older multimorbid patients (176-179). Others have failed to find an effect on preventing ADR or medication-related hospitalizations (180, 181). Unfortunately, few criteria on the STOPP/START list can be applied without clinical information like indication, duration of therapy, lab results or medication history, making it less suitable to be used with prescription-only data as in **Paper I** (182). In the IMMENSE intervention (**Paper II-IV**), both the NORGEP-NH list and the STOPP/START list were incorporated into the medication reviews. Whatever tool is used, advice from PIM lists is only a supplement to a risk-benefit assessment of a patient's medication regime. PIMs may be well tolerated and needed in some patients while potentially harmful in others. Consequently, advice from PIM lists should never replace clinical judgment.

Although the prevalence of PIM use was dependent on the list applied (**Paper I**), PIM use was frequent both before and after hospitalization, affecting 51% and 69% of patients after discharge when using the NORGEP-NH list or the EU (7)-PIM list. Our findings are supported by a systematic review that identified a pooled PIM prevalence of 46-65% in hospitalized older adults. Studies applying the NORGEP-NH list (part A and B) to Norwegian nursing home patients have

found a prevalence of PIM use in the range of 44-70%, depending on the inclusion of "as-needed medications" also in line with our findings (92-94). The EU(7)-PIM list has not been used to identify PIMs in a Norwegian setting (Table 1), but in studies from other countries, 67-80% of older hospitalized patients have used PIMs defined by the list (183, 184). Altogether, our findings indicate a need for interventions that reduce the burden of PIM use in geriatric patients.

Alerting hospital physicians of PIMs have the potential to increase prescribing appropriateness and reduce ADRs and costs (179, 185). However, for any intervention focusing on prescribing to have an impact, it has to lead to changes in prescribing. Many potential barriers and enablers influence the prescribers' choice to continue or discontinue PIMs (186). How prescribers perceive the relevance of the PIMs in their patients is an important factor influencing whether recommendations lead to changes in prescribing (186, 187). In multimorbid older adults, it may be especially difficult to balance the benefit and harms of therapy (186). A multidisciplinary setting like a geriatric ward should have the skills to make these risk assessments in collaboration with the patients. However, one of the barriers for hospital physicians to implement PIM-reducing recommendations includes a belief that changing long-term prescriptions is the GPs´ responsibility (181, 186). Indeed, some medications need to be tapered off and can not be resolved during a short hospitalization, like hypnotic medications found in **Paper I** to be the most common PIMs. A qualitative study investigated factors influencing Norwegian GPs prescribing of fall-related drugs like hypnotics. In this study, GPs expressed they 'appreciated discharge letters in which someone had done a medication review and made suggestions for alterations on their prescribing', as this triggers reflections about whether the medication could be terminated or doses changed (188). In **Paper III,** we observed that 22.9% of MRPs were communicated to primary care to be solved there. These findings support that medication optimization initiatives in hospitals need to be a joint effort with primary care.

While PIM lists are valuable aids to guide initiatives such as deprescribing, they are insufficient in identifying all types of MRPs. For example, in a Dutch study where pharmacists performed medication reviews, Verdoorn *et al.* found that 81% of identified MRPs were not covered by the STOPP/START list (version 1) (189). Furthermore, Steinman et al. found the Beers list (version 2003) to identify only 8% of the medications that an expert panel judged problematic in older adults

(190). Also, emergency hospitalizations and ED visits in older adults are often caused by adverse drug events of medications that are not defined as inappropriate in older adults, like warfarin, insulin, and oral antiplatelet agents (29, 191, 192). This may be why focusing solely on PIM in older hospitalized patients may be insufficient to affect patient outcomes (180, 181, 193, 194). Given the complexity of medication optimization in older adults, the large number of stakeholders involved (195), and the aim to improve patient outcomes, evidence points to multifaceted interventions not simply focusing on PIMs (110, 111). Future studies will discuss how the IMMENSE intervention affected PIM use.

In **Paper III,** clinical pharmacists identified MRPs by performing comprehensive medication reviews. The focus was to optimize the entire medication regime, systematically focusing on ten risk categories, including untreated indications, PIMs, and problems with adhering to medication therapy. We identified MRPs in almost every patient (94.6%), with a median of one medication discrepancy and four MRPs per patient. Hospital physicians accepted 67% of solutions to MRPs presented by pharmacists, confirming that integrating pharmacists in ward teams and face-to-face interactions with physicians is an effective way to implement recommendations from medication reviews (196). Even though the IMMENSE intervention identified and solved many MRP in the hospital, this was not enough to significantly affect health care use (**Paper IV).**

The overall aim of medication therapy is to improve patient outcomes. Thus, we want to identify and solve the MRPs (like PIMs) with the highest risk of adverse patient outcomes and where actions are needed. As for PIMs, there is no uniform definition of what constitutes an MRP, and different classification systems exist internationally (197). Consequently, the number, types and severity of MRPs presented in trials vary (197). There is no clear relationship between the MRPs identified and solved in trials and the effect of the interventions on health care use (198). This may be because MRPs differ concerning their potential for improving patient outcomes. In RCTs investigating the effect of clinical pharmacists interventions on health care use in older hospitalized patients in a Scandinavian setting, MRPs presented to physicians wary from 1.0-8.6 MRPs per patient (141, 146, 199-205). Ravn-Nielsen et al. identified only 1 MRPs per patient, but it is one of the studies with the greatest effect size on readmissions (203). There are likely other factors than MRPs reported by trials that affect if interventions are effective or not in affecting health outcomes. With

MRPs we often measure actions taken by health care personnel to optimize prescribing or monitoring of medications. Of equal importance is perhaps how an intervention affects patients' adherence to medication therapy and patients' ability to self-manage their diseases. Other process outcomes may be needed to capture this and will aid understanding of the causal mechanisms between the intervention and the outcome.

6.2 Evaluating the effect of clinical pharmacist services on health care use in older hospitalized patients

In **Paper IV,** we found that the IMMENSE intervention failed to significantly affect primary and secondary outcomes related to health care use or mortality. No significant differences between the groups were seen in subgroup analysis or in the per-protocol analysis. Many studies have investigated the impact of clinical pharmacist services on health care use in older hospitalized patients, and Table 4 summarizes the RCTs performed in Scandinavia up to 2021. Especially two recent studies, not yet included in systematic reviews and meta-analysis (Table 2), are together with the IMMENSE study likely to impact on the overall evidence of the impact of clinical pharmacist services on health care use. These are the studies by Lea et al. and Kempen et al. (146, 205).

Lea et al. randomly assigned 399 multimorbid patients admitted to a Norwegian internal medicine ward to an IMM-based intervention comparable to steps 1-4 in the IMMENSE study or standard care (146). The pharmacist-led intervention had no statistically significant effect on time until readmission or death or the number of patients with unplanned hospitalization, similar to our finding. However, unlike us, they saw a reduction in mortality, reaching significance 20 months after discharge. Although the follow-up time is longer than in comparable studies, the finding of reduced mortality in the intervention group was surprising. Systematic reviews and meta-analyses have not found clinical pharmacist services in the hospital to impact survival (81, 110, 120, 121, 124, 127, 129, 206) in line with the findings from **Paper IV**.

Several factors may explain the differences in mortality between The IMMENSE study and Lea et al.. The most important is perhaps the longer follow-up time in the trial by Lea et al.. The mortality rate at 12 months found by Lea et al. (23% vs. 29%) was higher than the IMMENSE study (19.7% vs. 19.5%) despite the IMMENSE patients being older; thus, the different inclusion criteria (age

and medication use) and case-mix of patients at the wards may contribute to the difference in results. Furthermore, their choice to perform a strictly unadjusted analysis could also have impacted their findings. The control group had a higher median age (2.7 years), more unplanned hospitalizations in the year before and a higher Charlson comorbidity index than the intervention group. Finally, the pharmacists in the study by Lea et al. all had a post-graduate master's degree in clinical pharmacy and had received standardized training in IMM, while no post-education requirements or clinical experience was required of pharmacists performing interventions in the IMMENSE study (146). While the interventions applied almost identical working procedures for medication reconciliation and the medication review, Lea et al. identified more MRPs that led to changes in medication therapy than in the IMMENSE study. The clinical implication for this is unknown, but it might imply that post-graduate training and experience should be a priority of pharmacists working in hospital wards.

The Medbridge trial by Kempen et al. is the most extensive study of clinical pharmacist services in Scandinavia. In this pragmatic cluster randomized crossover trial including 2644 patients ≥ 65 years, eight wards were randomized to standard care, a hospital-based comprehensive medication review (CMRs) or CMR plus postdischarge follow-up calls to patients (205). Like the IMMENSE study, the primary endpoint was the incidence of all-cause unplanned hospital visits (readmissions plus visits to the emergency department) within 12 months after the index admission. In the MedBridge trial, neither CMR nor CMR plus postdischarge follow-up decreased the incidence of unplanned hospital visits within 12 months compared with usual care. The incidence of hospital visits was 1.74 visits for CMR (adjusted rate ratio [RR], 1.04; CI, 0.89-1.22), 1.95 for CMR plus follow-up (adjusted RR, 1.15; CI, 0.98-1.34), and 1.63 for usual care patients. They found an unexpected increase in the incidence of ED visits for CMR plus follow-up compared with standard care. An increase in ED visits was not observed in the IMMENSE study, perhaps related to differences in the elements included in interventions (i.e., post-discharge follow-up with patients vs. health care professionals). Based on the findings in the MedBrigde trial, the authors postulate that comprehensive medication reviews perhaps should not be undertaken in hospitalized patients without adequate follow-up procedures (205). Multiple changes in medication therapy may increase complexity and create misunderstandings for the patients and GPs. The results from **Paper**

IV do not call for a similar caution, although the extensive follow-up with primary care may have been adequate to address changes.

In addition to the studies of Lea et al. and Kempen et al., eight other RCTs have investigated the effect of clinical pharmacists' interventions in hospitalized patients on health care use in Scandinavia (Table 4). Of these, Gillespie et al., Ravn-Nielsen et al., and post-hoc analysis by Gustavsson et al. found significant effects of their interventions on the primary outcome (141, 199, 203). Table 4 also shows some of the variability in study settings, interventions contents, and outcome measures between trials. All trials include complex and bundled interventions, depending on numerous factors to affect the outcome. The complexity and the diversity of the trials as well as the heterogeneity of the results, make it impossible to conclude on the effectiveness of clinical pharmacy services in a Scandinavian hospital setting. Nevertheless, the pooled results indicate that readmission may be challenging to influence despite interventions being multifaceted and including transition of care elements. The following subsections discuss some factors that would be worth considering in the design of future studies and help explain why the IMMENSE study failed to meet its primary outcome, and provide a more in-depth discussion than **Paper IV**.

Table 4 *Overview of RCT (incl cluster RCT) investigating the impact of clinical pharmacist services on health care use (primary and secondary outcomes) in older hospitalized patients (mean/median age over 65) in Scandinavia.*

AUTHOR, YEAR PUBLISHED, COUNTY	DESIGN, SETTING	PATIENT SELECTION	NUMBER RANDOMIZED (N) INCLUDED AGE [a]	INTERVENTION ELEMENTS PERFORMED BY HOSPITAL PHARMACISTS	MRP, PRESENTED (%ACCEPTED BY HOSPITAL PHYSICIANS)	PRIMARY ENDPOINT (MONTHS FOLLOW UP)	SECONDARY ENDPOINTS (MONTHS FOLLOW UP)
KEMPEN TGH ET AL. 2021(205) SWEDEN	Cluster randomized crossover design, tree-arm (1:1:1), multi-center medical wards,	>65 years	N= 2644 Median age: CG: 80 IG1: 81 IG2: 81	**IG1**: MedRec admission, MedRev, MedRec discharge **IG2**: IG1+ post-discharge phone call to patients, written medical referral to GP	2.1 (73)	😐 Incidence of unplanned hospital visits (12) **IG1:** 1.74 visits, HR 1.04 (95% CI: 0.89-1.22) **IG2:** 1.95 visits, HR 1.15 (95% CI:0.98-1.34) CG: 1.63 visits	☹ Incidence of ED visits (12) (IG2 vs. CG) 😐 Unplanned hospital admissions (12), medication-related admissions (12), GP visits (12), time to first unplanned visit (12), mortality (12), costs (12)
LEA M ET AL. 2020(146) NORWAY	RCT two-arm (1:1), single-center, one internal medicine ward	>18 years > 4 regular drugs from minimum 2 ATC-groups	N = 399 Median age: CG: 80.7 IG: 78.0	IMM based. MedRec admission, MedRev during the inpatient stay, MedRec discharge with written recommendations, and patient information.	8.6 (62)	😐 Time to first readmission or death (12). 116 vs 184 days HR 0.82 95% CI: 0.64-1.04	☺ Overall survival (20) 😐 Number of unplanned hospitalizations per patient (12)
BONNERUP DK ET AL. 2020(202) DENMARK	RCT two-arm (1:1), single-center, acute admission unit	>18 years	N= 375 Mean age: CG: 72.8 IG: 72.4	MedRev performed by a clinical pharmacist or pharmacologist based on a risk score algorithm. 64/187 in IG receiving MedRev.	2.8 (65)	😐 Number of prescribing errors (0) 0.11 vs 0.13 per drug p= 0.65	😐 ED-visits (3), GP-visits (3), time to first ED-visit (3), mortality (3), HRQol (3).

GRAABÆK T. ET AL. 2019(204) DENMARK	RCT, tree-arm (1:1:1), single-center, acute admission unit	>65 years Medical patient	N= 600 Median age: CG: 75 IG1: 74 IG2: 74	**IG1:** MedRec and MedRev at admission **IG2**: IG1 + MedRev at inpatient stay, patient counseling, and medication report at discharge	2.3 (57)	😐 Medication-related readmissions (1) IG1: 4.5%, IG2: 2.5% CG: 6.5% p= 0.33	😐 LOS (0), mortality (6), number of readmissions (6), ED visits (6), GP visits (6)
RAVN-NIELSEN LV ET AL. 2018(203) DENMARK	RCT, tree-arm (1:1:1), multi-center, acute admission wards	>18 years > 5 prescribed drugs daily	N = 1499 Median age: CG:73 IG1:72 IG2: 71	**IG1:** MedRev **IG2:** IG1 + MedRec discharge, motivational interview with patients at discharge, at one month and six months post-discharge, post-discharge follow-up primary care, written and calls to GPs.	1.0 (61)	🙂 The number of patients readmitted or ED-visit (6). IG2 vs CG 40.5% vs 48.8% HR 0.77 95% CI: 0.64-0.93 IG1 vs CG: not significant.	😐 Medication-related readmission (6), mortality (6)
LISBY M ET AL. 2018(200) DENMARK	RCT, two arm (1:1), orthopedic ward	>65 years > 4 drugs	N = 108 Mean age CG: 80.5 IG: 80.4	MedRec and MedRev at admission in collaboration with clinical pharmacologist.	4.2 (18)	☹ Time to first med unplanned contact with a physician (3). IG vs CG 14.9 days (95% CI: 8.9-21.0) vs 27.3 days (95% CI, 18.9-35.7) p = 0.05	🙂 Number and time to first ED visit (3) 😐 Readmission (3), Unplanned GP visits (3), Mortality (3), LOS, HRQol (3)
NIELSEN TRH ET AL. 2017(207) DENMARK	RCT Two-arm (1:1), multi-center, acute medical wards.	>18 years > 4 drugs daily, incl. OTC	N = 404 Mean age: CG[b]:72.1 IG: 74.1	MedRec and MedRev at admission, not during inpatient stay.	Not reported	😐 Proportions of patients with Inpatient harm identified using triggers. 11% vs 13% p = 0.52	😐 Median LOS (0), readmission rate (12), mortality (12)

GUSTAFSSON M ET AL. 2017(199) SWEDEN	RCT Two-arm (1:1), multi-center, acute internal medicine wards and orthopedic ward	>65 years Dementia or cognitive impairment	N= 460 Mean age:	MedRev admission, MedRev during inpatient stay.	1.4 (74)	😐 Risk for drug-related hospital readmission (6) 18.9% vs 23% HR= 0.80 95% CI= 0.53-1.21)	☺ Risk for drug-related hospital readmissions (1) 😐 Readmission (6), time to drug-related hospitalization (6), mortality (6)
LISBY M ET AL. 2010(201) DENMARK	RCT Two-arm (1:1), single-center, acute internal medicine ward	>70 years ≥1 drug daily	N= 100 Mean age: CG: 78.2 IG: 80.2	MedRec and MedRev at admission in collaboration with clinical pharmacologist.	3.7 (39)	😐 Length of in-hospital stay in hours (0) 239.9 vs 238.6 log-rank test 0.47	😐 Readmission (3), ED visits (3), health-care visits (3), time to first readmission (3), mortality (3)
GILLESPIE U ET AL. 2009(141) SWEDEN	RCT Two-arm (1:1), single-center, acute internal medicine wards	>80 years	N = 400 Mean age: CG: 87.1 IG: 86.4	MedRec admission, MedRev during inpatient stay, patient counseling (stay and discharge), MedRec discharge with written recommendations to GP, and Post-discharge phone calls to patients after two months.	2.6 (69)	☺ Frequency of hospital visits (ED-visit+ Readmissions) (12) 266 vs 316 estimate 0.84 (95% CI: 0.72-0.99)	☺ ED visits (12), Drug-related readmissions (12), Cost of hospital care (12) 😐 Readmissions (12), mortality (12)

Abbreviations: CI; confidence interval, CG; control group, ED; Emergency department, HR; Hazard rate, HRQoL; Health-related quality of life, IG; intervention group, LOS; length of stay, MedRec; medication reconciliation, MedRev: medication review, OTC; over the counter medicines, RCT; randomized controlled trial. a) age of patients included in analysis. b) study also had a historical control group not included in this table

6.2.1 Effects of standard care

In studies with health care interventions, it is common to compare the intervention to standard care. Standard care regarding medication management will vary depending on the national health systems and between hospitals and wards, resulting in similar interventions giving different results in different care settings. Standard care will also change over time. In Norway, several initiatives have been taken in the last ten years that may enhance the quality of medication use both in hospitals and in primary care. The National Patient Safety Program “In Safe Hands” includes work packages on medication reconciliation and medication review in-home care services and nursing homes (208). In 2012 a national guidance on medication review was published by the Norwegian Directorate of Health, and GPs were obligated and paid to perform medication reviews on patients using more than four medications (43, 209). Also, developments in electronic communication, like electronic discharge summaries, electronic medication lists from primary care at admissions and lastly, the introduction of national summary care records, including medications dispensed in the last three years, may have improved the transfer of medical information (210). Improvements in standard care over time may explain why findings in studies performed over ten years ago could not be replicated today. As an example, the results by Gillespie et al., showing a 16% reduction in readmission and ED visits, were not reproduced by Kempen et al. 12 years later in a similar setting in Sweden (141, 205). The conflicting results between these two Swedish studies may also result from intervention elements, like medication reconciliation and medication review, being introduced into standard care since 2005 and improving medication management in standard care (205).

In **Paper IV**, patients were mainly recruited (77%) from a specialized geriatric ward where knowledge and interest in geriatric pharmacotherapy generally are high. Standard care in geriatric wards may be more proactive in optimizing patients' medications than in regular medical wards (86), but geriatric hospital stay was not associated with reduced 30-day readmission rates compared to other medical wards in a Norwegian observational study (211). While clinical pharmacist services have been shown to increase medication appropriateness in a geriatric ward setting (212), RCTs investigating effects on health care use in this setting are limited. However, in **Paper IV** we found that the effect of the intervention was independent of the study ward.

6.2.2 Intervention content

When different intervention elements are bundled together, it is impossible to separate the elements that are more or less important to the overall effects. The IMMENSE intervention was comprehensive, aiming to reduce medication errors at care transitions, optimize the medication regime and improve communication with patients and primary care. Still, there may be additional intervention elements that could have been included. Some of the studies finding effects of clinical pharmacist interventions on health care use have included more patient-focused interventions like motivational interview techniques and phone calls to patients post-discharge (141, 203). Patients not adhering to their medication therapy is an important cause of medication-related readmissions and ED visits (34, 213). Ravn-Nielsen et al. found an enhanced pharmacist-led intervention in hospitals, including motivational interviews and post-discharge follow-up with patients and primary care, to significantly reduce the risk of hospital readmission after six months (214). Post-discharge follow-up calls with patients, focusing on the patient's motivation and ability to adhere to treatment recommendations, were found to further reduce readmissions rates compared to the standard IMM in a quasi-experimental study from North Ireland (215). However, the patient population in the study by Ravn-Nielsen et al. had a median age of ten years younger than the IMMENSE study population. Almost 90% were handling medications themselves were, as only 36% in IMMENSE study. It seems reasonable to expect the effects of motivational interviewing to be lower in a population with cognitive challenges like in **Paper IV**. Intervention content must be tailored to the needs of the patient population. Thus, the IMMENSE intervention prioritized communication of medication issues with health personnel post-discharge. Nevertheless, motivational interviewing techniques and post-discharge follow-up with patients should be considered as intervention elements in future interventions.

6.2.3 Pharmacist role and integration in health care teams

Since pharmacists are the primary catalyst of change in the IMMENSE study, integration into the ward team is important. Adding a pharmacist does not automatically integrate the new work methods into the established interdisciplinary team. The success of clinical pharmacist interventions is especially dependent on good cooperation with the prescribing physician. Qualitative research has identified both facilitators and barriers for ward pharmacists' interventions to be successfully implemented (216-219). For successful implementation, some key factors are

the pharmacist's personal and clinical competencies, the need for clearly defined roles and responsibilities within the team, and personal contact to establish mutual trust and good communication (216, 217, 219). As the working methods adopted in the IMMENSE study were new to both the wards and the pharmacist, effective collaboration building trust between professions might have taken some time to establish (218, 220). In **Paper III,** we found that 67% of the pharmacist recommendations to solve MRP were accepted by physicians, suggesting that the pharmacists and their knowledge were respected. However, one or more steps of the intervention were missed for many patients. This may be because not all intervention steps were well integrated into the working routine, perhaps because only some ward patients were allocated to the intervention. Ensuring that interventions are properly implemented is imperative for future interventions and is elaborated on further in the methodological discussion on evaluations of complex interventions

6.2.4 Choice of outcomes and outcome evaluation

One important decision when designing a trial is the choice of its primary outcome. Notably, the selected outcome must be modifiable by the intervention and considered relevant to stakeholders and patients (221). The primary outcome is used to determine the main effect of the intervention, while it often is necessary to include a variety of secondary outcomes to evaluate additional effects of the interventions and address the interest of different stakeholders (222). There is no consensus on which outcomes to select when evaluating the effect of clinical pharmacist services, making it hard to compare results across studies (158). A core outcome set is ‘an agreed standardized collection of outcomes that should be measured and reported for a specific area of health’ (223). Core outcome sets for evaluating clinical pharmacist services in a hospital setting have not been developed (223). However, core outcome sets exist for clinical trials of medication reviews in multimorbid older patients with polypharmacy (224) and medication interventions for different patient groups in primary care (225, 226). In these outcomes sets, hospitalizations or ED visits are not included as prioritized outcomes (224-226). It has been argued that preventable ADR and patients reported outcomes (like health-related quality of life) might be better outcomes of clinical pharmacist interventions as interventions often seek to reduce medication-related risks and improve the benefits of medication use (222). Thus, these outcomes could be more susceptible to change by the intervention than a multifactorial outcome like readmissions.

The choice of the primary outcome also has implications for the power calculations. In the IMMENSE study, we anticipated that the interventions would reduce the occurrence of emergency medical visits in the year after discharge. We based our power calculation on the effects of a similar intervention in a different study setting (141). Many elements may have implications for the power calculation; i) the prevalence of medication-related hospital visits in the study population, ii) how many of the medication-related visits are preventable, and iii) how many of these could possibly be prevented by an intervention like the IMMENSE intervention. The IMMENSE study was powered to find a 16% reduction in unplanned readmission and ED visits and had sufficient power to do so given the primary outcome's event rates. In retrospect, reductions in this magnitude may have been over-optimistic. First, even though up to 20% of readmissions and ED visits (likely more in frail older adults (169, 213)) are judged to be possibly medication-related (28, 50), causes of readmissions are often multifactorial, and the actual contributions of medication are often unknown. Second, while a large proportion of these medication-related hospitalizations are assumed to be preventable, the literature does not give a reliable estimate (28, 32). Like stated in 2018 by El Morabet et al. in their systematic review '*because only a limited number of studies have focused on preventability, an accurate estimate of the proportion of preventable drug-related readmission is impossible'* (28). ADRs are the most frequent cause of medication-related readmissions (28), but not all ADRs are easily preventable, i.e., bleedings events occurring with anticoagulants, anticoagulants being the medication group implicated in most medication-related readmission (28, 191). More evidence is needed to guide power calculations of medication optimization studies making sure studies are power to identify realistic yet meaningful effects.

Timing and length of follow-up of the selected outcomes are also significant factors in the design and interpretation of trial results. We evaluated the primary outcome a year after discharge. The impact of optimization of medications during a single point of time when the patients are experiencing an acute illness may be insufficient to have an impact on events a whole year after the index hospital stay. Approximately 50% of the study population had subsequent hospitalizations in the year after discharge and, as shown in **Paper I,** are likely to have new medications added. It would be expected that the effect of the intervention will taper off when no new intervention is provided (227, 228). Selecting a timeframe for evaluating effects depends on the effects' mechanisms under evaluation. Supposed the effect of the intervention is thought to be

primarily driven by the prevention of ADR, a shorter time frame than one year would be reasonable. If, on the other hand, the effect is driven by adding, optimizing, or increasing adherence to prophylactic medications that prevent long-term events, it may take a longer time to see the results, as suggested in the study by Lea et al., where an effect on mortality was seen after 20 months (146). Investigating the long-term and short-term effects of the outcomes seems reasonable, as we did in **Paper IV**.

6.2.5 Patient selection

Performing an intervention like the IMMENSE study is quite time-consuming (229). Even in the context of a randomized control trial, **Paper III** identified challenges in providing all elements of the intervention to all patients. With a high turnover of patients and limited pharmacist resources, it is probably impossible to provide the intervention in the IMMENSE study to all patients in a ward. Aside from age, we did not apply inclusion criteria to select patients more likely to experience MRPs, like patients with polypharmacy or patients with high-risk medications, being inclusion criteria's in some trials (133, 146, 203). Although the subgroup analysis did not find the effects on the primary outcome to change according to prespecified patient groups (like numbers of medications), finding the patients who might benefit from a clinical pharmacist intervention is an important research area. Many studies have tried to find tools to identify patients with increased risk of medication errors, ADE or medication-related admissions, implying that those with increased risk are the ones with the most to gain from a medication-related intervention, like a medication review (230). Both biomarkers, the number of medications, PIMs, history of ADE, and specific medications giving risk scores have been used (202, 231, 232). However, predicting the risk of clinically relevant MRPs (present and future) from the complex interplay of clinical, medication-related and social variables is challenging (233). The optimal way to select patients who might benefit the most from a clinical pharmacist intervention remains to be established; a recent review found no tools that met the four stages required to create a quality risk model: development, validation, impact and implementation (230).

6.3 Medication optimization and the role of the pharmacist – reflections from the results of this thesis

A final conclusion of the IMMENSE study's potential effects remains to be established as the impact on medication-related readmissions, health-related quality of life and medication appropriateness are yet to be evaluated. However, we can conclude that in the IMMENSE study population, the intervention has no significant effect on the rate of emergency medical visits. This, together with recent studies on medication optimization interventions in hospitals failing to meet their primary outcomes, could question if a hospitalization is the ideal setting for medication optimization (180, 181, 205). The patients often only spend a short time in hospitals compared to time under the responsibility of primary care. In Norway, the Coordination reform in 2012 placed a greater responsibility on the municipalities and primary care for providing health services, leading to a further reduction in hospital bed-days (234, 235).

Optimizing medication regimes is a continuous effort, especially in older adults where frailty and limited functional reserve may require frequent changes in medication therapy. It is often advisable to abstain from too many simultaneous alterations in a medication regime to enable monitoring of the effects and side effects of changes (236). Introducing pharmacists in care settings where patients could be followed over time, like home-care services, GP practices or nursing homes, are promising arenas for the use of pharmacist skills in interdisciplinary collaboration (237-239). In other countries like the UK, USA, and Australia, the pharmacist is more involved in primary care follow up, both from pharmacies, in primary care centers, and conducting home medicines reviews. Some municipalities in Norway have included pharmacists in their primary care teams serving nursing homes and home care services (240). Other municipalities have joined forces with the local hospital to form person-centered care teams, working in the intercept between primary and secondary, to care for multimorbid older adults. Clinical pharmacists are part of these teams where the patient-centered, integrated and proactive way of caring for older adults are associated with reductions in emergency admission (241). However, introducing pharmacists in new care settings should be accompanied by research to evaluate the cost-benefit compared to other measures to improve medication-related outcomes.

There will be an increased demand for health care personnel in the coming years (242). The increased demand could facilitate changes in traditional professional roles, where specially trained pharmacists or nurses could perform some tasks traditionally performed by physicians. In Norway, pharmacists do not have prescribing permissions, and all changes in patients' medications need to be accepted and implemented by a physician. In the IMMENSE study, all MRPs that involved modifying the medication regime had to be presented to a physician to be changed, even those that involved obvious errors in the medication list. This may be challenging, as it demands time from the physician for discussion. Other countries have expanded the role of clinical pharmacists in the interdisciplinary team, allowing the pharmacist to become independent prescribers (243). Pharmacist prescribing may provide opportunities for effective use of pharmacist skills and facilitate better inter-professional collaboration around medication optimization. However, the evidence on pharmacist prescribing in a hospital setting is limited (243), and future research may expand the role of the pharmacist in medication optimization for older adults.

While pharmacists have valuable knowledge and skills to aid in the complex task of medication optimization in older adults, this is only one approach to optimize medication use. Increased cooperation between geriatricians and GPs may also be a way forward, as shown in a cluster-randomized Norwegian trial from 2020. In this trial, 70 Norwegian GP practices were randomized to a three-step intervention, including a clinical geriatric assessment with a medication review, a meeting between the geriatrician and the GP, and a clinical follow-up. Among 174 home-dwelling patients ≥70 with ≥ 7 regular medications administered by home-care services, the intervention had a positive effect on health-related quality of life at 16 weeks (244).

6.4 Discussion of methodology

The choices made in designing the trials, selecting the participants, and assessing the outcomes affect the validity and generalizability of study findings. Internal validity in this context means how well we have measured what we intended to measure and whether the conclusions are representative of the study population (245). External validity implies that the study results can be generalized to individuals beyond the study population (245). Below, methodological concerns and limitations for each paper are addressed, which adds to the discussions in the individual papers. Subsequently, some perspective on conducting future complex health interventions is provided.

6.4.1 Paper I

In this paper, we used the Norwegian prescription database (NorPD) to investigate the impact of a geriatric hospital stay on medication use. We assumed that all medications (ATC-codes) dispensed in a fixed time window of 120 days before and after hospitalization were used by the patients and used this measure to describe changes in medication use and PIM use. Using a fixed time window approach to identify active medications in prescription databases has been found to have variable sensitivity (48%-93%) but high specificity (82%-100%) compared to other sources of active medication lists (153). In NorPD, a fixed time window was found to be better than other approaches like legend-time when defining the current use of coronary heart disease medications (246). Still, the results are sensitive to the choice of the time window, and the sensitivity may be lower for as-needed medications (153, 246). To investigate the impact of the time window, we calculated medication use with a time window of 90 days or 150 days, but the findings regarding changes in medication use were the same.

Although we measured the medications dispensed before and after a hospital stay, our data does not inform us whether changes originate from the geriatric hospital stay or from visiting the GP. Medication changes suggested by hospital physicians in discharge papers are not always implemented in primary care, and medication regimes in older patients in primary care frequently change regardless of hospital visits (156, 247). Also, the increase in medication use may be temporary. A register-based study from England investigating the impact of emergency hospitalization on prescribing in a general population found that overall prescribing increased after discharge but prescribing fell to below pre- hospital levels within six months (248).

To measure changes in PIM use, we selected two explicit PIM-lists, the NORGEP-NH list and the EU(7)-PIM list, suitable for application with registry data and on Scandinavian patients. The two lists came to different conclusions regarding the association of geriatric hospital stay and PIM use post-discharge, confirming that the findings are sensitive to the PIM-lists applied. Both the NORGEP-NH list and the EU(7)-PIM list have been evaluated for face and content validity through a Delphi process (68, 75). Face validity relates to relevance, credibility, and acceptability, while content validity implies that the criteria should be evidence-based and according to guidelines (249). The NORGEP-NH list was constructed to be used in nursing homes, and its content validity has not been established in an older hospitalized population. Consequently, we decided to exclude part C of the NORGEP-NH list as these deprescribing criteria might be less relevant in our population. Furthermore, we could not apply all of the criteria in the two PIM lists due to limitations in the dataset and had to make some adjustments to the criteria (available in supplement material to paper II). This means that our findings on PIM prevalence are not directly comparable to other studies reporting using the same PIM lists.

To be able to measure changes in medication and PIM use after a hospital stay, we had to exclude 2/3 of the patients with a geriatric hospital stay in 2013. This will reduce the generalizability of the findings to the general geriatric population in Norway. When excluding patients, we may have introduced a selection bias, where the population we have selected may differ from the average geriatric patient in Norway.

6.4.2 Paper II and IV

Internal validity

A randomized controlled trial is considered the gold standard when assessing the effect of an intervention and has high internal validity. Nevertheless, different forms of biases may have impacted the study findings. The most important probably is bias due to contamination, as the same health care professional team treated intervention and control patients. Ward physicians may have learned from the work methods of the pharmacists and adapted this to control patients as well, reducing the difference between groups. The pharmacist frequently addressed medication-related

topics in ward meetings, and this could have increased the overall awareness of medications issues in the wards. Cluster randomization could have been performed to reduce contamination, but cluster randomization requires a significantly larger sample size (more wards and patients) and is susceptible to recruitment bias (205, 250). Conducting a cluster-randomized trial was impossible within the funding and time frame of the IMMENSE study. Contamination bias may also have occurred after discharge as 10% of patients in both groups were referred to a novel person-centered, integrated care project for the multi-morbid elderly at discharge. The person-centered care team also included a pharmacist working by IMM procedures. The results of this project indicate an effect on readmissions (high-level emergency care) (241). This may have biased the IMMENSE study towards no effect, but sensitivity analysis, removing patients known to be included in the team at discharge, did not affect the results.

When health care personnel and patients are part of a study that investigates medication optimization, they may modify their behavior knowing that they are observed. This is called the Hawthorne effect (251). Physicians may write better medication reports in discharge letters if being aware that this is compared between groups. The Hawthorne effect could, like contamination bias, lead to less differences between groups. This bias is hard to avoid in a study setting like the IMMENSE study.

The risk of selection bias introduced by pharmacists foreseeing the allocation sequence was low. The sequence generation and allocation of patients were performed by internet service provided by a third party with blocks of unknown and variable size, so the pharmacists could not predict group allocation. Workload with study administrating tasks and performing the intervention restricted the ability to include more than 1-2 patients a day (229). When several patients were available for inclusion, there could be an opportunity for the pharmacists to prioritize asking patients in whom they would like to work, and were able to consent by themselves (faster and easier to get consent) though including a population different from the general population in the wards. To prevent this, the study pharmacists had to approach patients in reverse order of admittance to the wards (last admitted asked first). Randomizing the order in which patients were asked for consent could also be an option, but as including patients early in the stay was considered favorable, asking for consent in reverse order of admittance seemed reasonable.

Blinding participants and ward personnel to group allocation were not deemed feasible given the nature of the intervention. The lack of blinding may have introduced bias through intervention patients being treated differently from control patients in areas unrelated to the intervention itself. For example, physicians may pay less attention to medication-related issues knowing that the pharmacist was involved. A strength is that we blinded all steps that were possible to blind. The investigator performing the primary analyses and the study nurse performing the health-related quality of life measurements were not aware of group allocation. Regarding outcome assessment, the outcomes presented in **Paper IV** are collected from health registers and consist of health care episodes; consequently, they are less susceptible to biases resulting from lack of blinding than, i.e., patient-reported outcomes like the EQ-5D measures to be presented in later studies.

In order to preserve the benefit of randomization that allows interference about the cause of group differences, all randomized participants should be included in the analysis in the group they were allocated. This is called an intention to treat (ITT) analysis (252). It was stated in **Paper II** that the analysis would be an ITT analysis, but in **Paper IV**, we excluded patients with missing outcome data (death during index hospital stay and patients withdrawing informed consent). We called this a modified ITT analysis. Any deviation from the ITT principle may introduce bias into the trial (253). An option to adhere to the ITT principle could be to impute the missing data for patients withdrawing informed consent (252). We could not register trial data on patients without informed consent, and consequently, we could not perform ITT sensitivity analysis on imputed outcome data to investigate the possibility of bias. The practice of randomizing patients after oral consent from the next of kin should not have been allowed as the next of kin did not return the written informed consent in nine cases, more in the control group (6 patients) than in the intervention group (3 patients). Also, patients withdrawing their informed consent by phone during data collection could have been asked if they allowed us to keep anonymized registered data, giving us the possibility to impute missing data.

External validity

Many issues in the design of the IMMENSE study may potentially affect external validity, such as the setting of the trial, selection of patients, characteristics of randomized patients, and differences between the trial protocol and routine practice (254). In **Paper IV,** we report both settings, baseline

clinical characteristics of included patients and medication handling in standard care, factors that may help clinicians/stakeholders decide if the results are transferable to their setting.

The broad inclusion criteria (age ≥ 70 years, acute admission, and written informed consent) enhanced the external validity of the trial. However, there were exclusion criteria (related to pharmacist capacity) that hindered us in including many patients admitted to the study wards. The most frequent exclusion criteria were patients admitted to study wards for more than 72 hours before being assessed for eligibility. Also, approximately 20% of patients/next of kind asked for informed consent refused to participate. Patients invited to participate but refuse to do so may be systematically different from those accepting. However, the age and sex distribution of patients refusing participation did not differ from those accepting (data not shown). We did not collect information on the reason why patients refused to participate, so how this may have impacted the external validity is hard to tell.

Another issue that may influence the external validity is the feasibility of the intervention. The intervention as performed in the IMMENSE study was time-consuming, with quite rigid procedures for conducting medication reconciliation, medication review and follow-up at discharge. A time and motion study observed on average 3.5 hours spent performing clinical tasks per intervention patient (229), but may not reflect a real clinical setting as the time and motion study was conducted in a period with limited turnover at the ward and few available patients. The workload associated with following the IMM procedures has also made hospital pharmacies in Norway question the feasibility of the complete IMM model (255). Several pharmacies have modified their work methods to fit better with electronic tools, and with the limited time most clinical pharmacists have on wards, full-time clinical positions still being infrequent (255). In addition to the IMM model, the IMMENSE intervention included a phone call to the GP for patients at discharge. As described in **Paper III,** it could take time to reach the GPs. Calling the GP at discharge for every patient with unsolved MRPs is probably not feasible, and a Danish study concludes that it should be reserved for complex older inpatients (214).

Statistical considerations (Paper II and IV)

Randomization is no guarantee that baseline characteristics between groups will be identical (256). The groups are unequal with respect to some factors that may be related to the outcome; there are differences in sex, numbers of regular medicines, and comorbidity. However, we did not test for statistical differences in baseline characteristics between groups as any difference is inherently random by design (257). We could have stratified the randomization for other variables than the study site, like sex, but decided in the design phase to keep the numbers of strata low. Adjusting for differences in baseline covariates observed post hoc is controversial, and covariates to be included in the analysis should be specified in advance (257). The European medicines agency advises against adjusting for baseline imbalance observed post hoc in the primary analysis (164). As a consequence, we only included two covariates in the adjusted analysis. First, covariates used to stratify the randomization, in our case, study site, should be included in the analysis. Second, when baseline measurements of the primary outcome are known, including this covariate in the analysis is also recommended (164). Consequently, we adjusted the analysis with the number of emergency medical visits 365 days prior to the index hospital stay, as this likely is the covariate with the strongest relationship to the outcome. Adjustments for strong predictors of an outcome give a more relevant effect estimate (258). In Paper IV, adjustments led to smaller differences between groups suggesting that some of the emergency medical visits in the control group could be attributed to baseline imbalances. We decided not to perform sensitivity analysis, including other covariates in the analysis, as this was not a part of the statistical analysis plan, and could be regarded as “vibration of effects” (259).

6.4.3 Paper III

Process outcomes of the IMMENSE study were captured as medication discrepancies at admission and MRPs, and we also registered proposed solutions to MRPs by the pharmacist and if the solution were accepted. There is no consensus on the optimal way to classify or define an MRP (197). We decided to use a Norwegian classification system developed by Ruths et al. as this has been validated in Norway and was familiar to the study pharmacists (157). This system was developed by a modified Delphi technique to be useful in research and different clinical practice settings and divides MRPs into six main categories and 12 subcategories. It was validated with 26 case reports

classified by a panel of 36 reviewers (pharmacists and physicians) and achieved an average agreement of 70% on the MPR category (157). The choice to use this classification system will impact the type of MRPs identified (197). A limitation in **Paper III** is that we have not performed reliability testing to confirm that study pharmacists classified similar MRP or discrepancies in the same way. We prioritized continuously classifying MRPs, relying on the clinical judgment of the individual pharmacist doing the intervention to describe the problems, suggested solutions and results. To aid reliability in classifying MRPs between pharmacists, pharmacists were encouraged to note cases that were hard to classify. These cases were discussed in study meetings with the aim of reaching a consensus. The classification system by Ruths et al. does not separate between actual (MRP has manifested itself, i.e., adverse drug reactions) or potential MRPs (MRP could result in an actual problem if left unchanged) (157). We have not evaluated if the MRPs identified by the pharmacist and the solutions proposed are likely to convey meaningful effects to the patients. Assessing the importance of the MRPs identified could have been done with a multi-professional expert panel. A validated tool for evaluating the significance and impact MRPs and the proposed solutions should have been applied (260). Doing so would have aided understanding of the lack of effect on health care use.

Regarding MRPs, it is also worth reflecting on the fact that the MRPs are identified from the pharmacists/health care teams' perspective, although the IMMENSE intervention aimed to be patient-focused. Existing taxonomies for categorizing MRPs may not address MRPs related to fear, communication and social and emotional impacts of medication use, found to be important MRPs from the perspective of older adults (261).

6.4.4 Developing and evaluating complex health care interventions

Complex interventions can be defined as interventions that comprise multiple interacting components (262). Elements that further increase the complexity are many, e.g., the difficulty in implementation and delivery of the intervention, the number of interaction components in the intervention, the number of organizational levels targeted, and the number and variability of outcomes (262-264). The IMMENSE intervention includes all these elements of complexity, with the five interventions steps exerting their potential effects through different mechanisms. The IMMENSE intervention has some components that directly affect prescribing (via communication

with physicians), like identifying and preventing PIMs in the medication review. Other elements like patient counseling work through psycho-social mechanisms in the individual patients, creating knowledge and changing medication behavior. Finally, it has components influencing the organizational structure, like the system of communication with primary care (265). In addition, optimizing medication therapy in older adults is inherently complex and multifactorial, and a change in medication therapy may have unpredictable effects on patients outcomes.

To be able to design and properly evaluate complex interventions in health care, frameworks have been developed, like the UK medical research council's guidance on developing and evaluating complex interventions (264, 266). Recommendations given by such frameworks could have been adopted in the IMMENSE study to strengthen the intervention and the ability to explain findings; some examples are provided below.

Intervention development: We did not use a theory-based approach to underpin intervention development and understand the likely change processes (267). For example, the Theoretical Domains Framework could have been applied to better understand and characterize the domains of behavior that the IMMENSE intervention should be targeting (267, 268). Developing a Logic model where the causal assumptions underlying the interventions are presented would also have been helpful, given an explicit overview of what the intervention is and how it is expected to work (269). Furthermore, no patient representative was involved in the design and planning of the IMMENSE study. Patient and public involvement could have helped us select patient-relevant outcomes, design a more patient-focused intervention, and improve the written study material used to recruit patients (270).

Feasibility study: Before entering into the main trial, a feasibility study could have provided valuable information on improving the design of the study, like identifying initiatives to improve recruitment and reduce the time spent on data collection and handling (266). A feasibility study could also have helpt improve the intervention, adapting the procedures to the context in the two wards and identifying measures to increase fidelity in the main trial (271).

Process evaluation: While a randomized controlled trial is considered the best study design for identifying causal relationships, it will often not provide information on why a complex

multicomponent intervention worked, making it difficult to adopt in other settings/contexts (271). In retrospect, the IMMENSE study should have been accompanied by a more comprehensive process evaluation alongside the trial (262). The UK medical research council states that a '*process evaluation nested inside a trial can be used to assess fidelity and quality of implementation, clarify causal mechanisms, and identify contextual factors associated with variation in outcomes'* (264). A better process evaluation could have provided information on how well the intervention was delivered in the trial (i.e., did an intervention fail because it was inherently ineffective or not delivered correctly) (262). We could also have better understood how the study context affected the results and give us a better foundation to evaluate the generalizability of the findings (262). In **Paper III,** we measure which patient received which element of the intervention, but not the quality of the intervention delivered, nor how patients, health care workers or pharmacists perceived the intervention. However, the research team evaluated how the study pharmacists spent their time in the IMMENSE study, providing estimates for use in economic evaluations, showing that only about half of their time was spent directly on clinical work (229).

If we were to plan a new process evaluation of the IMMENSE study, we would need to capture both the quality and quantity of the intervention delivered. To assist the implementation of the intervention on a broad scale, it is also of interest to investigate moderators influencing the degree of fidelity achieved (272). Examples of moderators influencing fidelity can be participant responsiveness, comprehensiveness of policy description, strategies to facilitate implementation, recruitment, and context (273). We would need qualitative and quantitative methods to capture this full picture of intervention fidelity (262). The process evaluation should measure the quality and sufficiency of training of study pharmacists, the completeness of intervention description, monitoring of how the intervention was delivered (observation, interviews, review of pharmacist notes), and investigate adoptions of intervention steps to the local context by the pharmacists. We would use interviews to find barriers and enablers to the implementation of the intervention.

7 Future research and perspectives

In future research, we will investigate how the IMMENSE study impacted the secondary outcomes defined in **Paper II** but not presented in **Paper IV.** This will enable a full analysis of the potential effects of the intervention. A health economic evaluation based on the health-related quality of life measurements assessed by the EQ-5D tool is underway. We will also investigate how the intervention affected medication use by evaluating its impact on potentially inappropriate prescribing from admission to discharge. We have collected information on medication use from both NorPD and GPs/Nursing homes in the year after discharge, enabling us to investigate how changes in medication therapy were followed in primary care. We also plan to evaluate the effect of the intervention on medication related-readmissions.

The optimal medication therapy for a patient is unknown and continuously changing with disease progression. Also, goals of therapy change towards the end of life, requiring reassessment of medication regimes. Suboptimal medication therapy in older adults is an ongoing issue, which demands continuous and coordinated efforts from all levels of healthcare directed at the causes of MRPs. Both identification and prevention of PIMs in older adults and clinical pharmacist services in interdisciplinary collaboration have the potential to contribute to medication optimization, but how to measure meaningful effects of interventions that are generalizable to a broader population is indeed challenging.

Future studies should acknowledge that medication optimization interventions are inherently complex and incorporate research methods evaluating complex health interventions both in the design and performance of the trial (266, 271). Conducting process evaluations alongside future trials are highly recommended (262). To move the field of research on medication optimization for older adults further, researchers need to agree on common terminologies, outcome measures, and interventions components. However, interventions need to be adapted to the local context to be effective. Further studies should be methodologically rigorous and powered to find effects on outcomes that are meaningful to both patients and stakeholders. Emphasis should be put on including user representatives in the planning and monitoring studies. More patient-focused

interventions and closer collaboration with primary care and patients to sustain the changes from the interventions might be worth investigating in future studies.

To guide medication optimization, we need more evidence concerning the effects and safety of medications, especially in multimorbid frail older patients (274). More evidence would enable us to focus our efforts on the medications that cause the most harm, limiting some of the variability between PIM lists (174). Future developments in personalized medicine, like pharmacogenetic testing, could enable better tailoring of medications to individual patients (275), providing new opportunities for medication optimization.

In a Norwegian setting, clinical pharmacist services are continuously being introduced into standard hospital care, yet studies investigating effects on patient outcomes are few. **Paper IV** and the RCT performed by **Lea et al.** show that a reduction in readmissions might not be an effect that should be anticipated for IMM-based pharmacist services in settings similar to these studies (146). This does not necessarily mean that clinical pharmacist services are without value to the patients and the health care system. Pharmacist's services in Norway contribute to improving the quality of care by reducing medication discrepancies at care transitions, identifying and solving MRPs, and counseling patients on medication use (52, 53, 146, 276). The findings from Lea et al. of reduced mortality after 20 months in multimorbid patients suggest high-value effects are possible in the right study context. More evidence is needed to conclude on how clinical pharmacists' services should be provided, in what setting, and to which patients. A full evaluation of the IMMENSE study will hopefully provide some new answers.

8 Conclusions

This thesis provides knowledge on PIM use in hospitalized older patients and has investigated if clinical pharmacists' services in an interdisciplinary setting can contribute to medication optimization and improve patient outcomes in older hospitalized patients.

Our findings demonstrate that PIMs are frequent in older hospitalized patients and were not reduced post-discharge in a geriatric patient group. Including clinical pharmacist services into wards teams caring for older adults may be one way to optimize prescribing by solving MRPs. Still, we could not find that a five-step IMM based intervention, including enhanced communication with primary care, significantly reduced the rate of emergency medical visits in the year after discharge. There is a need for further studies to identify interventions that optimize medication use and simultaneously produce meaningful improvements in patient outcomes. More patient-focused interventions, and interventions that follow patients over time may be considered.

Future studies of similar complex interventions should have a preplanned process evaluation alongside the trial to help understand why the intervention failed or succeeded in affecting the outcomes, enabling better evaluations of the generalizability of the findings.

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Paper I

Johansen et al. BMC Geriatrics (2020) 20:190
https://doi.org/10.1186/s12877-020-01585-w

BMC Geriatrics

RESEARCH ARTICLE Open Access

The impact of hospitalisation to geriatric wards on the use of medications and potentially inappropriate medications - a health register study

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Abstract

Background: The use of potentially inappropriate medications (PIMs) are associated with negative health effects for older adults. The purpose of this study was to apply national register data to investigate the impact of hospitalisation to geriatric wards in Norway on the use of medications and PIMs, and to compare two explicit PIM identification tools.

Methods: We included 715 patients ≥65 years (mean 82.5, SD = 7.8) admitted to Norwegian geriatric wards in 2013 identified from The Norwegian Patient Registry, and collected their medication use from the Norwegian Prescription Database. Medication use before and after hospitalisation was compared and screened for PIMs applying a subset of the European Union (EU)(7)-PIM list and the Norwegian General Practice – Nursing Home (NORGEP-NH) list part A and B.

Results: The mean number of medications increased from 6.5 (SD = 3.5) before to 7.5 (SD = 3.5) (CI:1.2–0.8, $p < 0.001$) after hospitalisation. The proportion of patients with PIMs increased from before to after hospitalisation according to the EU(7)-PIM list (from 62.4 to 69.2%, $p < 0.001$), but not according to The NORGEP-NH list (from 49.9 to 50.6%, $p = 0.73$). The EU(7)-PIM list and the NORGEP-NH list had more than 70% agreement on the classification of patients as PIM users.

Conclusions: Medication use increased after hospitalisation to geriatric wards. We did not find that geriatric hospital care leads to a general improvement in PIM use after hospitalisation. According to a subset of the EU(7)-PIM list, PIM use increased after hospitalisation. This increase was not identified by the NORGEP-NH list part A and B. It is feasible to use health register data to investigate the impact of hospitalisation to geriatric wards on medication use and PIMs.

Keywords: Potentially inappropriate medications, Health register data, Drug therapy, EU(7)-PIM list, NORGEP-NH list, Hospitalization, Health services for the aged

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Background

The risk of hospitalisations increases with age. In 2018, 25% of the Norwegian population over 70 years had one or more hospitalisations [1]. Large specialised hospitals often have geriatric wards to care for older patients, where one core feature is the presence of a multidisciplinary health care team. For most patients, this team performs a comprehensive geriatric assessment, which also includes reviewing medications [2, 3]. Medication reviews are important as nearly half of hospitalised older adults use potentially inappropriate medications (PIMs) [4]. PIMs are normally defined as medications where the benefits are outweighed by the potential risks of adverse drug events (ADEs). Identification of PIMs is particularly relevant when safer or more effective treatment alternatives exist [5]. In older adults, PIMs are associated with an increased risk of ADEs and hospitalisations and is a public health concern [6].

A medication review may identify and prevent the use of PIMs. Despite this being an integrated part of the geriatric assessment, study results are conflicting concerning the impact of a geriatric ward stay on PIM prevalence [7–9]. Most previous studies have used admission and discharge summaries to determine medication use. We are not aware of studies applying prescribing registries to explore medication and PIM use related to hospitalisations in geriatric wards.

Several tools have been developed to identify PIMs in older adults. These are either explicit (criterion-based) or implicit (judgment-based), or a mix of both. The major advantage of explicit tools are that they are applicable with little clinical judgment, making them ideal for use in registry studies [5].

Due to inter-country variability in medication therapy traditions and the medications available, several country-specific PIM identification tools have been developed [5]. In Norway, two national PIM-lists exist; The Norwegian General Practice (NORGEP) list from 2009 [10], and The Norwegian General Practice Nursing Home (NORGEP—NH) list from 2015 [11]. NORGEP-NH is an updated version of NORGEP, and although developed primarily as a tool for nursing home patients, it can be useful in the general older population and for pharmacoepidemiological research [11]. Recently, The European Union (EU)(7)-PIM list initiative developed an explicit tool to identify and compare PIM use between European countries, including Scandinavian countries [12]. Application of different PIM lists will influence both the type and number of PIMs identified, and it is important to be aware of similarities and differences between the tools and their strength and limitations, both in daily clinical practice and when used in research. No published studies to date have compared PIMs identified applying the EU(7)-PIM list with NORGEP-NH list.

Aim

The primary aim was to apply national registry data to explore how hospitalisation to a geriatric ward impact use of medication and PIMs use among older adults. The secondary aim was to compare the EU(7)-PIM and the NORGEP-NH list with regards to PIM identification.

Method

Study population

We included all patients ≥65 years admitted to geriatric wards in Norway during 2013. We identified patients using data from the Norwegian Patient Registry, holding information on all hospitalisations for all Norwegian citizens through unique personal identification numbers. Their first admission in 2013 was used as their index stay. We excluded all patients with hospital admissions 120 days before or 120 days after discharge from the index hospital stay because we wanted to measure the effect of a single hospitalisation. See Fig. 1 for patient flow.

To identify medication use before and after hospitalisation, we retrieved data from the Norwegian prescription registry, holding information on all dispensed medications from Norwegian pharmacies on an individual level. Because data on medications used during hospital stays, in nursing homes or over the counter medications are not collected by the registry, we excluded patients who were discharged to an institution or nursing home. Patients who died in 2013 were excluded as they could have died in the 120 days following the index stay. If no medication dispensing was identified 120 days before or after discharge from index stay, patients were also excluded (Fig. 1).

Medication use and comorbidities

We defined medication use before and after hospitalisation as all medications dispensed in the 120 days before and after the index stay, respectively. We chose 120 days because reimbursed medications in Norway (i.e. all medications used for chronic diseases) can only be dispensed for a maximum of 90 days. Consequently, medications dispensed 120 days before and after hospitalisation should represent regular use for chronic conditions, leaving a 30-day window to account for non-adherence and stockpiling. We collected medication data using the medications unique Anatomical Therapeutic Chemical (ATC)-code provided by the World health organisation [13]. We excluded all antibiotics when counting the number of medications (ATC-code: J01), except methenamine, which is commonly used for long term prophylaxis for urinary tract infections.

Information in the Norwegian prescription registry allows for indirect identification of patient comorbidities through reimbursement codes for medications used for

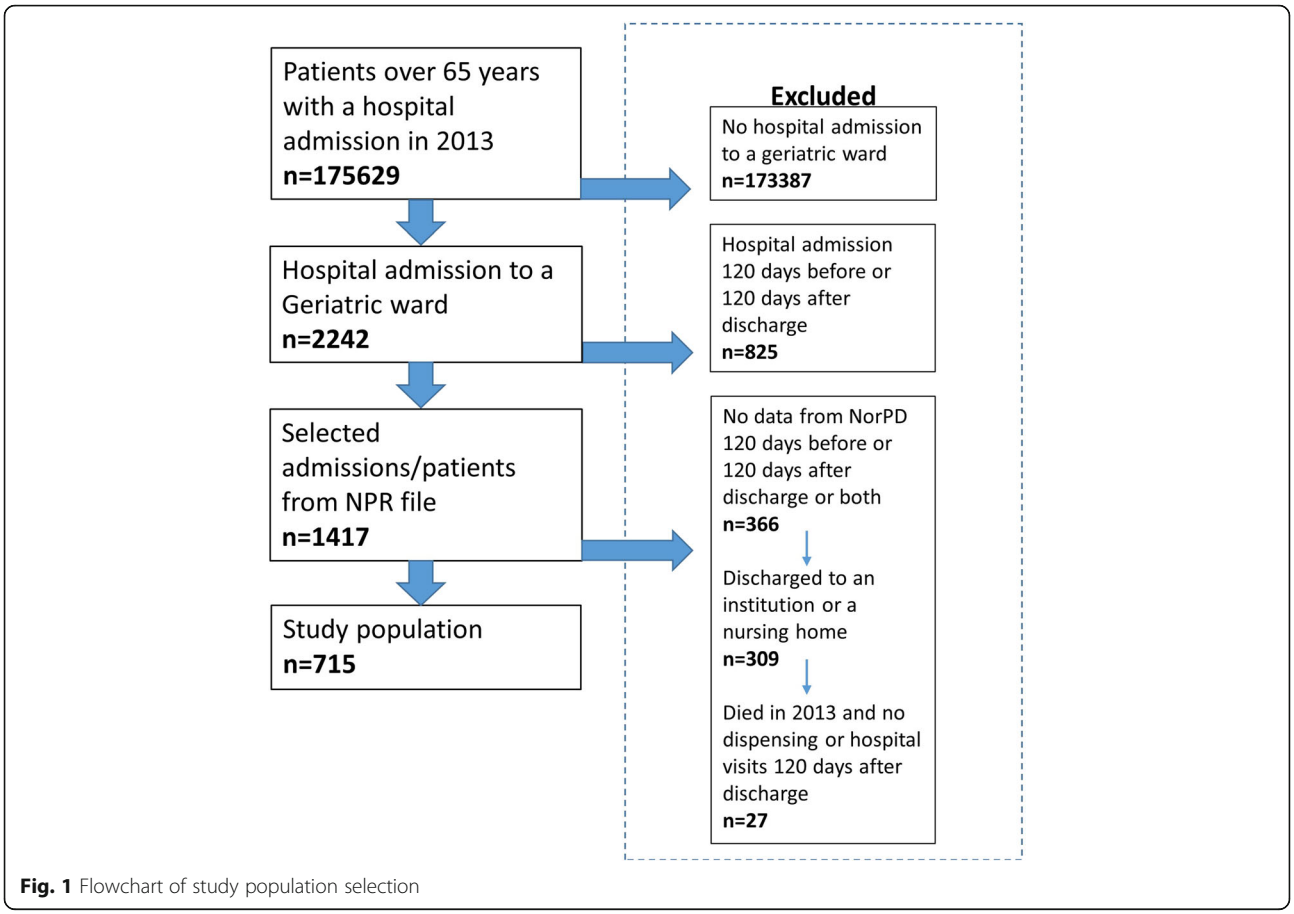

Fig. 1 Flowchart of study population selection

chronic diseases. To identify important comorbidities at the time of hospitalisation (description of the study population), we identified reimbursement codes (ICD or ICPC codes) for all medications dispensed 365 days before index hospitalisation and created clinical relevant medical diagnose classes.

PIM identification

We identified PIM use by applying two explicit tools; the EU(7)-PIM list [12] and the NORGEP-NH list [11]. NORGEP-NH was chosen over NORGEP as it is considered an updated and expanded version of the NORGEP list published in 2009.

From the 282 criteria in the EU(7)-PIM list [12], we applied 263 criteria. We excluded five criteria due to lack of information on the length of therapy (e.g. proton pump inhibitors), 12 criteria specifying medication doses that are unavailable in our dataset and two criteria not specifying ATC codes. See supplement 1 for an overview of exclusions.

From the NORGEP-NH list, we applied all the 26 criteria in part A and B and excluded the de-prescribing criteria in part C as these criteria are most relevant for a nursing home population. We defined "regular use" of hypnotics (criteria 11) as the dispensing of 60 defined daily doses (DDD) or more over 120 days.

Analysis and statistics

We present continuous variables as means with standard deviation (SD) and categorical variables as proportions. We compared the mean number of medications before and after hospitalisation by applying a dependent paired sample t-test. We compared the proportion of patients with PIM use before or after hospitalisation by applying the related samples McNemar test. Change in the number of identified PIMs before and after hospitalisation was examined applying the related samples Wilcoxon signed-rank test. Agreement in PIM identification between EU(7)-PIM and NORGEP-NH was explored using a Venn diagram. Statistical analysis was performed using IBM SPSS Statistics Version 25.0. A two-sided *P*-value of < 0.05 was considered statistically significant.

Results

Study population

Of the 175,629 patients ≥65 years with a hospital admission in 2013, 2242 were hospitalised to geriatric wards, of which we included 715 in our analysis (see Fig. 1).

The mean age of the study population was 82.5 years (SD = 7.8 range 65–101), and 64.8% were female. The mean length of hospital stay was 5.8 days (SD = 3.8 range 1–32). The most common medical diagnosis (identified from reimbursement codes) were hypertension (56.8%), atherosclerotic and cardiovascular disease (34.3%), mood disorders (19.3%), heart failure (17.9%), gastro-oesophageal reflux disease (17.9%), atrial fibrillation (14.1%) and chronic pain (13.8%).

Medication and PIM use

After hospitalisation, the mean number of medications increased from 6.5 (SD = 3.5) per patient to 7.5 (SD = 3.5) (CI:1.2–0.8 $p < 0.001$), with a similar increase across all age groups. The medications prescribed to more patients after hospitalisation were paracetamol, atorvastatin, calcium and vitamin D, pantoprazole, metoprolol and dipyridamole, while the combination of paracetamol and codeine and ethylmorphine were prescribed to fewer patients after hospitalisation.

According to the EU(7)-PIM list, the proportion of patients with PIMs increased from 62.4% before hospitalisation to 69.2% after hospitalisation ($p < 0.001$), see Table 1. The median number of PIMs per patient after hospitalisation was higher than before hospitalisation ($p < 0.001$). Most of the PIMs originated from medications belonging to ATC group N05, zopiclone being responsible for most PIMs. The PIMs mostly added after hospitalisation were dipyridamole, rivaroxaban, zopiclone and nifedipine, see Table 2. All PIMs identified by EU(7)-PIM are found in supplement 2.

According to the NORGEP-NH list, the proportion of patients with a PIM did not change from before to after hospitalisation (49.9 to 50.6%) ($p = 0.73$), see Table 1, nor did the median number of PIMs per patient ($p = 0.79$). Also here zopiclone was responsible for most PIM. Disregarding zopiclone, we identified PIM use in 39.2 and 37.6% of the patients before and after hospitalisation. Table 3 summarise PIMs identified by the NORGEP-NH list.

Overall, we identified a higher prevalence of PIM users with the EU(7)-PIM list compared to the NORGEP-NH list. Before hospitalisation, the tools agreed on the classifications of patients as PIM users or non-PIM users in 76.9% of patients (44.6% PIM users in both tools) and 71.9% after hospitalisation (45.9% PIM users with both tools) see Fig. 2. If excluding zopiclone, responsible for most PIMs in both tools, the agreement between the tools decreased, to only 28% after hospitalisation.

Table 1 Number of PIMs identified per patient ($n = 715$) before and after hospitalisation to a geriatric ward

Number of PIMs	EU(7)-PIM				NORGEP-NH			
	PIMs before		PIMs after		PIMs before		PIMs after	
	n	%	n	%	n	%	n	%
1	227	31.7	249	34.8	129	18.0	130	18.2
2	142	19.9	148	20.7	108	15.1	117	16.4
3	45	6.3	70	9.8	73	10.2	73	10.2
4	22	3.1	20	2.8	28	3.9	27	3.8
5	7	1.0	7	1.0	10	1.4	12	1.7
6	2	0.3	–	–	5	0.7	3	0.4
7	1	0.1	–	–	3	0.4	–	–
8	–	–	1	0.1	–	–	–	–
9	–	–	–	–	1	0.1	–	–
Patients with PIMs	**446**	**62.4**	**495**	**69.2**	**357**	**49.9**	**362**	**50.6**

Discussion

In this study, we have shown the feasibility of applying health registry data for the identification of changes in PIM use in an older patient population admitted to hospitals in Norway. From the registry data, we were able to identify PIM use, compare PIM use before and after hospitalisation to a geriatric ward, and to compare the application of two different explicit PIM lists. Our study shows that the number of medications used increased significantly after hospitalisation to geriatric wards, which was also the case for PIM use according to the EU(7)-PIM list.

Applying registry data to investigate the effect of hospitalisation on PIM use is a novel approach. Although the registries did not contain information like a full list of medical diagnosis and laboratory data, we were able to apply most of the criteria and identify changes in PIMs. Previous studies have collected medication use data from hospital admission and discharge summaries [7–9]. Discharge summaries may not be fully representative for actual medication use after hospitalisation, as changes suggested by hospital physicians in discharge summaries are not necessarily effected in primary care [14]. There are numerous reasons for recommendations not being followed, but the most important may be poor communication between primary and secondary care [15]. The changes observed in medications use and PIMs after discharge in our study may be a result of prescriptions from both hospital and primary care physicians, as in real life.

Increase in medication use and PIM use

There may be many reasons why medication and PIM use increased after hospitalisation, the most important perhaps being the nature of a hospitalisation, implying an acute illness or event where a need for new medications is expected [14, 16]. Most studies investigating the impact of hospitalisation on medication use have, similar to us, found an increase in the number of medications [8, 9, 14, 17]. If we assess the clinical impact of such an

Table 2 Patients ($n = 715$) with PIMs identified with the EU(7)-PIM list before and after hospitalisation grouped at ATC-level 3 and with the most frequently prescribed medications highlighted

	Patients with PIMs									
	Before		After		Removed		Not changed		Added	
	n	%	n	%	n	%	n	%	n	%
N05 Psycholeptics	260	36.4	293	41.0	35	4.9	225	31.5	68	9.5
Zopiclone *(Dosage > 3.75 mg/day)*	190	26.6	208	29.1	31	4.3	159	22.2	49	6.9
Diazepam	56	7.8	50	7.0	27	3.8	29	4.1	21	2.9
Nitrazepam	26	3.6	21	2.9	8	1.1	18	2.5	3	0.4
Zolpidem	20	2.8	22	3.1	6	0.8	14	2.0	8	1.1
C08 Calcium channel blockers	45	6.3	49	6.9	14	2.0	31	4.3	18	2.5
Nifedipine	23	3.2	33	4.6	5	0.7	18	2.5	15	2.1
N06 Psychoanaleptics	42	5.9	36	5.0	14	2.0	28	3.9	8	1.1
Amitriptyline	18	2.5	14	2.0	7	1.0	11	1.5	3	0.4
B01 Antithrombotic agents	39	5.5	110	15.4	12	1.7	27	3.8	83	11.6
Dipyridamole	23	3.2	55	7.7	9	1.3	14	2.0	41	5.7
Dabigatran	10	1.4	17	2.4	3	0.4	7	1.0	10	1.4
Rivaroxaban	6	0.8	33	4.6	2	0.3	4	0.6	29	4.1
N02 Analgesics	37	5.2	48	6.7	21	2.9	16	2.2	32	4.5
Tramadol	6	0.8	33	4.6	2	0.3	4	0.6	29	4.1
A10 Drugs used in diabetes	31	4.3	31	4.3	5	0.7	26	3.6	5	0.7
Glimepiride	25	3.5	22	3.1	4	0.6	21	2.9	1	0.1
G04 Urologicals	35	4.9	32	4.5	13	1.8	22	3.1	10	1.4
R05 Cough and cold preparations	28	3.9	17	2.4	23	3.2	5	0.7	12	1.7
Ethylmorphine	28	3.9	17	2.4	23	3.2	5	0.7	12	1.7
C01 Cardiac therapy	23	3.2	25	3.5	5	0.7	18	2.5	7	1.0
Digoxin	15	2.1	19	2.7	4	0.6	11	1.5	8	1,1
M01 Antiinflammatory and antirheumatic products	22	3,1	15	2.1	17	2.4	5	0.7	10	1.4
A03 Drugs for functional gastrointestinal disorders	21	2.9	22	3.1	16	2.2	5	0.7	17	2.4
Metoclopramide	21	2.9	22	3.1	16	2.2	5	0.7	17	2.4
R06 Antihistamines for systemic use	16	2.2	14	2.0	6	0.8	10	1.4	4	0.6
A02 Drugs for acid-related disorders	14	2.0	15	2.1	3	0.4	11	1.5	4	0.6
G03 Sex hormones and modulators of the genital system	14	2.0	15	2.1	3	0.4	11	1.5	4	0.6
J01 Antibacterials for systemic use	12	1.7	12	1.7	12	1.7	–	0.0	12	1.7
N04 Anti-parkinson drugs	12	1.7	11	1.5	2	0.3	10	1.4	1	0.1
A06 Drugs for constipation	9	1.3	21	2.9	6	0.8	3	0.4	18	2.5
C02 Antihypertensives	9	1.3	7	1.0	2	0.3	7	1.0	–	–
C07 Beta-blocking agents	9	1.3	6	0.8	5	0.7	4	0.6	2	0.3
C03 Diuretics	7	1.0	4	0.6	4	0.6	3	0.4	1	0.1
N03 Antiepileptics	7	1.0	11	1.5	1	0.1	6	0.8	5	0.7
A07 Antidiarrheals, intestinal anti-inflammatory/ anti-infective agents	4	0.6	11	1.5		0.0	4	0.6	7	1.0
M03 Muscle relaxants	4	0.6	3	0.4	1	0.1	3	0.4	–	–
R01 Nasal preparations	3	0.4	3	0.4	3	0.4		0.0	3	0.4
A04 Antiemetics and antinauseants	1	0.1	1	0.1	1	0.1		0.0	1	0.1
M04 Antigout preparations	1	0.1	2	0.3	–	–	1	0.1	1	0.1
C04 Peripheral vasodilators	0	0.0	1	0.1	–	–	–	–	1	0.1

Table 3 Patients ($n = 715$) with PIMs identified with the NORGEP-NH list before and after hospitalisation

	Patients with PIMs									
	Before		After		Removed		Not changed		Added	
	n	%	n	%	n	%	n	%	n	%
Part A: Single substance criteria										
1.Combination analgesic codein/paracetamol	94	13.1	83	11.6	47	6.6	47	6.6	36	5.0
2. Tricyclic antidepressants (TCAs)	25	3.5	17	2.4	11	1.5	14	2.0	3	0.4
3. Non-steroid anti-inflammatory drugs (NSAIDs)	47	6.6	27	3.8	31	4.3	16	2.2	11	1.5
4. First-generation antihistamines	26	3.6	29	4.1	8	1.1	18	2.5	11	1.5
5. Diazepam	56	7.8	50	7.0	27	3.8	29	4.1	21	2.9
6. Oxazepam: Dosage > 30 mg/day	10	1.4	11	1.5	7	1.0	3	0.4	8	1.1
7. Zopiclone: Dosage > 5 mg/day	144	20.1	142	19.9	28	3.9	116	16.2	26	3.6
8. Nitrazepam	26	3.6	21	2.9	8	1.1	18	2.5	3	0.4
9. Flunitrazepam	1	0.1	–	–	1	0.1	–	–	–	–
10. Chlometiazole	2	0.3	9	1.3	1	0.1	1	0.1	8	1.1
11. Regular use of hypnotics[a]	196	27.4	206	28.8	28	3.9	168	23.5	38	5.3
Total part A	**316**	**44.2**	**322**	**45.0**	**60**	**8.4**	**256**	**35.8**	**66**	**9.2**
Part B: Combinations to avoid										
12. Warfarin + NSAIDs	2	0.3	–	–	2	0.2	–	–	–	–
13. Warfarin + SSRIs/SNRIs[b]	13	1.8	13	1.8	5	0.7	8	1.1	5	0.7
14. Warfarin+ ciprofloxacin/ofloxacin/erythromycin/clarithromycin	3	0.4	2	0.3	3	0.4	–	–	2	0.3
15. NSAIDs/coxibs[c] + ACE-inhibitors/AT2-antagonists	16	2.2	13	1.8	11	1.5	5	0.7	8	1.1
16. NSAIDs/coxibs + diuretics	8	1.1	7	1.0	7	1.0	1	0.1	6	0.8
17. NSAIDs/coxibs + glucocorticoids	6	0.8	6	0.8	3	0.4	3	0.4	3	0.4
18. NSAIDs/coxibs + SSRI/SNRIs	7	1.0	4	0.6	7	1.0	–	–	4	0.6
19. ACE-inhibitors[d]/AT2-antagonists[e] + potassium or potassium-sparing diuretics	19	2.7	23	3.2	9	1.3	10	1.4	13	1.8
20. Beta blocking agents + cardioselective calcium antagonists	2	0.3	2	0.3	1	0.1	1	0.1	1	0.1
21. Erythromycin/clarithromycin + statins	1	0.1	2	0.3	1	0.1	–	–	2	0.3
22.Bisphosponate + proton pump inhibitors	18	2.5	22	3.1	4	0.6	14	2.0	8	1.1
23. Concomitant use of 3 or more psychotropics	52	7.3	65	9.1	18	2.5	34	4.8	31	4.3
24. Tramadol + SSRIs	2	0.3	7	1.0	1	0.1	1	0.1	6	0.8
25. Metoprolol + paroxetine/fluoxetine/bupropion	1	0.1	2	0.3	–	–	1	0.1	1	0.1
26. Metformin + ACE-Inhibitors/AT2-antagonists + diuretics	9	1.3	6	0.8	5	0.7	4	0.6	2	0.3
Total part B	**129**	**18.0**	**139**	**19.4**	**49**	**6.9**	**80**	**11.2**	**59**	**8.3**
Total PART A and B	**357**	**49.9**	**362**	**50.6**	**73**	**10.2**	**284**	**39.7**	**78**	**10.9**

[a] regular use defined as dispensing of 60 DDD or more in the 120-day period
[b] selective serotonin reuptake inhibitors/selective norepinephrine reuptake inhibitors
[c] cyclooxygenase-2-selective inhibitors
[d] angiotensin-converting enzyme inhibitors
[e] angiotensin II receptor antagonists

increase in an older population, it is not without risk. Polypharmacy has been associated with non-adherence to medication therapy, drug-interactions, ADEs, and readmissions [18, 19]. Increasing the number of medications prescribed also increases the risk of PIM-prescribing [20, 21]. Prescribing new medications to patients should prompt a medication review to optimize medication therapy.

We identified no reduction in PIM use, and this finding is coherent with results from studies investigating the impact of hospitalisation on PIM use in general. In a large longitudinal study from Ireland, using data from general practice records, hospital admissions were found to be independently associated with PIM-prescribing [22]. Norwegian studies examining the impact of hospitalisation on PIM use also support our findings. Bakken

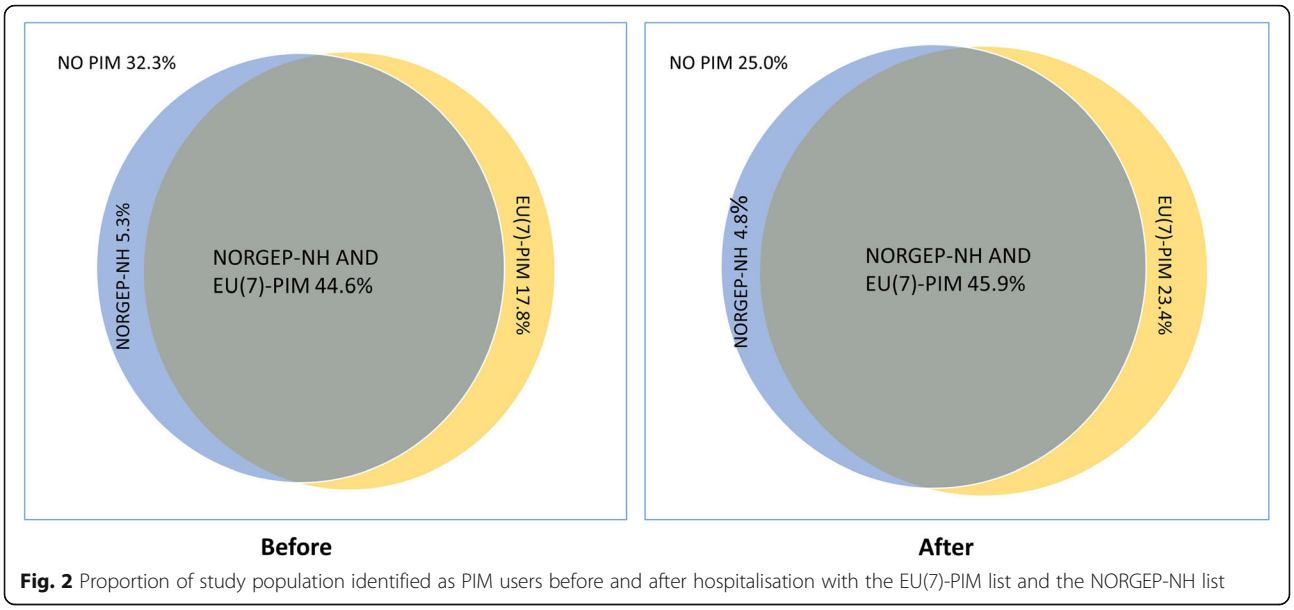

Fig. 2 Proportion of study population identified as PIM users before and after hospitalisation with the EU(7)-PIM list and the NORGEP-NH list

et al. found that stays in an intermediate-care nursing home unit or hospital wards increased PIM use identified by the NORGEP list from 24.1 to 34.8% of the population [23]. In two other Norwegian studies, no significant changes in PIM use were identified from admittance to discharge in geriatric and medical wards [24, 25]. International studies show conflicting results on the effect of a geriatric ward stay on PIMs [7–9].

The type of PIMs identified

Although we found no overall reduction in PIM use, PIM changes occurred on the patient level. A large proportion of patients actually had PIMs removed, while an equal or larger proportion of patients had PIMs added (Tables 2 and 3). The most frequently identified PIMs with both tools were hypnotics, and zopiclone in particular. Nearly 30% of our study population used zopiclone ≥3.75 mg after hospitalisation (Table 2), a result supported by other Norwegian studies [26]. Given the considerable evidence relating hypnotics to ADEs in older adults, the widespread use of zopiclone is alarming, and interventions are warranted [27].

Difference between PIM identification tools

This study suggests that the identification of PIMs is highly dependent on the tools applied, which was also the argument for applying two different PIM-lists. We found them to agree on the identification of PIM users in 76.9% before and 71.9% after hospitalisation. The EU(7)-PIM list, including 263 criteria is more sensitive but less specific than other tools, and thus identifies a higher prevalence of PIM use than the country-specific PIM lists [28]. In contrast the NORGEP-NH list only includes 34 criteria. We acknowledge that other criteria list also could have been used, however, to be applicable some of them require additional clinical information that is not recorded in our health registries, i.e. the Screening tool of older people's prescriptions (STOPP) and screening tool to alert to right treatment (START) [29].

Looking into the specific difference between these two tools, the increase in PIMs identified by the EU(7)-PIM list after hospitalisation is primarily driven by the increased use of dipyridamole and direct oral anticoagulants (DOACs), which are not included in the NORGEP-NH list. A Norwegian geriatric hospital ward receives many stroke patients and increased use of antithrombotic agents is expected because extended-release dipyridamole in combination with aspirin is the first-line treatment for stroke according to Norwegian guidelines [30]. Consequently, an increase in dipyridamole use after a stay in a geriatric ward is regarded as appropriate in Norway. The EU(7)-PIM list also includes DOACs as inappropriate because of limited information on use in older adults and the risk of bleeding events [12]. This is not in accordance with one of the most popular and investigated PIM lists, i.e. the STOPP/START LIST [29], where failure to start DOACs in patients with chronic atrial fibrillation is defined as a potentially prescribing omission in the older adults [29]. There are obvious discrepancies between the different PIM identification lists concerning what is considered inappropriate prescribing. Consequently, we may not consider all PIMs identified by the EU(7)-PIM list to represent inappropriate prescribing in our population. Unlike the START/STOPP-list [6], the relationship between the EU(7)-PIM list and the NORGEP-NH list and adverse health outcomes in older adults is yet to be established. Research is needed to validate the ability of these newly developed PIM lists

to identify patients at risk of ADEs. Applying explicit criteria PIM lists in direct patient care should always be done with individual clinical judgement.

Admittance to a geriatric ward is an opportunity to improve the quality of medication use in older patients. Geriatric wards, being tailored to care for older patients, should have the expertise to improve the appropriateness of medical treatment. Future research should find means to make a hospitalisation an opportunity for reducing PIMs in older patients. Pharmacist interventions have been shown to improve the appropriateness of prescribing at discharge [31], but in Norway, few geriatric wards had in 2013 included clinical pharmacists in their teams. Given the complexity of medication optimisation, a patient-focused multidisciplinary intervention targeting both primary and secondary care should be developed.

Strengths and limitations

To our knowledge, our study is the first to use health registry data to investigate the impact of a geriatric ward stay on medication and PIM use on a national level. It is also the first study to apply the EU(7)-PIM list to a Norwegian population and to compare it to the country-specific NORGEP-NH list [29]. The main strength of our study is the quality of our health registry data enabling identification of all patients admitted to geriatric hospital wards and all prescription medications dispensed to community-dwelling patients.

The main limitation of this study is our definition of medication use as "all medications dispensed from the pharmacy during 120 days before or after hospitalisation". This will likely overestimate use as patients may not use all of the medicines dispensed. On the other hand, compared to previous studies investigating the impact of geriatric ward stays on PIM use, we know for certain that the medications have been dispensed from the pharmacy, both before and after hospitalisation. A second limitation is that we could not apply all of the criteria in the EU(7)-PIM list because of limitations in our dataset. For example, use of proton pump inhibitors (PPI) for more than 8 weeks were excluded from our analysis, but is found to be the most frequent PIM identified with the EU(7)-PIM list [28]. A third limitation is that the provision of geriatric services and the criteria for admission to geriatric wards may be different in-between countries, and our results may not be directly transferable to other healthcare systems. A fourth limitation is that we excluded 1527 of the 2242 patients who had a hospital stay in a geriatric ward in 2013, mostly because of hospitalisations or lack of prescriptions in 120 days surrounding the index stay (Fig. 1). The population we have selected may be healthier than the average patients at geriatric wards because they only had one hospitalisation in 240 days and because lack of prescriptions in this population often means that they reside in a nursing home. This may introduce selection bias into our study, and limit the generalisability of our finding to the average patients at geriatric wards.

Conclusion

Applying health registry data for identification of change in medication and PIM use after hospitalisation to geriatric wards in Norway is feasible. Medication use seems to increase significantly after hospitalisation to a geriatric ward. PIM use is prevalent both before and after hospitalisation, and did not identify any reduction after hospitalisation. A subset of the EU(7)-PIM and the NORGEP-NH list part A and B have a more than 70% agreement on the classification of patients as PIM users, but do not agree on whether PIM use increases after hospitalisation. More research is needed to validate if the increase in PIM use seen after hospitalisation with the EU(7)-PIMs list truly represent a risk of ADEs.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12877-020-01585-w.

Additional file 1: Online Resource 2. The table shows medications from the EU(7)-PIM-List [1] that are included in our analysis and the adjustments that are done. For some of the medications, we include only some package sizes or strengths, while others we had to be excluded due to limitations in our dataset. Many of the medications in the list are not licensed in Norway but are not excluded as some patients may be allowed to use special imported non licensed medication.

Additional file 2: Online resource 3. All PIMs identified with the EU (7)-PIM list by ATC-level 5.

Abbreviations

ADE: Adverse drug events; ATC-code: Anatomical Therapeutic Chemical Code; DDD: Defined daily doses; EU(7)-PIM: European Union (EU)(7)-PIM list; NORGEP-NH: Norwegian General Practice – Nursing Home; PIM: Potentially inappropriate medications; STOPP: Screening tool of older people's prescriptions; START: Screening tool to alert to right treatment lists

Acknowledgements

We would like to thank associate professor Lars Småbrekke with help in editing the manuscript.

Authors' contributions

JSJ contributed with the study design, data analysis and writing of the paper. KHH and BHG contributed with the study design, data interpretation and the writing of the paper. KS contributed with the study design, data analysis and writing of the paper. KH contributed to the writing of the paper. All authors reviewed and approved the final manuscript.

Funding

The publication charges for this article have been funded by a grant from the publication fund of University of Tromsø (UiT) The Arctic University of Norway.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to restrictions from the Norwegian data protection authority and risk of identifying patients when linking registers but are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
The regional ethics committee and the Norwegian Data Protection Authority approved the study before we got access to the relevant data from our national health registers. Norwegian health registers are regulated by Norwegian low (Helseregisterloven¸ LOV-2014-06-20-43) and no consent to participate is needed from the individuals contributing data to our dataset.

Consent for publication
Not applicable.

Competing interests
The authors declare that there are no conflicts of interest.

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Received: 9 March 2020 Accepted: 19 May 2020
Published online: 01 June 2020

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Publisher's Note

Online Resource 2

The table shows medications from the EU (7)-PIM-List [1] that are included in our analysis and the adjustments done. For some of the medications, we included only some package sizes or strengths. Other medications had to be excluded due to limitations in our dataset. Many of the medications in the list are not licensed in Norway but are not excluded as some patients may be allowed to use special imported non-licensed medication.

ATC-Code	Potentially inappropriate	Included	Excluded	Included with modifications	Added	Comment
A02AA04	Magnesium hydroxide	X				
A02AB, A02AD	Aluminium-containing antacids	X				Medication group
A02AD01	Ordinary salt combinations				X	Group specified, added ATC level 5 for medications in the group available In Norway.
A02BA01	Cimetidine	X				
A02BA02	Ranitidine	X				
A02BA03	Famotidine	X				
A02BC	Proton pump inhibitors (PPI) (>8 weeks) e.g. omeprazole, pantoprazole		X			Excluded because our data cannot separate use over or under eight weeks
A03AA04	Mebeverine[c]	X				
A03AA05	Trimebutine	X				
A03AA08	Dihexyverine	X				

A03AB06	Otilonium bromide	X				
A03AB17	Tiemonium (iodide)	X				
A03AX04	Pinaverium[c]	X				
A03BA03	Hyoscyamine	X				
A03BA04	Belladonna alkaloids	X				
A03CA02	Clidinium-Chlordiazepoxide	X				
A03DA02	Pitofenone	X				
A03FA01	Metoclopramide	X				
A03FA03	Domperidone (>30 mg/d)[c]		X			Excluded, not licensed in Norway and no data on dose in our dataset
A03FA05	Alizapride	X				
A04AB02	Dimenhydrinate	X				
A04AD01	Scopolamine	X				
A04AD05	Metopimazine	X				
A06AA01	Viscous paraffin (=Liquid paraffin)	X				
A06AA02	Docusate sodium (oral)			X		Removed suppository as criteria specified oral use
A06AB02	Bisacodyl (>3 days)			X		Included package size of 100 and 250 tablets as these are intended for prolonged use.

A06AB05	Castor oil (=Ricinus communis, =Neoloid)	X				
A06AB06	Senna glycosides	X				
A06AB07	Cascara sagrada	X				
A06AB08	Sodium picosulfate	X				
A06AB13	Aloe	X				
A06AX05	Prucalopride	X				
A07DA01	Diphenoxylate-Atropine	X				
A07DA03	Loperamide (>2 days)			X		Included package size of 100 and 250 tablets as these are intended for prolonged use.
A07XA04	Racecadotril	X				
no ATC, treatment concept PIM	Insulin, sliding scale		X			No information in dataset if insulin is used in sliding scale
A10BB01	Glibenclamide	X				
A10BB02	Chlorpropamide	X				
A10BB06	Carbutamide	X				
A10BB07	Glipizide	X				
A10BB12	Glimepiride	X				
A10BF01	Acarbose	X				
A10BG03	Pioglitazone	X				

A10BH01	Sitagliptine	X				
A10BH02	Vildagliptine	X				
B01AA07	Acenocoumarol	X				
B01AC05	Ticlopidine	X				
B01AC07	Dipyridamole	X				
B01AC22	Prasugrel	X				
B01AE07	Dabigatran[c]	X				
B01AF01	Rivaroxaban[c]	X				
B01AF02	Apixaban[c]	X				
B03AA	Iron supplements / Ferrous sulfate (>325 mg/d)		X			Largest tablets strength is 200 mg no information on number of tablets prescribed each day.
C01AA02	Acetyldigoxin	X				
C01AA04	Digitoxin	X				
C01AA05	Digoxin	X				
C01AA08	Metildigoxin	X				
C01BA01	Quinidine	X				
C01BA02	Procainamide	X				
C01BA03	Disopyramide	X				

C01BA51	Quinidine in combination with verapamil	X				
C01BC03	Propafenone	X				
C01BC04	Flecainide	X				
C01BD01	Amiodarone	X				
C01BD07	Dronedarone	X				
C01EB15	Trimetazidine	X				
C01EB17	Ivabradine	X				
C02AA02	Reserpine	X				
C02AB01	Methyldopa	X				
C02AC01	Clonidine	X				
C02AC02	Guanfacine	X				
C02AC05	Moxonidine	X				
C02AC06	Rilmenidine	X				
C02CA01	Prazosin	X				
C02CA04	Doxazosin	X				
C02CA06	Urapidil	X				
C02CC02	Guanethidine	X				
C02DB02	Hydralazine	X				
C03DA01	Spironolactone (>25 mg/d)[c]	X		X		Included dispensed tablets with a strength over 25 mg

C04AD03	Pentoxifylline	X				
C04AE02	Nicergoline	X				
C04AE04	Dihydroergocristine	X				
C04AE54	Raubasine-Dihydroergocristine	X				
C04AX01	Cyclandelate (=Cyclospasmol)	X				
C04AX07	Vincamine	X				
C04AX10	Moxisylyte	X				
C04AX17	Vinburnine	X				
C04AX20	Buflomedil	X				
C04AX21	Naftidrofuryl	X				
C05CA05	Hidrosmin	X				
C05CA07	Escin (=Aescin)	X				
C05CA51	Vincamine-Rutoside	X				
C05CA54	Troxerutin-Vincamine	X				
C07AA02	Oxprenolol	X				
C07AA03	Pindolol	X				
C07AA05	Propranolol	X				
C07AA07	Sotalol	X				
C07AA12	Nadolol	X				

C07AG01	Labetalol	X				
C08CA04	Nicardipine	X				
C08CA05	Nifedipine (non-sustained-release)	X				
C08CA05	Nifedipine (sustained-release)	X				
C08DA01	Verapamil	X				
C08DB01	Diltiazem	X				
C10AD02	Niacin (=Nicotinic acid)	X				
G03C	Oestrogen (oral)	X				Medication group
G03CA03	Østradiol			X	X	Included only tablets, removed vaginal tablets
G03CA04	Østriol			X	X	Included only tablets, removed vaginal tablets
G03CX01	Tibolon				X	
G04BD02	Flavoxat	X				
G04BD04	Oxybutynine (non-sustained-release)	X				
G04BD04	Oxybutynine (sustained-release)	X				
G04BD07	Tolterodine (non-sustained-release)	X				
G04BD07	Tolterodine (sustained-release)	X				
G04BD08	Solifenacin	X				
G04BD09	Trospium	X				
G04BD10	Darifenacin	X				

G04BD11	Fesoterodin	X				
G04CA03	Terazosin	X				
J01MA01	Ofloxacin	X				
J01XE01	Nitrofurantoin (>1 week)			X		Included only 100 package of 50 mg as these are intended for prolonged use
M01AA01	Phenylbutazone	X				
M01AB01	Indometacin	X				
M01AB05	Diclofenac	X				
M01AB11	Acemetacin	X				
M01AB15	Ketorolac	X				
M01AB16	Aceclofenac	X				
M01AC01	Piroxicam	X				
M01AC05	Lornoxicam	X				
M01AC06	Meloxicam	X				
M01AE01	Ibuprofen (>3 x 400 mg/d or for a period longer than one week)[c]		X			No information on dose and length of therapy in dataset.
M01AE02	Naproxen (>2 x 250 mg/d or for a period longer than one week)[c]		X			No information on dose and length of therapy in dataset.
M01AE03	Ketoprofen	X				
M01AE09	Flurbiprofen	X				

M01AE17	Dexketoprofen	X				
M01AG01	Mefenamic acid	X				
M01AH01	Celecoxib	X				
M01AH05	Etoricoxib	X				
M01AX01	Nabumetone	X				
M03BA02	Carisoprodol	X				
M03BA03	Methocarbamol	X				
M03BC01	Orphenadrine	X				
M03BX01	Baclofen	X				
M03BX02	Tizanidine	X				
M03BX07	Tetrazepam	X				
M03BX08	Cyclobenzaprine	X				
M04AC01	Colchicin	X				
M05BX03	Strontium ranelate	X				
M09AA	Quinine and derivatives		X			Medication group. No medications in this group is licensed for use in Norway
N02AB02	Pethidine (=Meperidine)	X				
N02AD01	Pentazocine	X				
N02AX02	Tramadol (sustained-release)	X				
N02AX02	Tramadol (non-sustained-release)	X				

N07BC02	Methadone	X				
N02BA01	Acetylsalicylic acid (>325 mg)		X			No information on dose over 160 mg, larger strengths not available on prescription in Norway
N02CA02	Ergotamine	X				
N02CC	Triptanes (e.g. Sumatriptan, Eletriptan, Naratriptan, Zolmitriptan)	X				Medication group. Added medications on the Norwegian market.
N02CC01	Sumatriptan				X	
N02CC02	Naratriptan				X	
N02CC03	Zolmitriptan				X	
N02CC04	Rizatriptan				X	
N02CC05	Almotriptan				X	
N02CC06	Eletriptan				X	
N02CC07	Frovatriptan				X	
N03AA02	Phenobarbital	X				
N03AB02	Phenytoin	X				
N03AE01	Clonazepam	X				
N03AF01	Carbamazepine	X				
N03AX11	Topiramate	X				
N04AA01	Trihexyphenidyl	X				
N04AA02	Biperiden	X				

N04AA12	Tropatepin	X				
N04AC01	Benzatropine	X				
N04BB01	Amantadine	X				
N04BC01	Bromocriptine	X				
N04BC02	Pergolide	X				
N04BC03	Dihydroergocryptine	X				
N04BC04	Ropinirole[c]	X				
N04BC05	Pramipexole[c]	X				
N04BC06	Cabergoline[c]	X				
N04BC08	Piribedil	X				
N04BC09	Rotigotine	X				
N04BD01	Selegiline	X				
N05AA01	Chlorpromazine	X				
N05AA02	Levomepromazine	X				
N05AA04	Acepromazine	X				Two ATC-codes in one criteria.
N05BA05	Clorazepate	X				
N05AA06	Cyamemazine	X				
N05AB02	Fluphenazine	X				
N05AB03	Perphenazine	X				

N05AB04	Prochlorperazine	X				
N05AB06	Trifluoperazine	X				
N05AC01	Propericiazine (=Periciazine)	X				
N05AC02	Thioridazine	X				
N05AC04	Pipotiazine	X				
N05AD01	Haloperidol (>2 mg single dose; >5mg/d)		X			No data on use of doses over 1 mg per day (larges tablet strength)
N05AD08	Droperidol	X				
N05AE03	Sertindole	X				
N05AE04	Ziprasidone	X				
N05AF01	Flupentixole	X				
N05AF03	Chlorprothixen	X				
N05AF05	Zuclopenthixol	X				
N05AG02	Pimozide	X				
N05AH02	Clozapine	X				
N05AH03	Olanzapine (>10 mg/d)			X		Include only tablets with strength over 10 mg
N05AN01	Lithium	X				
N05AX08	Risperidone (>6 weeks)		X			Excluded because our data cannot separate use over or under 6 weeks
N05AX12	Aripiprazole	X				

N05BA01	Diazepam	X				
N05BA02	Chlordiazepoxide	X				
N05BA03	Medazepam	X				
N05BA04	Oxazepam (>60 mg/d)		X			No data on use of doses over 30 mg per day (larges tablet strength available)
N05BA05	Dipotassium clorazepate	X				ATC-code included already
N05BA06	Lorazepam (>1 mg/d)		X			Not available in Norway, not able to adjust for dosing
N05BA08	Bromazepam	X				
N05BA09	Clobazam	X				
N05BA11	Prazepam	X				
N05BA12	Alprazolam	X				
N05BA13	Halazepam	X				
N05BA16	Nordazepam	X				
N05BA18	(Ethyl-) Loflazepate	X				
N05BA21	Clotiazepam (>5 mg/d)		X			Not available in Norway, not able to adjust for dosing
N05BC01	Meprobamate	X				
N05CC01	Chloralhydrate	X				
N05CD01	Flurazepam	X				
N05CD02	Nitrazepam	X				
N05CD03	Flunitrazepam	X				

N05CD04	Estazolam	X				
N05CD05	Triazolam	X				
N05CD06	Lormetazepam (>0.5 mg/d)		X			Not available in Norway, not able to adjust for dosing
N05CD07	Temazepam	X				
N05CD08	Midazolam	X				
N05CD09	Brotizolam (>0.125 mg/d)		X			Not available in Norway, not able to adjust for dosing
N05CD10	Quazepam	X				
N05CD11	Loprazolam (>0.5 mg/d)[c]		X			
N05CF01	Zopiclone (>3.75 mg/d)			X		Included only dispensing of 5 mg and 7.5 mg tablets
N05CF02	Zolpidem (>5 mg/d)			X		Included only dispensing of 10 mg tablets
N05CF03	Zaleplone (>5 mg/d)		X			
N05CM02	Clomethiazole	X				
N05CM06	Propiomazine	X				
No ATC	Aceprometazine		X			Excluded, no ATC
N06AA01	Desipramine	X				
N06AA02	Imipramine	X				
N06AA04	Clomipramine	X				
N06AA06	Trimipramine	X				
N06AA09	Amitriptyline	X				

N06AA10	Nortriptyline	X				
N06AA12	Doxepin	X				
N06AA16	Dosulepin	X				
N06AA17	Amoxapine	X				
N06AA21	Maprotiline	X				
N06AB03	Fluoxetine	X				
N06AB05	Paroxetine	X				
N06AB08	Fluvoxamine	X				
N06AF04	Tranylcypromine	X				
N06AX12	Bupropion	X				
N06AX16	Venlafaxine	X				
N06AX18	Reboxetine	X				
N06BA04	Methylphenidat	X				
N06BX03	Piracetam	X				
N06DX02	Ginkgo biloba	X				
C04AE01	Ergoloid mesylate (dihydroergotoxine)	X				
N07AB02	Bethanechol	X				
R01BA01	Norephedrine (=Phenylpropanolamine)	X				
R01BA02	Pseudoephedrine	X				

R03CC03	Terbutaline (oral)			X		Removed dispensing of injections (same ATC-code)
R03DA04	Theophylline	X				
R05DA01	Ethylmorphine	X				
R05DA04	Codeine (>2 weeks)		X			Excluded because our data cannot separate use over or under 2 weeks.
R05DA09	Dextrometorphan	X				
R06AA02	Diphenhydramine	X				
R06AA04	Clemastine	X				
R06AA08	Carbinoxamine	X				
R06AA09	Doxylamine	X				
R06AB01	Brompheniramine	X				
R06AB02	Dexchlorpheniramine	X				
R06AB03	Dimetindene	X				
R06AB04	Chlorpheniramine (=Chlorphenamine)	X				
R06AB05	Pheniramine	X				
R06AB52	Dexchlorpheniramine-Betamethason	X				
R06AC04	Tripelennamine	X				
R06AD01	Alimemazine	X				
R06AD02	Promethazine	X				

R06AD07	Mequitazine	X				
R06AD08	Oxomemazine	X				
R06AE01	Buclizine	X				
R06AE03	Cyclizine	X				
R06AE05	Meclozine	X				
R06AX02	Cyproheptadine	X				
R06AX07	Triprolidine	X				
R06AX12	Terfenadine	X				
R06AX22	Ebastine	X				
R06AX23	Pimethixene	X				
N05BB01	Hydroxyzine	X				

1 Renom-Guiteras A, Meyer G, Thurmann PA (2015) The EU(7)-PIM list: a list of potentially inappropriate medications for older people consented by experts from seven European countries. European journal of clinical pharmacology 71 (7): 861-875 DOI 10.1007/s00228-015-1860-9

Online resource 3.

All PIMs identified with the EU (7)-PIM list by ATC-level 5

	Number of PIMs		Number of PIMs removed, not changed or added		
ATC-code	PIM before	PIM after	Removed	Not changed	Added
N05CF01	190	208	31	159	49
N05BA01	56	50	27	29	21
N02AX02	36	45	20	16	29
R05DA01	28	17	23	5	12
N05CD02	26	21	8	18	3
A10BB12	25	22	4	21	1
B01AC07	23	55	9	14	41
C08CA05	23	33	5	18	15
A03FA01	21	22	16	5	17
N05CF02	20	22	6	14	8
N06AA09	18	14	7	11	3
C01AA05	15	19	4	11	8
A02BA02	14	15	3	11	4
C08DA01	14	11	5	9	2
G04BD08	13	12	5	8	4
M01AB05	12	7	9	3	4
N05BB01	12	16	3	9	7
G03CA04	11	12	3	8	4
J01XE01	11	11	11	0	11
N05AA02	11	6	6	5	1
R06AD01	11	10	4	7	3
B01AE07	10	17	3	7	10
G04BD07	10	8	4	6	2
C02CA04	8	6	2	6	0
C08DB01	8	5	4	4	1
G04BD11	8	8	4	4	4
N06AX16	8	8	2	6	2
A10BH01	7	5	3	4	1
C03DA01	7	4	4	3	1
A06AB08	6	15	5	1	14
B01AF01	6	33	2	4	29
C07AA07	6	2	4	2	0
N04BC05	6	4	2	4	0
N05AF03	6	4	3	3	1
C01AA04	5	3	2	3	0
M01AH05	5	6	4	1	5
N06AB05	5	7	1	4	3
N06AA06	5	2	3	2	0
A07DA03	4	11	0	4	7

G04BD10	4	4	1	3	1
N04BC04	4	4	0	4	0
R06AB02	4	3	2	2	1
A10BB07	3	4	0	3	1
C01BC04	3	3	0	3	0
C07AA05	3	4	2	1	3
G03CA03	3	3	0	3	0
M01AE03	3	0	3	0	0
M03BX01	3	3	0	3	0
N03AF01	3	6	0	3	3
N06AB03	3	3	0	3	0
R01BA01	3	3	3	0	3
A06AB02	2	5	1	1	4
M01AC01	2	0	2	0	0
N02CC01	2	1	2	0	1
N03AA02	2	1	1	1	0
N05AB04	2	3	1	1	2
N05AF01	2	2	0	2	0
N05AN01	2	2	0	2	0
N05CM02	2	9	1	1	8
N06AX12	2	1	1	1	0
A04AD01	1	1	1	0	1
A06AB06	1	2	0	1	1
A10BG03	1	1	0	1	0
A10BH02	1	3	0	1	2
C01BD01	1	1	0	1	0
C02AC05	1	1	0	1	0
J01MA01	1	1	1	0	1
M03BA02	1	0	1	0	0
M04AC01	1	2	0	1	1
N03AB02	1	1	0	1	0
N03AE01	1	3	0	1	2
N04BC06	1	1	0	1	0
N04AA02	1	1	0	1	0
N05AB03	1	1	0	1	0
N05AF05	1	1	0	1	0
N05BA12	1	1	0	1	0
N05CD03	1	0	1	0	0
N06AB08	1	1	0	1	0
N06AA10	1	1	0	1	0
N06AA12	1	0	1	0	0
R06AX22	1	1	0	1	0
B01AF02	0	6	0	0	6
C04AD03	0	1	0	0	1
M01AC06	0	1	0	0	1

M01AH01	0	1	0	0	1
N02CC04	0	1	0	0	1
N02CC06	0	1	0	0	1
N04BD01	0	1	0	0	1
N05CD08	0	2	0	0	2
SUM	**788**	**878**	**286**	**502**	**376**

Paper II

BMJ Open

Interdisciplinary collaboration across secondary and primary care to improve medication safety in the elderly (IMMENSE study): study protocol for a randomised controlled trial

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To cite: Johansen JS, Havnes K, Halvorsen KH., *et al*. Interdisciplinary collaboration across secondary and primary care to improve medication safety in the elderly (IMMENSE study): study protocol for a randomised controlled trial. *BMJ Open* 2018;**8**:e020106. doi:10.1136/bmjopen-2017-020106

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2017-020106).

Received 13 October 2017
Revised 7 December 2017
Accepted 12 December 2017

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ABSTRACT

Introduction Drug-related problems (DRPs) are common in the elderly, leading to suboptimal therapy, hospitalisations and increased mortality. The integrated medicines management (IMM) model is a multifactorial interdisciplinary methodology aiming to optimise 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 regard 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 randomised to control (standard care) or intervention group (1:1). The intervention comprises five steps mainly performed by pharmacists: (1) medication reconciliation at admission, (2) medication review during hospital stay, (3) patient counselling about the use of medicines, (4) a comprehensible and patient-friendly medication list with explanations in discharge summary and (5) postdischarge 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 and 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 NCT02816086.

Strengths and limitations of this study

- ► No randomised controlled trial investigating the effects of implementing an integrated medicines management-based intervention in the Norwegian healthcare setting has yet been published.
- ► National healthcare registries will enable us to collect high-quality data for several outcomes including the primary outcome.
- ► Collecting outcomes for a 1-year period after discharge allows us to measure sustainable effects of the intervention.
- ► Including control and intervention patients from the same wards may introduce education and contamination bias.
- ► As the intervention is complex this study will not allow for studying whether any of the specific steps are more or less responsible for any observed effects.

INTRODUCTION

Healthcare systems across the world are challenged by an ageing population. Ageing 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 pharmacodynamics 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 hospitalisation, 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 hospitalised 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 optimise 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 readmission 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 readmissions, 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 randomised controlled trial investigating the effects of implementing the IMM model in the Norwegian healthcare system has been published.

Based on the IMM model, we have designed an interdisciplinary collaboration structure aiming to optimise 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, 30-day readmissions, 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 supplementary file for SPIRIT 2013 checklist).

Study design

This is a non-blinded randomised 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.

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 specialised 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. Enrolment is only performed when a pharmacist is present. Readmitted study patients are not reincluded, 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 randomisation or in control group).

Randomisation and blinding

After collecting baseline data, patients are randomised into the two study arms using a web-based service supplied by a third party. The randomisation 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,

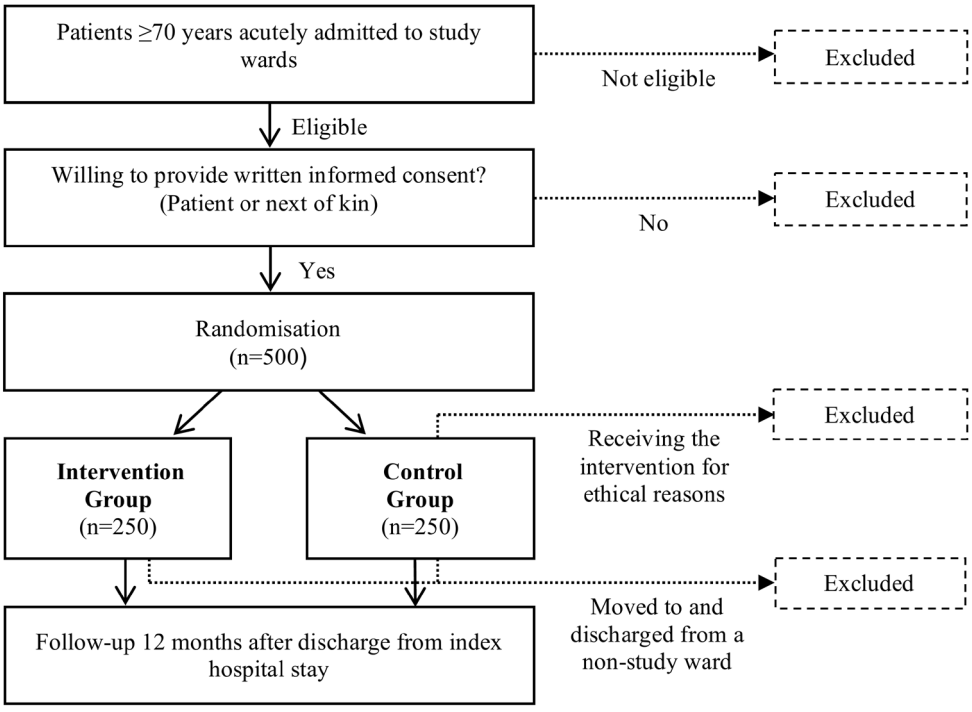

Figure 1 Flow chart of the study and study participants.

and 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 standardised, 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 programme. 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 require 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 arecared for by the home care services, 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 specialised patient care team before or at discharge. This team may include a pharmacist, which may supply pharmaceutical care services.

The intervention

Patients randomised 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 patient's 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.

Step 1: medication reconciliation

MedRec is performed using a standardised 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

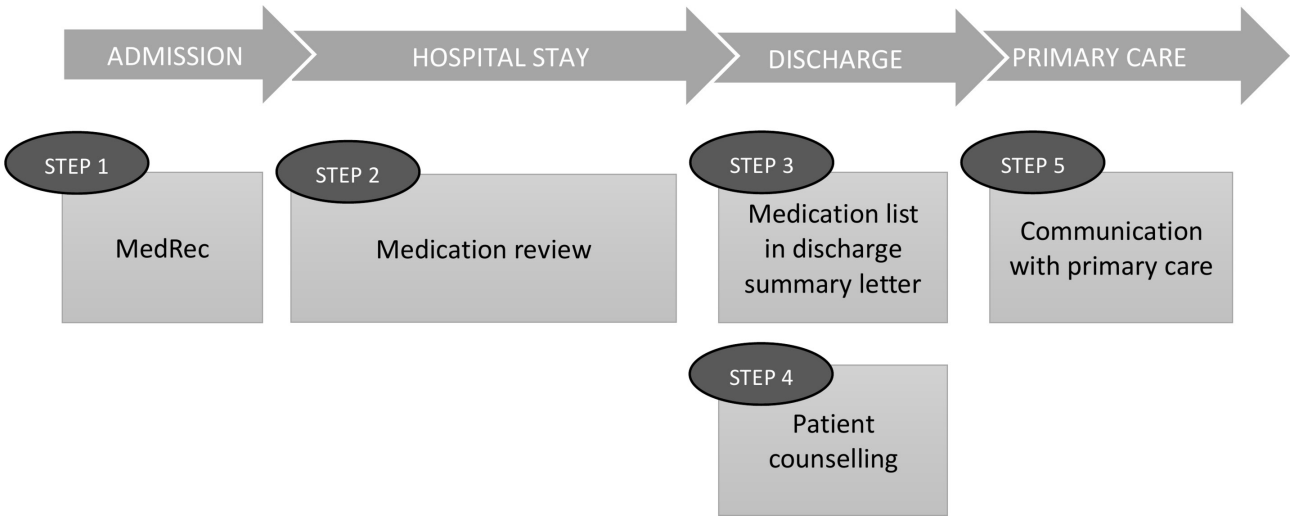

Figure 2 The intervention based on the IMM model (steps 1–4)[21]. Step 5 is added to the original model. IMM, integrated medicines management; MedRec, medication reconciliation.

own medication are interviewed if possible. If not, information about medication use is collected from other relevant sources, that is, 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 on during patient counselling or at hospital discharge (step 3).

During MedRec, the study pharmacists also perform a standardised 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 10 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 healthcare 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 standardised tool, developed in Sweden and adapted to Norwegian circumstances/conditions, 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 (eg, 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 on 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 on. 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 recommendations from the national patient safety programme. They make sure it is reconciled, structured and correct according to amendments done and include 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 call 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 call the responsible nurse to inform about medication changes, prescription and monitoring needs and other medication-related recommendations. Changes in multidosage 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 'acute readmissions and ED visits' 12 months after discharge from the index hospital stay in the intervention group compared with the 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 HRQoL from discharge to 1, 6 and 12 months after hospital discharge.
2. Length of index hospital stay.
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 of the Medication Appropriateness Index (MAI) from admission to discharge.
8. Change in potentially inappropriate medications prescribed identified by The Norwegian General Practice—Nursing Home criteria (NORGEP-NH), Screening Tool of Older Persons' Prescriptions (STOPP) V.2 and Screening Tool to Alert doctors to Right treatment (START) V.2 from admission to discharge.
9. Change in potentially inappropriate medications prescribed using START V.2, STOPP V.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. 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 randomised 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 randomised 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 randomisation 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 multidosage dispensed medications, medical diagnosis/medical history, weight, blood pressure, heart rate, relevant laboratory values (eg, 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 (eg, discrepancies identified during MedRec, DRPs, physician agreement with regard to identified discrepancies or DRP, counselling issues, etc) during hospitalisation and track communication between pharmacist, patients and healthcare 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 (hospitalisations and 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 prestudy 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 MAI by an experience pharmacist blinded to group allocation.[33 34]

Health-related quality of life

We use EuroQol 5 dimension (EQ-5D) and EuroQol visual analogue Scale (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 calls patients and performs the interview by phone. Patients where next of kin provide informed consent are 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, are 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 V.25 for data analysis. Data will be analysed according to intention-to-treat principle, and the reporting of results will follow the Consolidated Standards of Reporting Trials 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 endpoint during 12 months after discharge between the two study groups. Censoring of study participants will be accounted for, and adjustment for study site will be conducted. A two-sided alpha level of 5% will be used. We will 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 endpoint. In all analyses, adjustment for baseline variables will be conducted if appropriate.

We will analyse secondary outcomes applying appropriate statistical tests, for example, 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 70–79, 80–89 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 Declaration of Helsinki. 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 are 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 healthcare 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.

Acknowledgements We are extremely grateful to all participants in the study, employees at the departments where the study is performed, and our collaboration partners both at UNN Harstad, UNN Tromsø and the Hospital Pharmacy of North Norway Trust, in particular Kristian Svendsen. We would like to thank the clinical research department at UNN, and in particular Birthe Lund Angermo for help with data collection. We would also like to thank Inger Sperstad at UNN Tromsø for developing the Access Database and last but not least our funding body, the Northern Norway Regional Health Authority.

Contributors JSJ, KH, KHH, BHG, SH, EK, LWS, KKV, LM and AGG were involved in study design. JSJ, KH, KHH and BHG drafted the manuscript. SH, EK, LWS, KKV, LM and AGG read and commented on the draft. JSJ, KH, KHH, BHG, SH, EK, LWS, KKV, LM and AGG all read and approved the final manuscript.

Funding This work is supported by the Northern Norway Regional Health Authority grant number HST1314-16. The publication charges for this article have been funded by a grant from the publication fund of UiT—The Arctic University of Norway.

Disclaimer The sponsor has no part in collection, management, analysis and interpretation of the data, as well as writing and reporting study conclusions.

Competing interests None declared.

Patient consent Obtained.

Ethics approval The study has approval from the Norwegian Centre for Research Data and the Norwegian Data Protection Authority to collect, store and link research data.

Provenance and peer review Not commissioned; externally peer reviewed.

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Paper III

Received: 13 October 2021 | Revised: 12 November 2021 | Accepted: 23 November 2021

DOI: 10.1111/jcpt.13581

Journal of Clinical Pharmacy and Therapeutics WILEY

ORIGINAL ARTICLE

Intervention fidelity and process outcomes of the IMMENSE study, a pharmacist-led interdisciplinary intervention to improve medication safety in older hospitalized patients

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Funding information
Helse Nord RHF, Grant/Award Number: HST1314-16

Abstract

What is known and Objective: The majority of hospitalized older patients experience medication-related problems (MRPs), and there is a call for interventions to solve MRPs and improve clinical outcomes like medical visits. The IMMENSE study is a randomized controlled trial investigating the impact of a pharmacist-led interdisciplinary intervention on emergency medical visits. Its multistep intervention is based on the integrated medicines management methodology and includes a follow-up step with primary care. This study aims to describe how the intervention in the IMMENSE study was delivered and its process outcomes.

Methods: The study includes the 221 intervention patients in the per-protocol group of the IMMENSE study. Both intervention delivery, reasons for not performing interventions and process outcomes were registered daily by the study pharmacists in a Microsoft Access® database. Process outcomes were medication discrepancies, MRPs and how the team solved these.

Results and discussion: A total of 121 (54.8%) patients received all intervention steps if appropriate. All patients received medication reconciliation (MedRec) and medication Review (MedRev) (step 1 and 2), while between 10% and 20% of patients were missed for medication list in discharge summary (step 3), patient counselling (step 4), or communication with general practitioner and nurse (step 5). A total of 437 discrepancies were identified in 159 (71.9%) patients during MedRec, and 1042 MRPs were identified in 209 (94.6%) patients during MedRev. Of these, 292 (66.8%) and 700 (67.2%), respectively, were communicated to and solved by the interdisciplinary team during the hospital stay.

What is new and Conclusion: The fidelity of the single steps of the intervention was high even though only about half of the patients received all intervention steps. The impact of the intervention may be influenced by not implementing all steps in all patients, but the many discrepancies and MRPs identified and solved for the patients could explain a potential effect of the IMMENSE study.

KEYWORDS
aged, hospitalization, integrated medicines management, pharmacists, randomized controlled trial

1 | WHAT IS KNOWN AND OBJECTIVE

Providing optimal medication therapy to patients becomes more challenging with increasing age and morbidity. The majority of hospitalized older patients experience medication-related problems (MRPs), defined as events or circumstances involving medication therapy that actually or potentially interferes with desired health outcomes.[1,2] MRPs can cause serious harm followed by increased morbidity and healthcare costs, and older patients are particularly vulnerable.[3-5] Interventions to identify, prevent and solve MRPs are consequently warranted. Since medication reviews (MedRevs) alone have failed to show improved clinical outcomes,[6,7] interventions should preferably be multifaceted and multi-disciplinary.[7-9] This is the case for the integrated medicines management (IMM) model, a systematic approach that integrates the services medication reconciliation (MedRec), MedRev, patient counselling and correct dissemination of medication information at transition points, holding the clinical pharmacist as a key team member.[10,11] It is recognized that these might be common practices already in some countries. In 2012, the Norwegian hospital pharmacies decided to build their developing clinical services on the IMM model.[12] In Norway, as in many European countries, clinical pharmacy is still a novel role for hospital pharmacists[13]. Pharmacists performing MedRec, MedRev and patient educations as members of interdisciplinary ward teams is not a part of standard care in most hospitals.

The IMMENSE (Interdisciplinary collaboration across secondary and primary care to improve medication safety in the elderly) study is a two-armed randomized controlled trial (RCT) aiming to increase medication safety in older adults over 70 years (ClinicalTrials.gov Identifier: NCT02816086).[14] The intervention comprises an interdisciplinary team collaboration, applying the IMM methodology,[10,15] in addition to post-discharge communication with primary care, see Figure 1. Its primary endpoint is the rate of emergency medical visits (acute readmissions and visits to emergency departments) in intervention vs. control patients 12 months post-discharge.

The multistep intervention in the IMMENSE study aims to improve the complex process of medicines optimization and target different organizational levels. It requires trained pharmacists working in close collaboration with other health professionals and patients, and there will likely be many factors influencing the outcomes of the trial. Information about these factors is necessary to evaluate, interpret and understand the trial results and subsequently implement the intervention in routine practice or design improved interventions.[16] Information about whether the intervention was delivered according to protocol, often defined as fidelity, is important.[17] Process outcomes describe the MRPs identified and how these were solved due to the implementation of the intervention. Together, fidelity and process outcomes can be seen as potential mediators of the relationship between the intervention and its outcomes.[16,18]

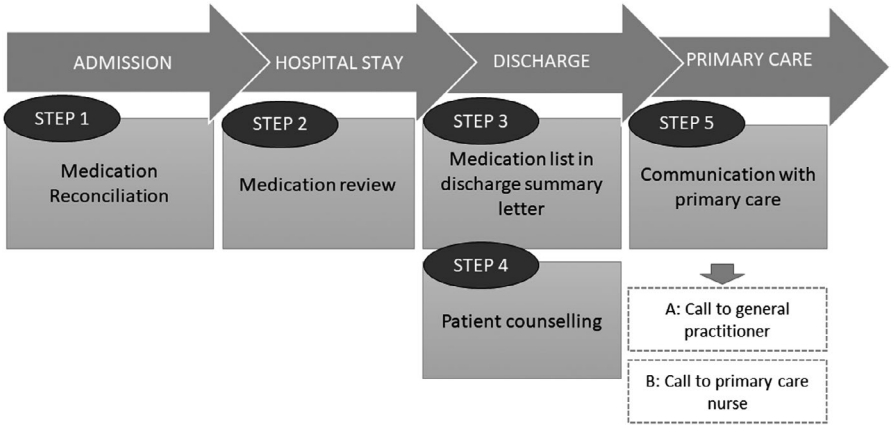

FIGURE 1 Intervention delivered in the IMMENSE (Interdisciplinary collaboration across secondary and primary care to improve medication safety in the elderly) study. Figure adapted from figure 2 in reference [12]

In this study, we aim to describe the IMMENSE study's intervention fidelity and process outcomes (see Table 1 for specific research questions).

2 | METHODS

2.1 | Study design

This study analyses data collected in The IMMENSE study, a two-armed RCT including patients from September 2016 to December 2019, finalizing follow-up in December 2020. The main results are expected in 2022.

2.2 | Setting and intervention

The IMMENSE study was conducted at two medical wards at the University hospital of North Norway.[14] Study ward A was a specialized geriatric acute care ward, with a pharmacist present every weekday from 8 am to 3.30 pm. Study ward B was a general internal medicine ward in a smaller hospital with a pharmacist present every other weekday from 8 am to 3.30 pm. Patients were randomized 1:1 to an intervention or control group. A full description of the intervention can be found in the published protocol.[14] Briefly, the intervention comprised five steps: (1) medication reconciliation (MedRec) at admission, (2) medication review (MedRev) during the hospital stay, (3) a comprehensible and patient-friendly medication list with explanations in discharge summary (draft made by the pharmacist), (4) patient counselling at discharge with updated medication list and (5) post-discharge phone calls to primary care (see Figure 1). Detailed standard operational procedures guided all steps. Control group patients received standard care, that is care *without* a pharmacist in the team.

2.3 | Participants

The IMMENSE study included patients aged 70+ years, as described in the study protocol.[14] Of the 516 included patients, 259 were randomized to the intervention group. The present study includes the 221 intervention patients in the per-protocol group, 181 from study ward A and 40 from study ward B.

2.4 | Data collection

The study pharmacists documented patient information and interventions delivered per patient in a Microsoft Access® study database, in addition to process outcomes (medication discrepancies and MRPs) and results from team discussions. Reasons for not delivering the intervention steps were also recorded. In addition, the pharmacists documented all patient counselling and communication with primary care in the patients' medical records.

2.5 | Intervention fidelity

We used the study database to identify which intervention steps had been delivered to each patient or whether there were protocol deviations when adapting the intervention in real life. For example, the protocol states that the patient's general practitioner should be contacted within 1 week of discharge, but this was not always possible. The full intervention coverage was calculated as the number of patients where the study pharmacist had self-declared delivering intervention steps, also including steps not delivered when not relevant to patients according to the study protocol. For this study, step five was dichotomized as following: a) call to general practitioners and b) call to primary care nurses.

2.6 | Process outcome assessment

A medication discrepancy was defined as an inconsistency between the medication list in the hospital and the medication list obtained by the study pharmacist after a structured MedRec process. Medication discrepancies were categorized applying categories developed and used in the Norwegian IMM procedure, with some local adaptions (Table 2). MRPs identified during MedRev, and considered by pharmacists to be relevant for team discussion, were categorized by applying the validated classification system for MRPs developed by Ruths et al.[19] Recommendations to solve MRPs were classified into 15 categories developed by the research team (Table 2). Outcomes from discussions within the interdisciplinary team were categorized as following: i) recommendation implemented, ii) MRP to be communicated to general practitioners, iii) recommendation not implemented by physician or rejected by patient, iv) implementation status unknown or missing.

2.7 | Data analysis and statistics

We used IBM® SPSS Statistics version 26 and Microsoft® Excel 2019 for data management and analysis. Results are described with numbers, means and standard deviations (SDs). The median, interquartile range (IQR) and minimum and maximum values have been applied for non-normally distributed data.

2.8 | Ethical approval

The IMMENSE study has approval from the Norwegian Centre for Research Data and the Norwegian Data Protection Authority to collect, store and link research data. Informed consent was

TABLE 1 Research questions for this study, table inspired by Kempen et al[24]

	Research questions
Intervention fidelity	What percentage of intervention group patients received the different intervention steps as defined in the study protocol?
	What were the reasons for protocol deviation?
	Is there a difference in fidelity between the two study wards?
Process outcomes	In what percentage of patients did the study pharmacist identify medication discrepancies?
	In what percentage of patients did the study pharmacist identify MRPs?
	What number and types of discrepancies were identified during MedRec?
	What number and types of MRPs were identified during MedRev?
	What proportion of discrepancies were discussed in the interdisciplinary team?
	What types of recommendations were made to solve MRPs?
	What was the outcome of the medication-related discussions in the interdisciplinary team?

obtained from patients or from next of kin when patients were not competent to consent.

3 | RESULTS

3.1 | Study population

Of the 221 patients, 63.3% were females, the mean age was 83.4 (SD 6.3), and the median length of hospital stay was five days (IQR: 3–8.5, range 0–48). Before MedRec, the median number of medications used regularly and as needed were 6 (IQR:4-9, range 0-23) and 2 (IQR:0-3, range 0-11). At discharge, only 49 patients (22.2%) self-administered medications.

3.2 | Intervention fidelity

A total of 121 (54.8%) patients received the full intervention, which was higher in study ward A (58.6%) compared to study ward B (37.5%). Most patients (34.8%) not receiving the full intervention missed only one step (see Figure 2)

Step 1–2. All patients (n = 221) received MedRec and MedRev.

Step 3. A medication list according to the study protocol was present in the discharge summary for 177 patients (80.1%), indicating that physicians used the pharmacist drafts as intended. In 36 patients, the medication list had elements in line with the pharmacist draft but did not fully adhere. The medication list for eight patients was not in line with the study protocol.

Step 4. A patient counselling session (including next of kin for some patients) was performed in 112 patients (50.7%). For 86 patients, patient counselling was not performed because they were not in charge of their medications at discharge. Consequently, 10.5% of the study population did not receive medication counselling when they should have. Only 62 (55.3%) patients received a written medication list as part of the counselling session.

Step 5a. The pharmacists communicated medication changes, the reason for the change, and follow-up issues, including unsolved MRPs, in a phone call to the general practitioner for 153 patients (69.2%). In 28 patients, there were no changes in medications or follow-up issues justifying a call to the general practitoner. Consequently, this step was not delivered for 18.1% of patients. The study protocol states that general practitioners should be contacted within 1 week from discharge, which was achieved for 108 patients (48.9%). The median time from discharge to contact was four days (IQR 2–9, range −1, 34). The primary reason for the delayed contact was difficulties in reaching the physicians.

Step 5b. The pharmacists or the hospital nurses communicated medication changes and monitoring needs to the primary care nurses for 112 and 38 patients (68%), respectively. For 49 patients, no primary care nurse was involved in medication handling, and no follow-up call was necessary. Consequently, 10% of patients missed this step.

3.3 | Process outcomes

3.3.1 | Medication discrepancies during MedRec

The pharmacists identified 437 medication discrepancies (median 1, IQR 0–3, range 0–10) in 159 patients (71.9%), see Table 2. Of the discrepancies, 92.9% were presented to and discussed with the physician, and changes were made in the medication charts for 292 discrepancies (66.8%). The discrepancies involved 164 different medications, most frequently paracetamol and zopiclone involved in 34 and 21 discrepancies, respectively.

TABLE 2 Prosses outcomes identified in the study patients ($N = 221$)

Outcome description	Number identified	Number of patients involved, *n* (%)
DISCREPANCIES DURING MEDICATION RECONCILIATION	437	159 (71.9)
Medication omission	191	101 (45.7)
Regular use	88	
Pro re nata or temporary use	102	
Medication no longer in use	89	52 (23.5)
Frequency/dosing incorrect	82	56 (25.3)
Strength incorrect	41	33 (14.9)
Timing incorrect	22	21 (9.5)
Administration form incorrect	9	9 (4.1)
Medication mix-up (wrong medication name)	3	3 (1.4)
MRPs DURING MEDICATION REVIEW	1042	209 (94.6)
1. Medication Choice	537	181 (81.9)
a) Need for additional medication	158	
b) Unnecessary medication	197	
c) Inappropriate medication choice	182	
2. Dosage	210	124 (56.1)
a) Too high	119	
b) Low dose	53	
c) Sub-optimal dosing scheme	9	
d) Sub-optimal formulation	29	
3. Adverse drug reaction	63	51 (23.1)
4. Interaction	83	60 (27.1)
5. Medication use	29	25 (11.3)
a) Administered by health personnel	5	
b) Administered by the patient	24	
6. Other	120	78 (35.3)
a) Need for/lack of monitoring of effect and toxicity	61	
b) Lack of or unclear documentation of the medication chart /prescription	28	
c) Other	31	

3.3.2 | Medication-related problems during MedRev

A total of 1042 MRPs (median 4, IQR 2–6, range 0–28) were identified in 209 patients (94.6%), see Table 2. The most prevalent MRPs were related to medication choice, identified in 181 patients (81.9%), and dosage, identified in 124 (56.1%) patients. A total of 700 MRPs (67.2%) were solved in the interdisciplinary team in hospital as recommended by the pharmacist, while 239 MRPs (22.9%) were communicated to primary care because the general practitioner was in a better position to initiate and follow-up on changes. For the MRPs discussed with the general practitioner in step 5, 46 were solved, 11 were not solved, and for 182, actions taken by the general practitioner are unknown. Figure 3 shows the distribution of agreement with the different solutions to MRPs proposed by the pharmacist. The medications most frequently involved in MRPs included zopiclone (37 MRPs), paracetamol (35 MRPs), pantoprazole (35 MRPs), polyethylene glycol (30 MRPs) and iron preparations (30 MRPs).

4 | DISCUSSION

4.1 | Intervention fidelity

This study shows an overall fidelity of the IMMENSE intervention of 54.8%, where only one step was missing for most patients not receiving the entire intervention. It is not known which part of the intervention (if any) is the most effective, consequently the implication of missing one or more steps on the trial outcome is unknown. For the single steps, all were delivered to over 80% of patients. An

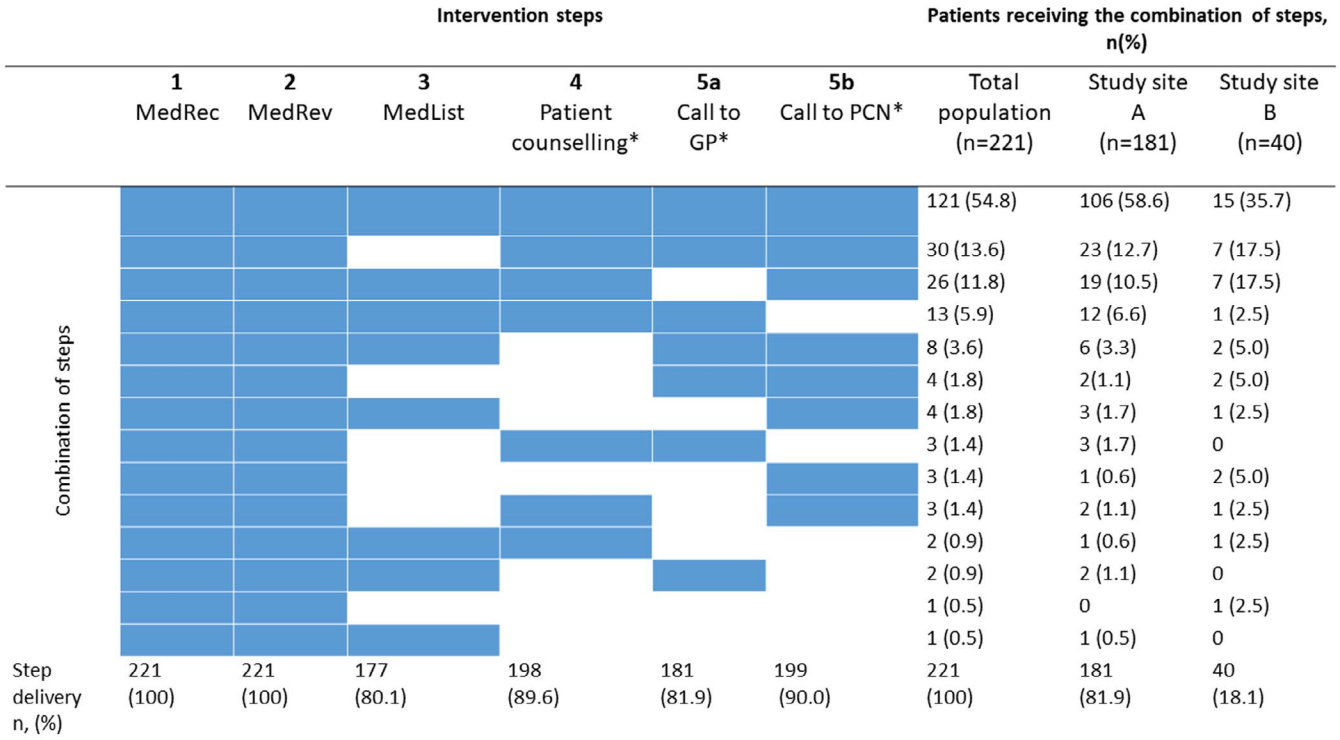

FIGURE 2 Intervention step delivery in the total population and at the two study wards. GP; General practitioner, MedRec; medication reconciliation, MedRev; Medication Review, MedLIst; Medication list at discharge, PCN; primary care nurse *Step delivery includes patients who were delivered the intervention and patients where an intervention was not indicated according to the protocol (ie patients with no primary care nurse)

overall fidelity of 54.8% is in line with other studies showing fidelity of 53–67% of similar complex interventions,[20,21] while many studies do not report overall fidelity.[9,10,22,23]

The study pharmacists performed MedRec and MedRev (step1&2) more frequently than the other steps, which has also been reported by others.[21,24] This may be because the pharmacist can perform both MedRec and MedRev independently of the team if electronic medical records and patients are available. The other steps are associated with more implementation barriers due to dependency of other team members and collaboration partners. For example, handing out written medication lists during patient counselling in step 4 was challenging as lists were often not finalized by the physicians when the pharmacist found time to speak with patients. However, we identified a high proportion (80.1%) of discharge summaries with medication lists according to the study protocol, showing a high fidelity of step 3. Timing of the delivery of the medication list may not be essential to the study results in this study population, as long as appropriate lists were transferred to primary care.

Patient counselling in step 4 was feasible in few patients due to cognitive disabilities and patients not handling medications themselves post-discharge. This may make communication with primary care (step 5) more important, contrary to findings in other patient populations showing patient counselling to be essential in similar interventions.[9] During analysis, we split step five into two sub-steps to clearly show how the intervention was carried out, which also reduces overall fidelity. The challenge of getting in contact with the general practitioner further reduced the fidelity of this step. Still, the pharmacists reached the general practitioner in 153 of the 193 patients with medication follow-up issues, 108 patients within the protocol-defined week. This is high compared with a Danish study by Ravn Nilsen et al.,[9] where the general practitioner was contacted/reached in 55.0% of patients. The authors did not report on time to reach, although their goal was within three working days.

Regarding differences between the study wards, we identified a lower fidelity in study ward B, which was expected as they did not have a full-time pharmacist at the ward. In addition, there was a higher turnover of patients in this ward (data not shown), reducing the opportunity for the pharmacists to follow-up patients.

4.2 | Factors influencing intervention delivery

We believe that slow patient recruitment in the study gave the pharmacists more time to work with individual patients compared to routine practice, which may have increased fidelity. An observational time and motion study on how the IMMENSE pharmacists spent their time identified that pharmacists used on average 3.5 hours performing clinical tasks per intervention patient, 14% of this time communicating with healthcare workers and patients.[25] It is important to note that this does not necessarily reflect the time needed to complete the clinical tasks, but when no new patients are available, more thoroughly performed MedRevs are possible.

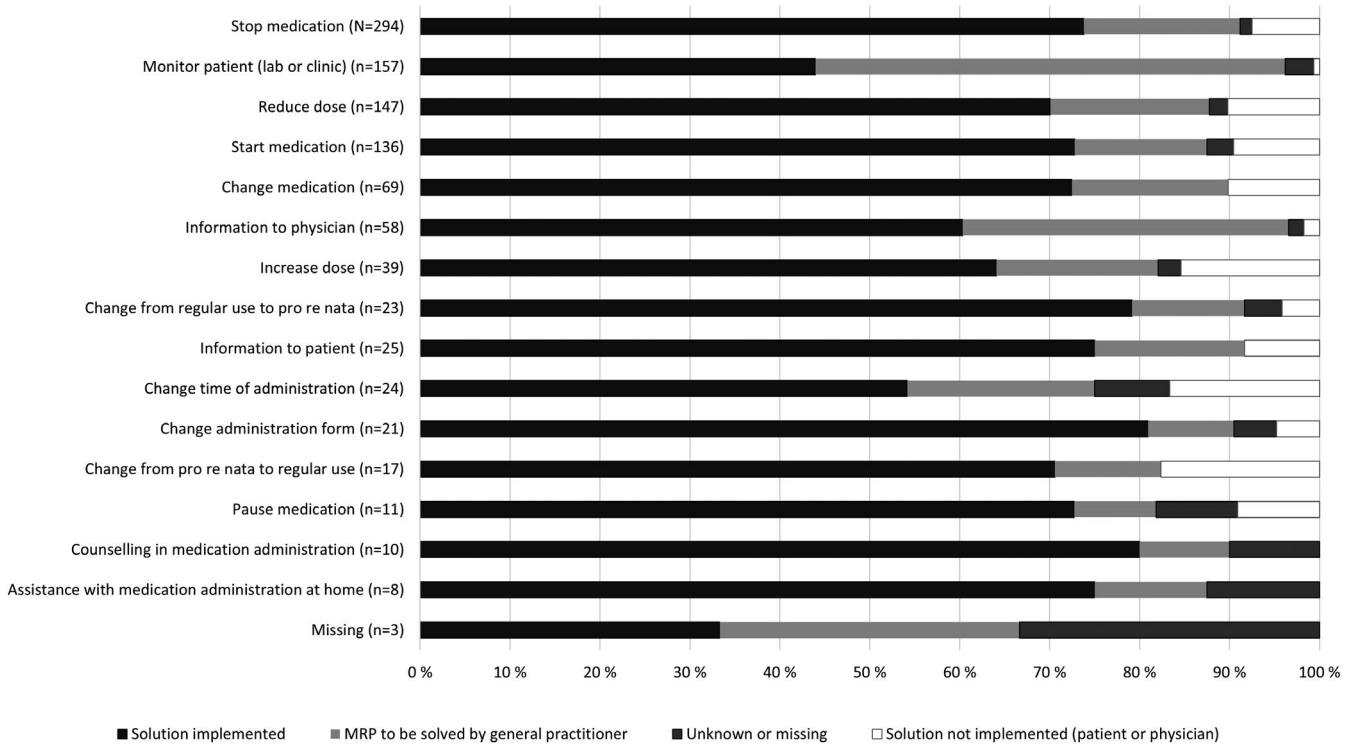

FIGURE 3 Implementation of suggested solutions to medication-related problems (MRPs) after discussion in the interdisciplinary team during the IMMENSE study ($N = 1042$)

Kempen et al. studied facilitators and barriers of ward-based pharmacist intervention in Sweden. They identified unclear roles and responsibilities of the pharmacists, the need to build personal relationships, being present at the ward, and the need for more clinical competence in pharmacists as some of the barriers to performing the intervention.[26] Similar barriers are likely to be present in our study. Having a pharmacist as an integrated team member was new both to the healthcare teams, pharmacists, patients and primary care. After study completion, both study wards have engaged clinical pharmacists in 50% positions working according to the IMM method, indicating that the other team members appreciated the pharmacist input.

4.3 | Process outcomes

The study pharmacists clearly contributed to optimizing medication use, identifying a median of one medication discrepancy and four MRPs per patient in the intervention arm. The number and frequency of discrepancies are in line with other Norwegian studies applying the IMM methodology identifying discrepancies in 70–84% of medical inpatients.[27-29] The number and frequency of MRPs are also in line with previous Norwegian and Scandinavian studies, where MRPs have been identified in 80–100% of hospitalized internal medicines patients,[2,21,23,30] in the range of 2–9 MRPs per patient.[2,22,24,30-32] The number and type of MRPs per patient vary across studies with similar interventions,[21,22,32,33] likely because of the lack of consensus concerning the classification of MRPs.[34] One outlier is the number of MRPs identified in a recently published study by Lea et al.[21] They tested IMM working procedures in an intervention similar to IMMENSE and identified 3826 MRPs in 193 intervention patients giving a mean of 19.7 MRPs per patient.[21] However, only 43% of the identified MRPs were discussed in the multidisciplinary team. Still, the difference from our findings is surprising given the similarity of the interventions and the patient populations. It may be caused by other factors like differences in pharmacist competence, adherence to the IMM procedures, and reporting and classification of MRPs.

The interdisciplinary team appreciated the pharmacist recommendations, as almost 70% were agreed upon. The high agreement rate is in line with other hospital pharmacist intervention studies in Scandinavia, showing agreement rates of 57–75%.[9,20-23,31] A reason for the high agreement in the IMMENSE study may be that the pharmacists discussed MRPs and solutions face-to-face in the interdisciplinary team, in addition to documenting in patients' records. This has been shown to increase agreement rates over written recommendations alone.[35,36]

It is to be expected that 23% of the MRPs identified by the pharmacists were communicated to the general practitioner rather than solved during hospitalization, as the general practitioners are in a better position to monitor patients when the patients are stable in their normal environment. For example, withdrawing sedative medication needs to be done over time in collaboration with the patients.[37] In addition, while optimizing medication use, it is preferable to make medication changes one by one, leaving time to monitor and evaluate the change.[38]

4.4 | Strength and limitations

By collecting and interpreting fidelity and process outcome data before the primary objectives of the IMMENSE study are analysed, we intend to give an unbiased presentation of some factors which may impact the results. The main strength of this study is the prospective day-to-day data collection in the study database as we capture the pharmacist interventions in real time and not through retrospective review, written notes and journal documents. In addition, we used a validated MRP classification system developed for a Norwegian setting and familiar to the study pharmacists.[19]

A significant limitation is that we have only measured what the study pharmacists have entered in the study database, not the quality of the intervention delivered, consequently capturing only the intervention dose delivered.[18,39] To achieve a complete fidelity description, a pre-planned process evaluation should have been performed applying a mix methods approach to measure the quality of intervention delivery, identify barriers to effective implementation, and adoptions to the context at the different study wards.[16]

Another limitation is the clinical relevance of both medication discrepancies and MRPs, as they are clearly not equally relevant. For example, paracetamol was one of the medications most often involved in MRPs and discrepancies. Although improving paracetamol use hopefully will benefit the patient, the use of paracetamol in regular doses is not frequently linked to hospitalizations.[4,40] Evaluating clinical relevance would have strengthened the interpretations of this study.

5 | WHAT IS NEW AND CONCLUSION

In the IMMENSE study, 54.8% of the patients received the full intervention, where only one step was missing in most patients not receiving the entire intervention. MedRec and MedRev were the only steps delivered to all patients. Fidelity was lower at one study ward, showing the need for the pharmacist to be continuously present in order to implement similar interventions. The impact of the intervention may be influenced by not implementing all steps in all patients, but the many discrepancies and MRPs identified and solved for patients could explain a potential effect of the IMMENSE study.

ACKNOWLEDGEMENTS

We are extremely grateful to all participants and collaborators in the IMMENSE study, that is patients, next of kin, pharmacist, physicians, physiotherapists, speech therapists, occupational therapists, general practitioners and nursing home employees. A special thanks to pharmacists Stine Haustreis, Lillann Wilsgård Skaue and Anne Synnøve Rian for their valuable contribution to the data collection for this study.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Johansen JS, Halvorsen KH, Havnes K, Wetting HL, Svendsen K, Garcia BH. Intervention fidelity and process outcomes of the IMMENSE study, a pharmacist-led interdisciplinary intervention to improve medication safety in older hospitalized patients. *J Clin Pharm Ther*. 2021;00:1–9. doi:10.1111/jcpt.13581

Paper IV

Submitted manuscript

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

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Trial registration status

Trial number in clinicaltrials.gov: NCT02816086 (date of first registration May30 st 2016)

ABSTRACT

Introduction: Suboptimal medication use contributes to a substantial proportion of hospitalizations and emergency department visits in older adults. We designed a clinical pharmacist intervention to optimize medication therapy in older hospitalized patients. Based on the integrated medicine management (IMM) model, the 5-step IMMENSE intervention comprise medication reconciliation, medication review, reconciled medication list upon discharge, patient counselling, and post discharge communication with primary care. The objective of this study was to evaluate the effects of the intervention on healthcare use and mortality.

Methods: A non-blinded parallel group randomized controlled trial was conducted in two internal medicine wards at the University Hospital in North Norway. Acutely admitted patients ≥70 years were randomized 1:1 to intervention or standard care (control). The primary outcome was the rate of emergency medical visits (readmissions and emergency department visits) 12 months after discharge.

Results: Of the 1510 patients assessed for eligibility, 662 patients were asked to participate, and 516 were enrolled. The modified intention-to-treat population comprised 480 patients with a mean age of 83.1 years (SD: 6.3); 244 intervention patients and 236 control patients. The number of emergency medical visits in the intervention and control group was 497 and 499, respectively, and no statistically significant difference was observed in rate of the primary outcome between the groups [adjusted incidence rate ratio of 1.02 (95 % CI: 0.82-1.27)]. No statistically significant differences between groups were observed for any of the secondary outcomes, neither in subgroups, nor for the per-protocol population.

Conclusion: We did not observe any statistical significant effects of the IMMENSE intervention on the rate of emergency medical visits or any other secondary outcomes after 12 months in hospitalized older adults included in this study.

KEY MESSAGES

What is already known on this topic. Providing clinical pharmacist services is an effective way to identify and solve medication-related problems in hospitalized older adults. The best way to provide clinical pharmacist services to reduce use of health care post-discharge is

unknown, but the need for multifaceted interventions bridging the transition to primary care has been suggested.

What this study adds. In this randomized controlled trial we did not observe any significant effect on healthcare use when providing a multifaceted clinical pharmacist intervention with enhanced primary care follow-up in old hospitalized patients.

How this study might affect research, practice or policy. Readmissions and ED visits might not be outcomes sensitive to the effects of hospital-based clinical pharmacist services in all study settings.

INTRODUCTION

Medications have a pivotal role in enhancing the quality of life and preventing morbidity and mortality, but are also an important cause of patient harm, especially in older adults[1, 2]. A medication-related problem (MRP) is defined as 'an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes[3, 4]. Among older adults, 10-20% of hospitalizations are caused by MRPs[5-9] and possibly even more in patients with multimorbidity or dementia[10, 11]. A large proportion of these medication-related hospitalizations may be preventable[5, 6, 8].

Providing clinical pharmacist services in hospitals, such as medication reconciliation, medication review, and patient counselling can reduce the number of medication discrepancies, identify, and solve MRPs, improve medication appropriateness, and improve adherence[12-16]. However, studies investigating the effects of clinical pharmacist services on patient outcomes such as readmissions and emergency department (ED) visits have shown conflicting results[16, 17]. Systematic reviews suggest that multifaceted interdisciplinary interventions with pharmacists as integrated team members may be necessary for interventions to impact patient outcomes[16, 18, 19].

The integrated medicines management (IMM) model, is an example of such an interdisciplinary intervention for which reduced rate of readmissions, increased time to readmission, and increased overall survival has been shown[13, 20-22]. The IMM model systematically integrates medication reconciliation, medication review, patient counselling and dissemination of correct medication information at transition points, holding clinical pharmacists as key team members[13, 20]. However, there are conflicting results on patient outcomes. A recently published randomized controlled trial (RCT) from Norway found no significant effects on readmissions in hospitalized multimorbid patients[22]. As older patients are particularly vulnerable to new hospitalizations in the time after discharge, bridging the transitions across secondary and primary care may be an important element in interventions aiming to reduce hospital visits[23].

Based on the IMM model, we designed an interdisciplinary intervention aiming to enhance communication with health care workers in primary care. The primary aim of the randomized controlled trial IMMENSE (IMprove MEdicatioN Safety in the Elderly) was to investigate the effects of the intervention on the rate of emergency medical visits (readmissions and ED-visits) 12 months after discharge in older inpatients[24]. Secondary aims were to investigate its impact on i) the length of index hospital stay ii) time to first acute readmission, iii) the proportion of patients readmitted acutely within 30 days and iv) mortality rate during the same period.

METHODS

Study design

This is a parallel group non-blinded RCT with an intervention group and a control group (1:1 ratio). Study enrolment started in September 2016, with follow-up of the last patient ending in December 2020.

The trial was conducted in compliance with the published study protocol[24], the principles of Good Clinical Practice and the Declaration of Helsinki and is reported according to The Consolidated Standards of Reporting Trials (CONSORT) reporting guideline and template for intervention description and replication (TIDieR) checklist[24-27]. The Norwegian Centre for Research Data and the Norwegian Data Protection Authority gave ethical approval, and the trial was registered in clinicaltrials.gov on May 30th 2016, before enrolment started (NCT02816086).

Settings and participants

The study was carried out at two study sites; a geriatric internal medicine ward and a general internal medicine ward at the University Hospital of North-Norway (UNN). The geriatric ward cares for older patients with complex acute medical needs, and physicians are 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.

Inclusion criteria were acutely admitted patients aged ≥70 years and willing to provide written informed consent (patient or next of kin). Patients were excluded if they had been admitted to the study ward more than 72 hours before evaluation of eligibility, moved to and discharged from other wards during the index stay, unable to understand Norwegian (patient or next of kin), considered terminally ill or with a short life expectancy, were 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 intervention from a study pharmacist was considered necessary for ethical reasons (before randomization or in the control group). Readmitted

study patients were not re-included but received standard care. Patients referred to a patient-centred care team project upon discharge, including pharmaceutical care, were not excluded.

Patients were screened for eligibility and recruited by study pharmacists. Enrolment and clinical work were performed from 8.00 am - 3.30 pm on weekdays. In the geriatric ward, the pharmacists were present every weekday, but only every other weekday in the general medicine ward. Patients were approached for inclusion in the inverse order of admittance to the ward to avoid selection bias.

Randomization and blinding

After collecting baseline data, patients were randomized by the study pharmacist using a web-based service supplied by a third party. The randomization block sizes were permuted, of unknown and variable size and stratified by the study site. As pharmacists were only involved with patients in the intervention group, blinding of group allocation for patients, pharmacists, and the interdisciplinary team was impossible. However, the primary analysis was performed by an investigator not involved in the data collection and blinded for group allocation (KS).

The intervention and standard care

The intervention was based on the IMM model, including a pharmacist in the interdisciplinary ward team working closely with the patients, physicians, and other team members, as described in the published study protocol[24]. Briefly, the five-step IMMENSE intervention comprised medication reconciliation, medication review, medication counselling, transmission of medication information upon discharge and finally, oral communication with primary care after discharge, see **Table 1**. Control group patients received standard care, which was care from the same ward team, except the services provided by the pharmacist. Six pharmacists were involved in delivering the intervention throughout the study period, all holding master's degrees in pharmacy and trained in the IMM study procedures.

TABLE 1 DESCRIPTION OF THE IMMENSE INTERVENTION STEPS WITH CORRESPONDING ACTIVITIES IN STANDARD CARE

	Description Intervention	Description standard care
Step 1: Medication reconciliation	If possible, patients were interviewed about their ongoing medications, applying a standardized IMM medication reconciliation interview, including questions about medication use, practical handling, knowledge and medication adherence. Information about the patients' medicines use was also collected from other relevant sources, and a best possible medication list was compiled. This pharmacist-compiled medication list was compared to the medication list in use in the hospital at study inclusion and medication discrepancies discussed with the physicians and corrected where necessary.	As part of the national patient safety program, medication reconciliation should be performed by a physician at admission and the sources used in the reconciliation process documented in the patient journal.
Step 2: Medication review	A standardized IMM procedure for identifying MRPs was applied. The structured and comprehensive medication review identifies MRPs in ten prespecified risk categories. Identified MRPs were discussed in the interdisciplinary team and with patients if possible, the physician being in charge of medication changes. The medication review was performed at study inclusion and updated regularly during the hospital stay when the study pharmacists were present at the ward.	Medication reviews performed by physicians are a part of standard care, especially in the geriatric ward, however it is not standardized or structured .
Step 3: Medication list in discharge summaries	The study pharmacists drafted medication lists in the electronic medical journals that were reconciled, structured and correct. The medication lists included information and explanations about medication changes made during the hospital stay and unsolved MRPs with recommendations, as well as needs for monitoring of medication therapy. This information was used by the responsible ward physician to compile the final discharge summary to be submitted to the primary care physicians.	Local procedures for communication of medication information at hospital discharge require that a discharge summaries, including updated medication lists in addition to assessments, amendments and recommendations made during the hospital stays, are submitted electronically to the GP upon discharge. This is the responsibility of the physician.
Step 4: Patient counselling	A patient counselling session with the study pharmacist was arranged before discharge for patients who would handle their own medication after discharge. The patients should receive an updated medication list, which was discussed and explained. In the counselling, the pharmacists focused on changes made during the hospital stay and the reasons for these changes. Patients were also encouraged to ask questions about their medications.	Physicians normally talk to all patients upon discharge; the focus on medications depends on the physicians´priorities and the patients' needs.
Step 5: Communication with primary care	Within a week after discharge, the pharmacists called the patients' GP to discuss medication therapy changes made in hospital, as well as recommendations and monitoring needs stated in the discharge summary (if relevant). The aim was to ensure that the changes and recommendations were implemented and acted upon. Upon discharge, the pharmacists or ward nurses called home care services or nursing homes if these were responsible for administering the patients' medications. Medication changes were discussed, and multi dosage dispensed medications changed in agreement with home care services.	Oral communication with GPs upon discharge is not part of standard care. For patients living in nursing homes or cared for by the home care services, ward nurses often call to investigate the need for prescriptions or medications to be sent home with the patients.

GP; general practitioner, IMM; integrated medicines management, MRP; Medication-related problem

Primary and secondary outcomes

The primary outcome was the rate of emergency medical visits 12 months after discharge from the index hospital stay. Emergency medical visits is a composite outcome of acute readmissions and ED visits. We defined acute readmissions as any subsequent admission following the index stay, excluding elective readmissions. ED visits included emergency visits to the hospital and visits to municipality-run emergency medical clinics if the patients were *not* subsequently admitted to the hospital. A prespecified secondary analysis of the time to reach the primary outcome and the proportion of patients reaching the primary outcome was performed.

Secondary outcomes included i) the length of index hospital stay ii) time to first acute readmission, iii) the proportion of patients readmitted acutely within 30 days and iv) mortality rate during 12 months of follow-up. Other prespecified outcomes relating to inappropriate prescribing, medication-related readmissions and health-related quality of life specified in the study protocol will be addressed in future articles.

Data collection and outcome assessment

Baseline data collected: age, gender, marital status, level of education, type and amount of help from home care services, delivery of multi dosage dispensed medications, medical diagnosis/medical history, and medication use at the time of hospital admission. Data was registered in a Microsoft® Access database.

Data on outcomes was collected from national health registries; readmissions and hospital ED visits from The Norwegian Patient Registry, emergency medical visits to ED run by local municipalities from The Norwegian Health Economics Administration Registry, and deaths from the National Cause of Death Registry[28]. Linking data was possible through the unique personal identification number assigned all Norwegian citizens. An ED visit within the six-hour window before a hospital stay was counted as a hospital stay only. We collected registry data from 12 months before and 12 months after the index stay to enable adjustments for pre-study risk factors.

Sample size calculation

Sample size calculation for the primary outcome was based on a Swedish RCT by Gillespie et al. applying the same composite endpoint[29]. This trial investigated the effectiveness of a multifaceted intervention including post-discharge interventions performed by ward-based pharmacists in reducing morbidity and hospital visits 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. We

estimated a rate of acute hospital admissions and ED visits of 1.7 per year in our patient population. Consequently, we needed to enrol 456 patients (228 in each group) to detect a 16% reduction in hospital visits with a 5% significance level and 80% power. Taking dropouts into account, we aimed to include 250 patients in each group. We extended the enrollment period three weeks after reaching 500 patients to compensate for exclusions.

Statistical analysis

Data was analyzed by an intention-to-treat (ITT) principle but modified as registry data on endpoints were unavailable for patients who withdrew the informed consent. We also excluded patients dying during the index hospital stay from the analysis. The statistical analysis plan (SAP) can be found in **Supplement 1**. A prespecified per-protocol (PP) analysis, including patients not excluded after randomization, was also performed.

The primary analysis was a multilevel Poisson regression to handle clustering on the study ward level and repeated measurements on the patient level. We applied time out of hospital alive (days at risk of an event) in the 365 days after discharge as an offset and adjusted for the number of emergency medical visits in the 365 days prior to the index hospitalization.

Time to first readmission and time to first emergency medical visit was analyzed by the Kaplan-Meier method and the log-rank test. A Cox proportional Hazards Model (adjusted and unadjusted) was applied to estimate hazard ratios (HRs), which are presented with 95% confidence intervals (CIs). The differences in lengths of stays between groups were assessed with an independent sample Mann-Whitney test. The differences in proportions of patients alive at 12 months and patients readmitted within 30 days were compared with logistic regression (adjusted and unadjusted). A two-sided alpha level of 5% with no adjustments for multiplicity was used as a statistical significance level.

The effect of the intervention on the primary endpoint was explored in the following prespecified subgroups i) number of medications upon admission or discharge; 0-5, 6-10, >10, ii) age groups; 70-80, 80-90 and >90, iii) patient responsible for their own medication after discharge; yes, no, partly, iv) Charlson Comorbidity Index score; 0-2, >2, v) the number of hospital visits in the 12 months prior to inclusion; 0-1, >1, vi) length of hospital stay; 0-6 days, >6 days, vii) living status before hospitalization; referred from home, home-care or nursing home, and viii) ability to self-provide informed consent or not.

The multilevel Poisson regression was performed in STATA® 16.1, data management and the remaining analyses in IBM® SPSS Statistics Version 28.

RESULTS

During the enrolment period, 3742 patients ≥70 years were admitted to the two study wards, 1510 were assessed for eligibility and 662 were asked to participate. Out of the 516 who consented, 256 were randomized to the control group and 259 to the intervention group, see **Figure 1**. The rate-limiting step of the inclusion process was the pharmacists' capacity to screen and include patients while working with study patients. Consequently, many patients were discharged or admitted for >72 hours (exclusion criterion) before they could be screened or invited to participate. Of the 516 patients included, 23 patients withdrew consent and 13 died during hospitalization, leaving 480 patients in the ITT population, see **Table 2** for baseline characteristics. The PP population comprised 442 patients, as 38 patients were transferred and discharged from non-study wards and consequently excluded from the ITT population, see **Supplement 2, Table 1** for baseline characteristics.

The groups were well balanced at baseline, but control group patients received more regular medications, more help in their home, and had more emergency medical visits in the year before index stay. Medication reconciliation and medication review were provided to all but three patients. Step 3, 4 and 5 were received by 74-83% of patients where the procedures were relevant (see **Figure 1**). See Johansen et al. for further details on intervention fidelity and process outcomes (MRP and medication discrepancies) of the PP population[30].

INSERT FIGURE 1 Flow diagram of patients included in the IMMENSE study

TABLE 2 BASELINE CHARACTERISTICS OF THE ITT POPULATION (N=480)

Characteristics	Intervention group n=244		Control group n=236	
Age, mean years (SD)	83.3	(6.4)	83.0	(6.3)
Sex, female, n (%)	152	(62.3)	127	(53.8)
Study Site, n (%)				
Geriatric ward (study site 1)	198	(81.1)	191	(80.9)
General medicine ward (study site 2)	46	(18.9)	45	(19.1)
Ability to self-provide consent, n (%)	174	(71.3)	160	(67.8)
Marital status, n (%)				
Widow/widower	107	(43.9)	104	(44.1)
Married/live in partnership	101	(41.4)	88	(37.2)
Single/ Divorced/separated	34	(13.9)	41	(17.4)
Missing	2	(0.8)	3	(1.3)
Educational level, ISCED level[a] n (%)				
Elementary school, level 1	107)	(43.9	109	(46.2)
Lower/upper Secondary education, level 2-3	93	(38.1)	81	(34.3)
Higher education (<4 years), level 5-6	22	(9.0)	18	(7.6)
Higher education (>4 years), level 7-9	11	(4.5)	12	(5.1)
Missing	11	(4.5)	16	(6.8)
Living status upon admission, n (%)				
Home, no help from home care services	88	(36.1)	69	(29.2)
Home, with help from home care services	116	(47.5)	139	(58.9)
Nursing home, short term	22	(9.0)	13	(5.5)
Nursing home, permanent	18	(7.4)	15	(6.4)
Discharge to home, n (%)	151	(61.9)	132	(55.9)
Handling medications themselves, n (%)				
Yes	94	(38.5)	80	(33.9)
No	104	(42.6)	101	(42.8)
Partly	46	(18.9)	54	(22.9)
Missing	0		1	(0.4)
Co-morbidity[b] (median score, IQR)				
Charlson comorbidity index	2	(1-3.75)	2	(1-4)
Number of medications (ATC-codes) in use at hospital admission, Median (IQR)				
Total	8	(5-12)	9	(6-13)
Regular use	6	(4-9)	7	(4-10)
Use as needed	2	(0-3)	2	(0-3)
Medical history in admission notes, n (%)				
Hypertension	125	(51.5)	113	(47.9)
Atrial fibrillation	67	(27.5)	65	(27.5)
Asthma or COPD	55	(22.5)	53	(22.5)
Diabetes Mellitus	50	(20.5)	52	(22.0)
Heart failure	40	(16.4)	36	(15.3)
Dementia	34	(13.9)	32	(13.6)
Emergency medical visits, one year before index hospital stay.				
Emergency medical visits, n (% with ≥1)	462	(68.4)	548	(72.5)
Emergency medical visits, median (IQR)	1	(0-3)	1	(0-3)

Abbrevations: ATC; anatomical therapeutic chemical classification system, IRQ; interquartile range, ISCED; international standard classification of education, SD; standard deviation.

***a)** educational level categorized by the international standard classification of education [31] **b)** Co-morbidity based on diagnosis found in admission and discharge papers from index admission, calculated in accordance with Charlson et al [32].*

After 12 months, the number of emergency visits was 497 in the intervention group and 499 in the control group, with a non-significant adjusted IRR of 1.02; 95% CI: 0.82-1.27 (**Table 3**). No significant differences were identified in the subgroup analyses (**Supplement 4, Table 2**). A post hoc analysis, removing 64 patients (intervention n=32, control n=32) referred to a patient-centred care team including clinical pharmacist services upon discharge did not significantly affect the primary outcome (adjusted IRR 1.08, 95 % CI: 0.85-1.38).

TABLE 3 PRIMARY AND SECONDARY OUTCOMES IN THE ITT POPULATION (N=480)

Primary outcome after 12 months	**Intervention** (n=244)	**Control** (n=236)	Crude	Adjusted[a]
	n, median (IQR)	**n, median (IQR)**	**Incidence rate ratio (95 % CI)**	
Emergency medical visits	497 1 (0-3)	499 1 (0-3)	0.95 (0.75-1.20)	1.02 (0.82-1.27)
ED-visits	277 1 (0-2)	276 1 (0-2)	0.95 (0.72-1.26)	1.02 (0.78-1.33)
Readmissions	220 1 (0-1)	223 0 (0-1.75)	0.96 (0.73-1.25)	1.01 (0.78-1.30)
Secondary outcomes				
Days to first event	**median (%)**	**median (%)**	**Hazard rate (95 % CI)**	
Emergency medical visit	137 (71.3)	110 (70.3)	0.93 (0.75-1.15)	0.96 (0.78-1.19)
Readmission	310 (50.8)	356 (47.5)	1.05 (0.81-1.35)	1.1 (0.85-1.42)
	n (%)	**n (%)**	**Odds ratio (95 % CI)**	
Readmissions within 30 days	26 (10.7)	33 (14.0)	0.73 (0.42-1.27)	0.82 (0.46-1.44)
All-cause mortality within 12 months	48 (19.7)	46 (19.5)	1.01 (0.64-1.59)	0.67-1.69)

IQR; Interquartile Range a) Adjusted for the number of emergency medical visits during 365 days prior to the index hospital stay.

Daily risk of emergency medical visits appeared to be higher in the control group the first two months after discharge (**Figure 2a**). Still, these differences after 30 days were not significant when controlling for the rate of emergency visits in the year before the index hospital stay, with an adjusted IRR of 0.77 (95% CI 0.48 – 1.44).

INSERT FIGURE 2 Emergency medical visits in the ITT population (n=480) illustrated by a) the daily risk of new emergency medical visits and b) Kaplan-Meier plot of time to first emergency medical visit

The secondary outcomes are presented in **Table 3**; no significant differences between the groups were identified. Although not statistically significant, the Kaplan Meier plot of time to first emergency medical visit (**Figure 2b**) slightly favours the intervention group over the control group, 137 days vs 110. On the other hand, median time to first hospital readmission was lower in the intervention group with 310 days compared to the control group with 356 days, adjusted HR of 1.1; 95% CI 0.85-1.42. The median length of the index hospital stay was similar in the intervention vs control group [median 6

(IQR:4-9) vs 6 (IQR:3-11) p = 0.536]. No significant differences were identified for any of the outcomes in the PP population, although the risk estimates moved slightly in favour of the intervention group (**Supplement 2, Tables 3 and 4**).

DISCUSSION

In this trial, we observed no significant effect of the 5-step IMMENSE intervention on the rate of emergency medical visits 12 months after discharge in hospitalized older adults compared to standard care. Nor did we observe any significant effects on the secondary outcomes related to healthcare use and mortality. The lack of observed effects is likely multifactorial, influenced by both the complexity and content of the intervention, study context, patient population, intervention fidelity, the healthcare team and acceptability by patients and collaborators.

Our results are in line with two other RCTs performed simultaneously in Scandinavia[22, 33]. Both studies failed to show a significant reduction in readmissions or ED visits after 12 months, despite having multifaceted interventions aiming to integrate the pharmacist in the ward teams[16, 18, 19]. However, there are conflicting results. Some of this could be explained by study settings, like the development in standard care. For example, the results of the study by Gillespie et al. used in our power calculations, where a 16% reduction in hospital visits were observed, were not reproduced 12 years later in a large cluster RCT by Kempen et al.[29, 33]. Kempen et al. argue that the conflicting results between the two studies could be caused by improved medication management in standard care in Sweden in the time period between the two studies[33]. Conflicting results could also be explained by the intervention content. A Danish study by Ravn-Nielsen et al. found that a pharmacist-led intervention in hospitals, including motivational interviews and postdischarge follow-up with patients and primary care, significantly reduced the risk of hospital readmission after six months[34]. Motivational interviewing was not a part of the IMMENSE intervention nor the intervention in the study by Kempen et al[33]. Hopefully, future research can provide clarity on the role of multifaceted clinical pharmacist services in preventing rehospitalizations and ED visits. A large pragmatic randomized trial planning to include nearly 10.000 older polypharmacy inpatients is underway[35]. Here, motivational interviewing is part of a peri-and postdischarge intervention. The study is also powered to find smaller effects on readmissions and ED visits than studies to date.

We did not observe any effects on one-year mortality. Thus, we can not support the findings of the recent Norwegian study published study by Lea et al.[22] where a significant reduction in 20 months all-cause mortality was observed. The study included 399 multimorbid patients admitted to an internal medicine ward and randomly assigned to an IMM-based intervention (corresponding to the IMMENSE study steps 1-4) or standard care[22]. Similar to the IMMENSE intervention, no statistically significant effects on time to first readmission or the number of patients with unplanned hospitalization were observed.

There may be several reasons for the conflicting findings between the studies on mortality. Despite the similarity in intervention, Lea et al. had a longer follow-up time, used pharmacists with post-graduate degrees in clinical pharmacy and identified more MRPs. The mortality rates in the study population was also higher than in the IMMENSE population, suggesting differences between the two study populations[30]. Finally, the study was performed in an internal medicine ward, not like the IMMENSE intervention where 77% of patients were recruited from a specialized geriatric ward. In geriatric wards health care personnel may take a more active approach towards medication optimization than other internal medicine wards[36], possibly reducing the effects of the intervention.

The risk of new events over time (**Figure 2a**), shows a small non-significant difference between groups in the first few months after discharge. Patients included in this study were old, using a median of eight medications upon admission, and over 67% were dependent on help with daily living. Medication changes frequently occur in older adults after hospital discharge[37]. The impact of pharmacotherapy optimization during a single time point when the patients are experiencing an acute illness may be insufficient to impact events in this population a full year after the index hospital stay. It would be expected for any potential effect of the intervention to taper off when no new intervention is provided[38, 39]. For this reason, we included the fifth step of the IMMENSE intervention providing oral feedback to GPs on medication changes, monitoring needs and opportunities for medication optimization to promote sustainable effects. However, we did not follow up on how recommendations were acted upon in primary care[30].

In the IMMENSE study, many MRPs (median 4, IQR 2-6) and medication discrepancies (median 1, IQR 0-3) were identified among intervention patients[30]. Of the medication-related problems, 67% were solved in the interdisciplinary team in the hospital as recommended by the pharmacist, while 23% were communicated to primary care[30]. While these process outcomes suggest that the intervention indeed optimized medications, they did not significantly affect health care use. In the future, a shift to more patient-focused outcomes should be considered[40]. This is confirmed by most stakeholders in the study by Beuscart et al. in 2018, developing a core outcome set for clinical trials of medication reviews in multimorbid older patients with polypharmacy, where outcomes related to healthcare use were not considered essential[41]. The only healthcare related outcome considered as a core outcome was medication-related hospital admissions[41]. In the current study, the effects of the intervention on secondary outcomes related to health-related quality of life, potentially inappropriate prescribing, and medication-related readmission remains to be established[24].

Strengths and limitations

This study has several strengths such as the randomized controlled design to create comparable study groups and control for bias, and the blinding of the investigator performing the primary analyses. Furthermore, the Norwegian health registries enable a complete and quality assured collection of outcomes. The collection of data for the 365 days prior to the index hospital stay, enabled us to adjust for pre-study patterns. Finally, including patients with dementia and cognitive impairment, increase the generalizability of findings.

There are also limitations that need to be addressed. First, intervention and control patients were included from the same wards and cared for by the same health professionals, which may have introduced a contamination bias, reducing between-group differences. Hawthorn effects may also be present. Second, the pharmacists were only able to include a limited number of patients each day due to the workload associated with study-related tasks and delivering the intervention[42]. Consequently, a small proportion of admitted patients were screened for eligibility or asked for participation, possibly introducing a selection bias. To prevent selection bias, the study pharmacists always approached patients in according to a "last-admitted-first" principle. Third, due to a slow inclusion rate, the enrollment period lasted for three years, which again enabled changes in standard care at the wards related to medication management, e.g., new methods for medication reconciliation. How changes in standard care may have influenced the study results is unknown. Finally, due to the complexity of the intervention, not all intervention steps were delivered to all patients[30]. A process evaluation alongside the trial could have enabled the identification of barriers and enablers to the effective delivery of the intervention, which would have provided valuable information on how to develop better interventions in the future[43].

CONCLUSION

We did not observe any statistical significant effect of the IMMENSE intervention on the rate of emergency medical visits after 12 months or any of the other secondary outcomes in hospitalized older adults included in this study. The study adds to recent evidence suggesting that reductions in healthcare use are not outcomes sensitive to the effects of hospital-based clinical pharmacist services[16, 22, 33]. However, these interventions are complex, and their ability to affect outcomes depends on numerous factors. Future studies should incorporate process evaluations alongside the trial to explain the factors that might influence study outcomes[43]. This might enable us to design better and more effective interventions in the future.

ACKNOWLEDGEMENT

We are extremely grateful to all participants in the study, employees at the departments where the study was performed, and our collaboration partners both at UNN Harstad, UNN Tromsø and the Hospital Pharmacy of North Norway Trust. We want to thank Anne Synnøve Rian, and Lillann Skaue Wilsgård for working as clinical pharmacists in the study, and Frode Skjold for valuable help with data management and statistical analysis. We also want to thank the clinical research department at UNN, particularly Birthe Lund Angermo, for help with data collection, and Inger Sperstad Køller for developing and servicing the study database. Last, we thank our funding body, the Northern Norway Regional Health Authority.

COMPETING INTERESTS

None of the authors has any competing interests to declare.

FUNDING

This work is supported by the Northern Norway Regional Health Authority grant number HST1314-16. The sponsors have no part in the collection, management, analysis and interpretation of the data, and writing and reporting study conclusions.

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

BHG, KHH, JSJ and EK had the original idea to the study. SH, HLW, KH and JSJ have collected study-related data, and registered the data in the study database. KS and JSJ have performed the statistical analyses. All authors have participated in discussion and interpretation of statistical analyses, and result presentations. JSJ have drafted the manuscript and prepared tables and illustrations. All authors have contributed in writing the manuscript, and confirmed the final submission.

LIST OF ABBREVIATIONS

MRP: medication-related problem, ED: emergency department, GP: general practitioner, IMM: integrated medicines management, ITT: Intention-to-treat, NORGEP-NH: The Norwegian general practice-Nursing Home criteria, 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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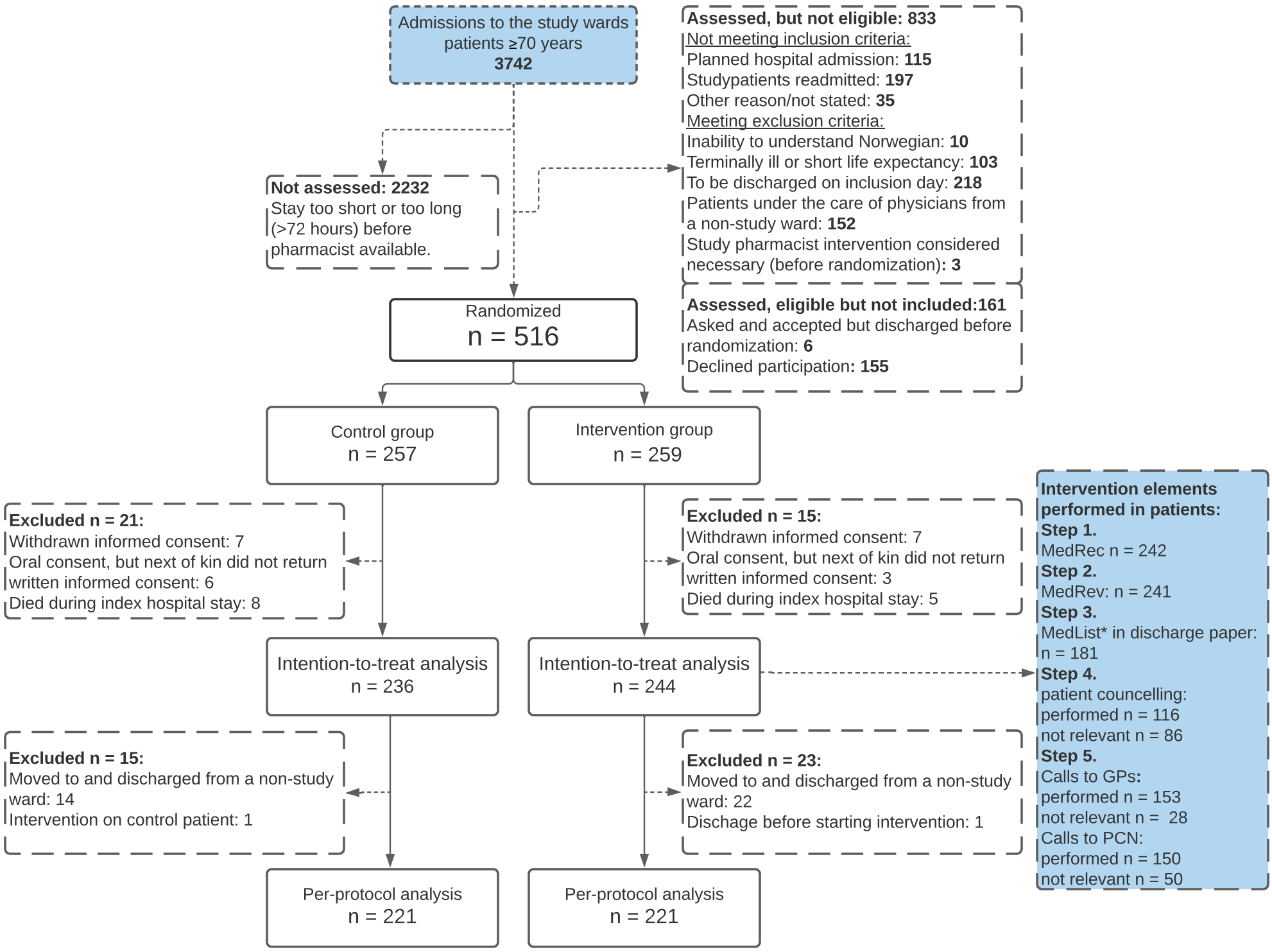
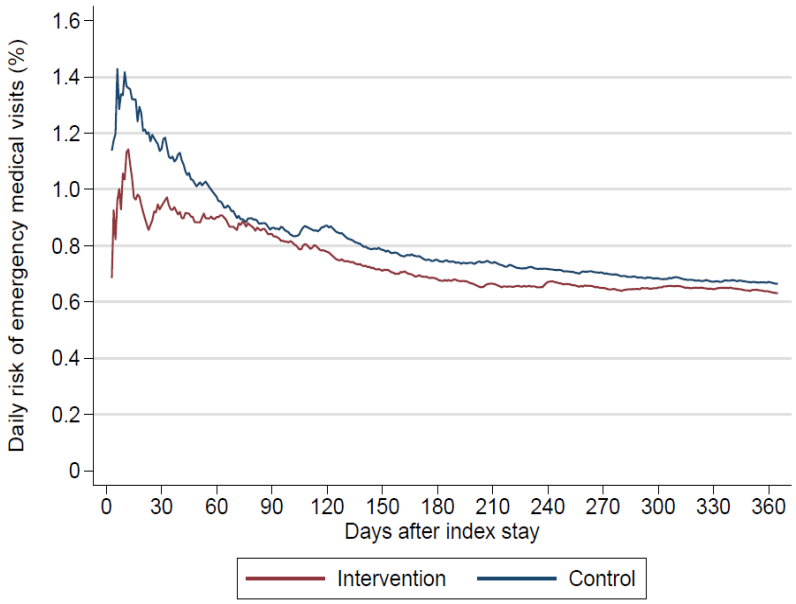


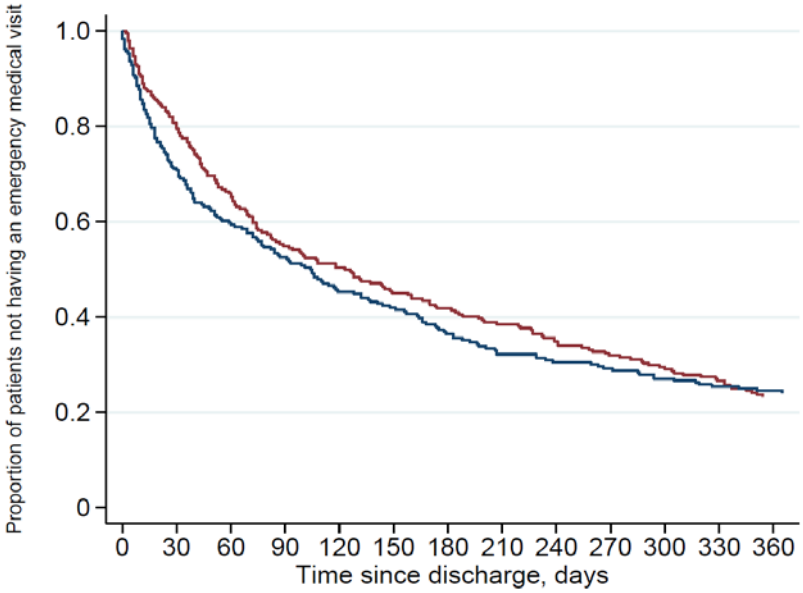
Figure 1: Flow diagram of patients included in the IMMENSE study

*Abbreviations: MedRec; medication reconciliation, MedRev; medication reconciliation, MedList: medication list, GP; general practitioner, PCN; Primary care nurses, * medication list according to study procedures in the discharge papers*

a)



b)



Number at risk

Group = Intervention	244	197	161	134	123	110	102	94	85	78	72	65	57
Group = Control	236	168	141	124	107	99	86	76	72	69	64	60	58

Figure 2: Emergency medical visits in the ITT population (n=480) illustrated by **a)** the daily risk of new emergency medical visits and **b)** Kaplan-Meier plot of time to first emergency medical visit

Supplementary material Paper IV

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

Supplementary material 1.

Statistical analysis plan.

Supplementary material 2.

STABLE 1 BASELINE CHARACTERISTICS IN THE PER-PROTOCOL POPULATION (N = 442)

STABLE 2 EFFECT OF THE INTERVENTION ON THE PRIMARY ENDPOINT (RATE OF EMERGENCY MEDICAL VISITS ONE YEAR AFTER DISCHARGE) IN THE DIFFERENT SUBGROUPS OF THE ITT-POPULATION

STABLE 3 PRIMARY AND SECONDARY OUTCOMES IN THE PER-PROTOCOL POPULATION (N=442)

Statistical Analysis Plan (SAP)

TRIAL FULL TITLE	A new interdisciplinary collaboration structure in secondary and primary care to improve medication safety in the elderly (IMMENSE study) – a randomized controlled trail
Protocol	https://bmjopen.bmj.com/content/8/1/e020106
PVO NUMBER	41366 The Norwegian Centre for Research Data and the Norwegian Data Protection Authority
SAP VERSION	1.0
CLINICAL TRIAL NUMBER	NCT02816086
SAP VERSION DATE	2021-03-18
TRIAL STATISTICIAN	Frode Skjold
TRIAL CHIEF INVESTIGATOR	Beate H. Garcia
SAP AUTHORS	Beate H. Garcia, Jeanette Schultz Johansen, Kjell H. Halvorsen and Frode Skjold

This SAP will concern the statistical analysis on the primary and secondary endpoints of the main article of the intervention study. Some secondary endpoints mentioned in the protocol article is excluded and will be presented in future SAPs.

SAP Signatures

I give my approval for the attached SAP entitled "A new interdisciplinary collaboration structure in secondary and primary care to improve medication safety in the elderly (IMMENSE study) – a randomized controlled trial" dated xx.xx.2020

Chief Investigator

Name: Beate H. Garcia

Signature: Beate Garcia

Date: 18.03.2021

Statistician

Name: Frode Skjold

Signature: Frode Skjold

Date: 18.03.2021

Abbreviations

CCI	Charlson Comorbidity Index
ED	Emergency Department
EQ5D-VAS	EuroQoL 5L - health-related quality of life
GP	General practitioner
HRQoL	Health related quality of life
MMS	Mini-mental Status
SAP	Statistical Analysis Plan
TILT	No; Tidlig Identifisering av Livstruende Tilstander Eng; Early Identification of Life-threatening Conditions.

Definitions

An "acute readmission" is defined as when a patient unplanned has been formally admitted to a hospital ward, independent whether the patient was visiting the ED before hospitalization.

An "ED visit", is defined as when a patient unplanned have been visiting the ED (including both the ED run by the municipality and the ED run by the hospital) but not formally admitted to the hospital. If the patient is admitted to hospital following an ED visit, it will be defined as a readmission.

Emergency department (ED) In Norway, the medical emergency service is divided in two; one run by the hospital (only localized in towns where there is a hospital) and one run by the municipalities (also localized in towns where there is a hospital and consequently a hospital-run ED). Patients are not supposed to arrive in the hospital-run ED without a referral from their GP, the municipality-run ED or arriving with the ambulance.

The EDs run by the municipality are employed by general practitioners (GPs) and open when the GPs´ offices are closed, normally 4 pm – 8 am. The EDs run by the hospital are open 24/7.

TABLE OF CONTENTS

1. Brief introduction

This non-blinded randomized controlled trial investigates whether an interdisciplinary intervention in geriatric patients (>70y) admitted to hospital will impact patient outcomes. The intervention is a new inter-professional collaboration structure between hospital physician, pharmacists and GPs focusing on medications applying the Integrated Medicines Management (IMM) methodology. The novelty is the inclusion of the clinical pharmacist in the team, who performs medication reconciliation, medication review, ensures correct communication about medications to patients and primary care and follows up with primary care after discharge. The study includes patients from two hospital sites; a geriatric ward at the University Hospital of North Norway (UNN) Tromsø and a general internal medicines ward at UNN, Harstad (1).

Following in the document, amendments from the published protocol will be pinpointed and ambiguities in the protocol descriptions will be clarified, see grey boxes.

2. Study Objectives and Endpoints

2.1 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:

- Acute readmissions
- Length of index hospital stay
- Time to first readmission
- 30-day readmissions
- Mortality rate

Specification:

- Regarding the primary objective, “Rate of emergency medical visits” is referring to the number of emergency medical visits per patient included in the trial.
- Regarding the secondary objectives, some that are described in the original published protocol will not be described in this SAP, but in SAPs for follow-up studies (see section 2.3).

2.2 Primary endpoint

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

Specification:

- This is a composite endpoint combining “Acute readmissions” and “ED visits”.
- We count all events per patient during 12 months from the index stay.

2.3 Secondary endpoints

Statistical analysis plan will be presented in this SAP only for the following secondary endpoints:

- Length of index hospital stay
- Time to first acute readmission after discharge from index hospital stay (12 months follow-up)
- The proportion of patients with acute readmissions within 30 days of discharge
- Mortality rate during 12 months' follow-up

Specification:
Some of the secondary endpoints from the protocol have been excluded from this SAP and will be presented in SAPs for follow-up studies.

3. Methods

3.1 General Study Design and Plan

We will recruit eligible participants to the study when they are admitted to the geriatric internal medicines ward (hereby called geriatric ward) in Tromsø or the general internal medicines ward (hereby called medicine ward) in Harstad. Participants will be randomized into two study arms, intervention and control (standard care) in a 1:1 relationship, stratifying on study site only. Randomization is performed after eligibility has been confirmed and patients have consented to participate. Consecutively, the intervention is commenced.
Study progress:

- The study started including patients in Tromsø on 22. September 2016
- The study started including patients in Harstad on March 2017
- Inclusion stopped in December 2019 in both study sites. The last patient was discharged from hospital on 22. December 2019
- Patients are followed-up for 12 months after discharge, and data will be collected after December 2020

3.2 Inclusion-Exclusion Criteria and General Study Population

Eligible patients were all patients aged ≥70 years admitted acutely to one of the study departments, independent of disease status, medication use, or whether they were able to consent.

Patients admitted to the intervention wards were included if they were willing to provide written informed consent during hospital stay (patient or next of kin).

Patients were excluded from the study if they met one of the following 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
- unable 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
- intervention from a study pharmacist considered necessary for ethical reasons (before randomization or in control group)

3.3 Randomisation and Blinding

Patients were randomized into intervention group and control group in a 1:1 relationship, only stratifying on study site. We applied block randomization with concealed and permuted randomization block sizes. The web-based randomization program was supplied by Unit for Applied Clinical Research, Faculty of Medicine Norwegian University of Science and Technology, Trondheim, which is an independent collaboration partner not involved in the project. Blinding was not feasible in this study, as everybody knew whether or not the intervention was delivered.

3.4 Sample Size

No data on hospitalization rates or visits to ED exist from our hospital. Therefore, data from a similar study in Sweden was applied as basis for sample size calculations. Gillespie et al. found a 16% reduction in visits to the hospital. In 12 months, patients in the intervention group had on average 1.5 visits and the intervention group 1.7 visits (2). If we expect a rate of 1.7 acute hospital visits per year in our control group, we would need a total of 456 patients to show a 16% reduction in hospital visits with a significance level of 5% and a power of 80% (Poisson regression). To compensate for dropout, we aimed to include 250 patients in each study group.

4 General Considerations

4.1 Timing of Analyses

The analyses of the endpoints specified in section 2.3 will be performed when 12 months follow-up data for all patients have been received, anticipated during May-June 2021.

4.2 Analysis Populations

Full Analysis Population: All patients included in the study and not withdrawing their consent, regardless of whether they were excluded after randomization.
Per Protocol Population: The full analysis population, except those who were excluded after randomisation.
Assigning patients to full analysis and per protocol population will be conducted before data on the primary endpoint is collected.

4.3 Variables, data sources and subgroups

Variables will be collected at the following time points during the study:
1) at baseline (during index hospitalization)
2) after follow-up from the following national registries:
- Norwegian Patient Registry (NPR) (hospitalizations and ED visits)
- The Norwegian Health Economics Administration Registry (ED visits)
- The National Cause of Death Registry (time and cause of deaths)

See **Appendix 1** for details on the variables.
Variables that may influence on the primary endpoint will be investigated for interactions.

Subgroups
The following subgroups will be analysed for different treatment effects:
1. Number of medications at admission and discharge
2. Age groups 70–79, 80–89 and 90+
3. Patient responsibility for own medication management at discharge
4. Number and types of comorbidities at discharge
5. Number of hospital visits prior to inclusion

6. Length of index hospital stay
7. Referral from home, homecare or nursing home
8. Able to self-provide informed consent
9. Differences between study sites

Specification:
We have added one subgroup (***No 9 differences between study sites***) which originally was not described in the published protocol.

4.4 Missing Data

We do not expect missing data for the primary endpoint as our national health registries are complete. When data is missing in independent variables, results will be presented with specified total number of patients contributing to each variable. In addition, for dependent and independent variables with more than 5% missing data, multiple imputation will be considered. Results of raw and imputed data will be presented.

4.5 Multi-centre Studies

The study sites in Tromsø and Harstad will be analysed together, but a subgroup analysis will be performed to investigate a possible centre effect. Regarding the intervention, the procedures, guidelines and working tools have been similar in both study sites and patients in the two study sites have been treated similarly. The only exception is with regard to collection of health-related quality of life. For this variable at baseline, all patients at study site Harstad were interviewed over telephone while for the Tromsø population, the first measurement was performed face-to-face.

4.6 Multiple Testing

To account for multiplicity, we will perform confirmatory significance testing for primary and secondary outcomes. All other significant tests will be treated as hypothesis generating. As we have conducted an RCT, we assume that any difference in baseline data is introduced by chance.

5 Summary of Study Data

5.1 Patient flow

The CONSORT flow diagram for the Patient flow will be developed, see **Figure 5.1** below for a draft. Numbers that remain to be established: 1) Patients admitted to the hospital wards during study period, 2) Patients meeting the inclusion criteria, 3) Patients excluded and reasons why, 4) Patients dying during hospitalisation, 5) Patients dying during follow-up, 6) Patients lost to follow-up, 7) Patients in intention-to-treat analysis (ITT).

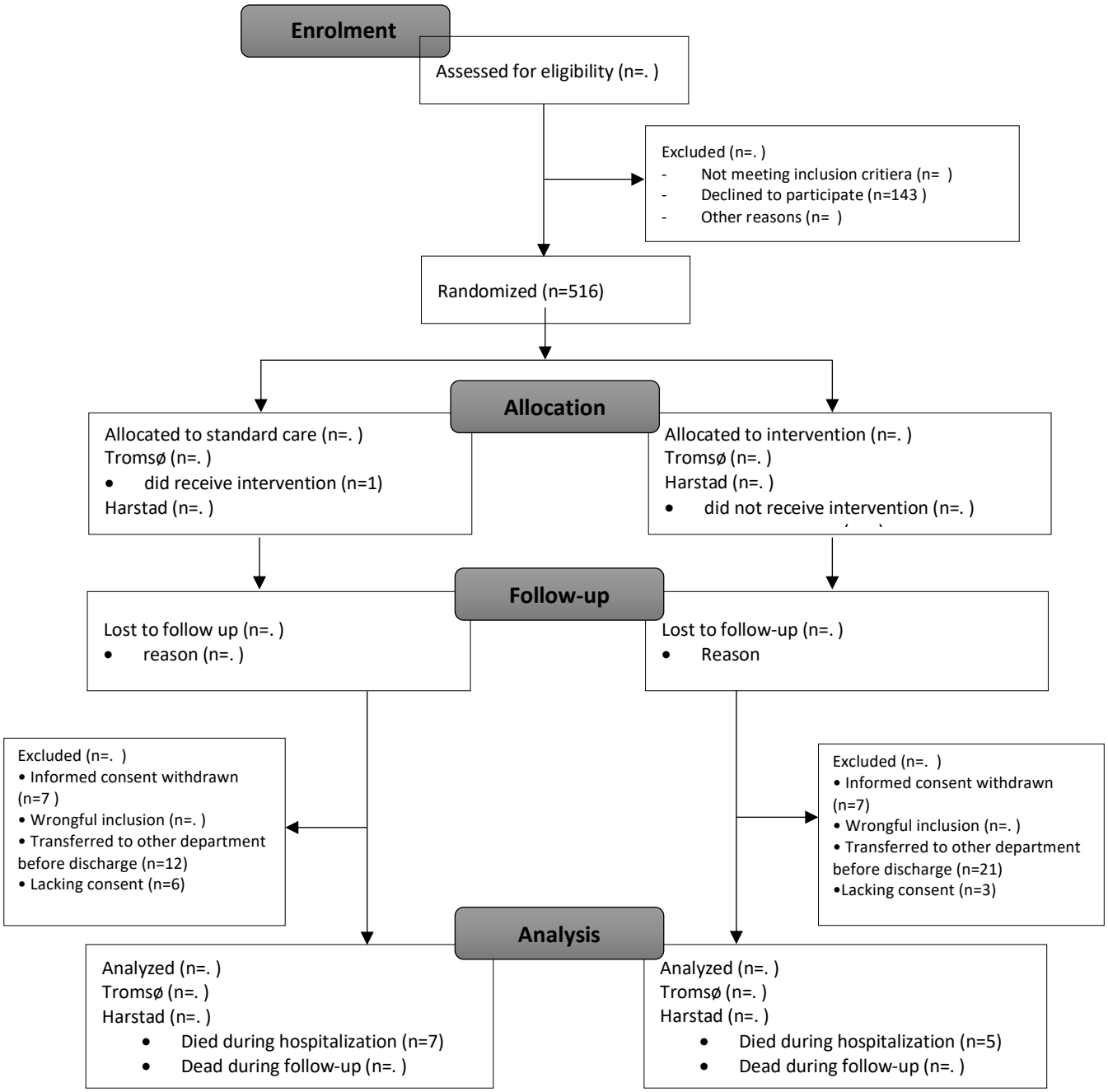


Figure 5.1 Participant flow diagram

5.2 Protocol deviations

Protocol deviations that we are aware of and could impact the analysis include:

- One patient randomised to control received intervention by a pharmacist for ethical reasons
- One patient randomized to intervention was wrongly excluded because due to discharge before the intervention could start

5.3 Demographic and Baseline Variables

See **Table 5.1** for baseline characteristics collected for the study population. Most data, including photocopies/print of laboratory values, TILT (No; Tidlig Identifisering av Livstruende Tilstander, Eng; Early Identification of Life-threatening Conditions) form, medication chart and admission notes (including information on medical conditions), were collected *before* randomization to avoid information bias. MMS-score (mini-mental status), walking test results and health-related quality of life (HRQoL) measurements was collected after study inclusion.

Table 5.1: Baseline characteristics of study population (n=xxx)

	Intervention group n=xxx	Control group n=xxx
Age, mean years		
Sex, F, n (%)		
Study Site, n (%)		
Tromsø		
Harstad		
Ability to self-provide consent, n (%)		
Marital status, n (%)		
Married		
Divorced		
Single		
Educational level, n (%)		
Elementary school		
High school (mandatory)		
Higher education (<4 years)		
Higher education (>4 years)		
Admitted from, n (%)		
Home		
Nursing home		
Other hospital		
Living status, n (%)		
Home		
Nursing home		
Handling medications themselves, n (%)		
Yes		
No		
Assistance from municipality to handle medications, n (%)		
Yes		
No		
Receiving medications as multidose packages, n (%)		
Yes		
No		
Co-morbidity (Mean score CCI)		
Number of medications in use at hospital admission/discharge, n (%)		
Total		

Regular use	
Use as needed	
MMS-score (n=??) (mean score)	
Walking test results	
Health-related quality of life (EQ5D-VAS mean score)	

CCI; Charlson Comorbidity Index, EQ5D-VAS; EuroQoL 5L - health-related quality of life, MMS; mini-mental status

5.4 Concurrent Illnesses and Medical Conditions

Comorbidities will be described applying the Charlson Comorbidity Index and potentially other comorbidity scores, e.g. Rx-Risk comorbidity index (3, 4). Comorbidities defined during hospital admission will be collected from admission and discharge notes. Information about ICD codes will also be achieved from the national registry (NPR) to ensure completeness in comorbidities.

5.5 Prior and Concurrent Medications

- Medications at admission is defined by information in the hospital admission letter and first medication chart provided
- Medications at discharge is defined by information in the hospital discharge letter

5.6 Treatment Compliance (intervention fidelity)

In our study, treatment compliance will be defined by describing which part of the intervention was performed by the pharmacists for which patient. We will also analyse the medication-related problems identified by the pharmacists, their recommendations and physician agreement and the recommendations. This is prospectively denoted in the study database.

6 Efficacy Analyses

6.1 General on statistics

We will investigate data for normality and apply the appropriate statistical tests. A two-sided 5% significance level will be applied, with no adjustments for multiplicity.

All analyses will be performed applying SPSS for windows or Mac. P-values < 0.05 will be regarded as statistically significant. P-values ≥0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001". The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data. Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

6.2 Intention to treat and per protocol analysis

The main analysis will be performed according to the intention to treat (ITT) principle. In the ITT analysis all patients are analysed according to their initially assigned study arm at baseline, regardless of adherence to study protocol. Patients who withdrew consent or patients with a protocol violation concerning eligibility are excluded from the ITT analysis. Patients lost to follow-up will likewise be excluded from the ITT analysis. Per protocol analysis will also be performed. All subjects from the ITT population without protocol violations and deviations regarding treatment will be included in the PP population. See **Figure 6.1** for illustration of ITT and PP analyses.

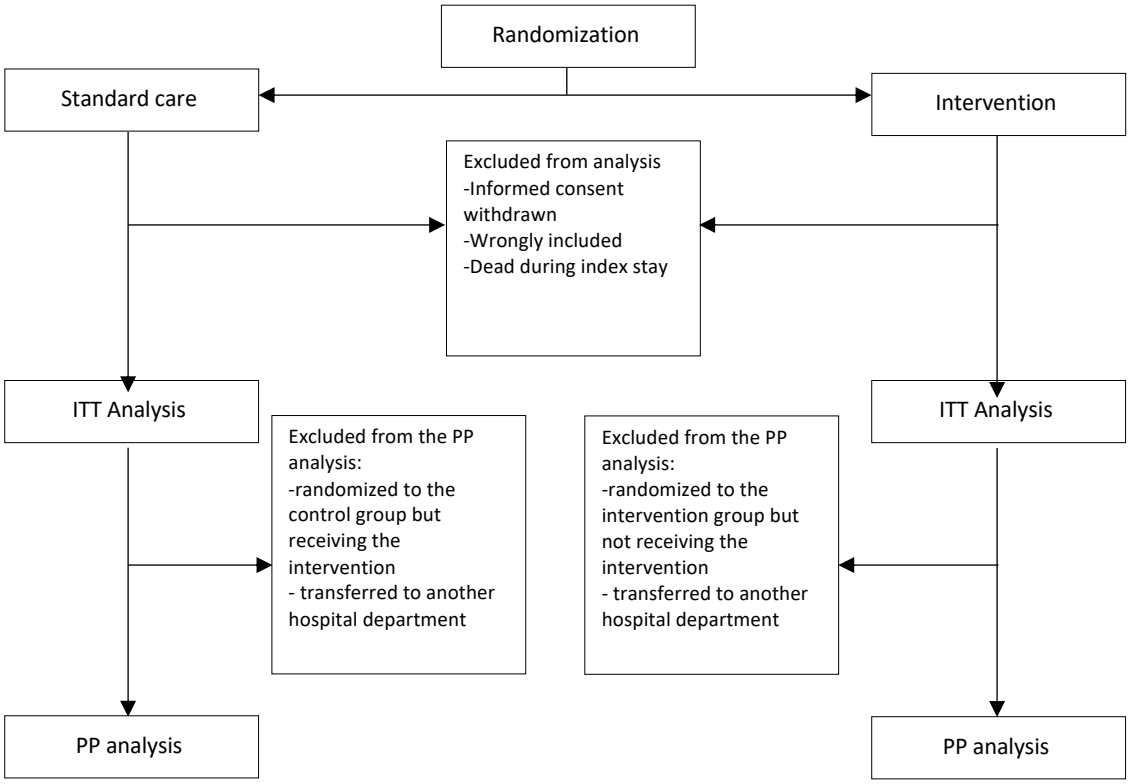


Figure 6.1: Patient inclusion for intention-to-treat (ITT) and per protocol (PP) analysis

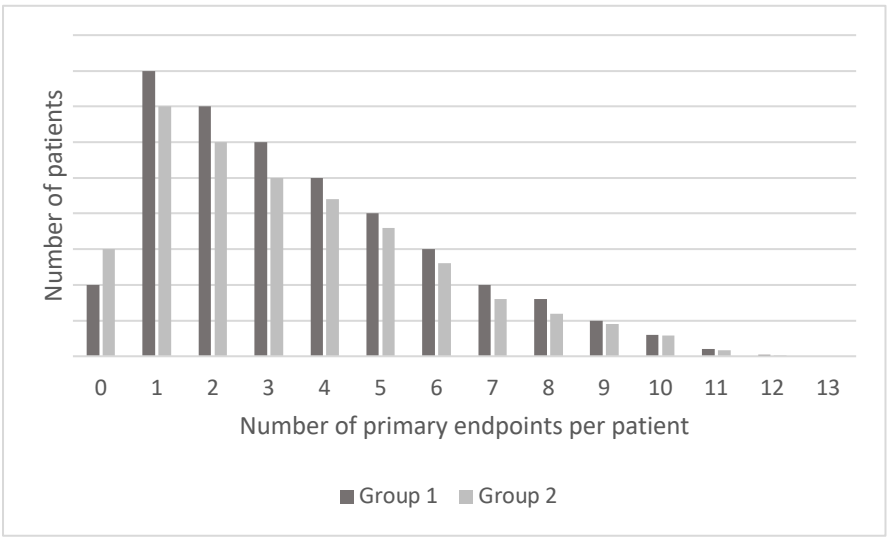
6.3 Primary endpoint analysis

The composite endpoint
The primary endpoint is defined as the composite endpoint "acute readmission and ED visits" 12 months after discharge from the index hospital stay in the intervention group compared with the control group. Consequently, the endpoint comprises both "readmissions" and "visit to emergency departments (ED)".

Hypothesis
- The **H0** hypothesis is: The intervention does not influence the number of primary endpoints during 12 months after index hospitalization.
- The **H1** hypothesis is: The intervention influences the number of primary endpoints during 12 months after index hospitalization.

Figure 6.2 illustrates how we assume that the endpoint will occur during the follow-up time.

a)



b)

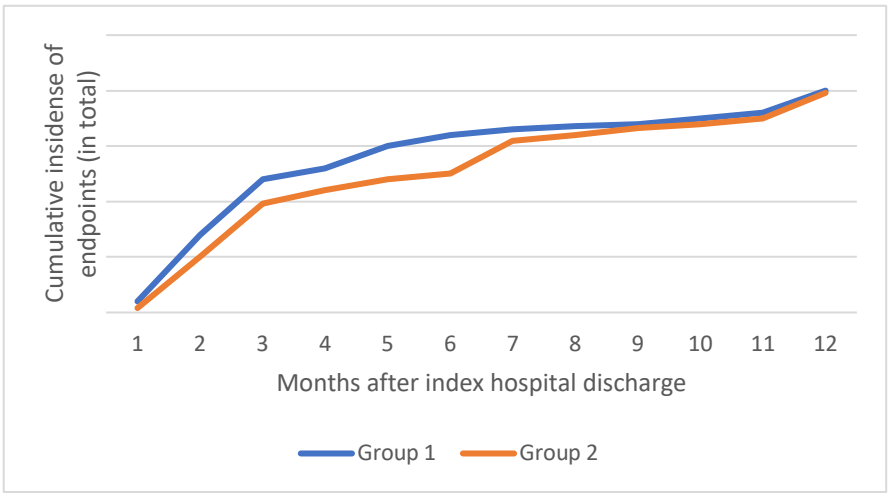


Figure 6.2: Illustrations of primary endpoints during a 12-month follow-up time for patients in the two groups, assuming that we will see a difference between the groups.
a) Number of patients having 1-x number of endpoints during the 12-month follow-up period.
b) Cumulative number of endpoints (in total) 1-12 months after index hospital discharge.

Person-time (time under risk for experiencing an endpoint) contribution
Each patient may experience many endpoints during the 12-month follow-up, and the primary endpoint per patient will be related to the patient´s person-time contribution during the 12-month follow-up period after index hospital discharge.

To account for that a new endpoint cannot occur in the period a patient is "in an endpoint" (i.e. time in hospital if patient is hospitalised), and that patients may die before the end of the 12-month follow-up period, we will calculate person-time contribution for all patients, which is "time outside hospital" in the follow-up period where the person is still alive. Consequently, total person time contribution per patient =
365 days follow-up time after hospital discharge, minus "time in an endpoint" minus time after (potential) death.

Primary endpoint analysis

Specification
According to our published protocol, the primary analysis will be a Poisson regression comparing the rate of the composite endpoint during 12 months after discharge between the two study groups. In this SAP, we specify that the primary endpoint will be investigated by comparing the rate of events (also recurring) happening in the intervention group and the control group during the 12-month follow-up period, taking into account the specific person-time contribution per patient (when the patients are at risk for experiencing an endpoint).

We will supplementarily perform a Poisson regression analysis if we need to adjust for crucial differences between the study groups. This we will not know before we have the data in house.

6.4 Secondary endpoint analysis

The secondary endpoints to be analysed is presented in **Table 6.1** together with the outcome measure and methodology.

Table 6.1: Overview of outcome measures and methods of analysis to investigate secondary endpoints.

Variable/outcome	Outcome measure	Methods of analysis
1) Length of hospitalisation (LOS) during index stay	Days [continuous]	T-test, and potentially Anova
2) Time to first unplanned readmission within 12 months after discharge from index hospital stay	Days [continuous]	Kaplan Meier method and the log-rank test. Hazard ratios (HRs) with 95% confidence intervals will be estimated using a Cox proportional hazards model.
3) The proportion of patients readmitted acutely within 30 days	Proportion	Xhi-square test
4) 12-month mortality	Proportion	Total mortality will be analysed as a time-to-event analysis. The **Kaplan Meier** method and the log-rank test will be applied. Further, a **Cox proportional HR model** will be applied to estimate HRs. HRs will be presented with 95% confidence intervals.

6.5 Blinding

The dataset will be prepared for analysis by the project administers who are familiar with the study and the variables (JSJ, KHH and BHG).

The main analyses will be performed by a statistician (FS) blinded for group allocation and not involved in data collection, data punching or in preparing the data files for analyses. To maintain blinding and prevent bias, data analyses on the primary endpoint will be performed as follows: JSJ/BHG/KHH prepare a data file including a new variable indicating whether patients are in the intervention group or in the control group. This new variable is blinded, and allocation code is stored safely and not provided to the statistician (FS). FS receives the dataset with the new code for the allocated group and carry out the primary analysis. When the statistical analysis is finalized, group allocation will be revealed by JJSH/BHG/KHH with FS present.

7 Summary of Changes to the Protocol

Compared to the published protocol and the information denoted in www.clinicaltrials.gov, the following amendments have now been made in the SAP:

1) The calculation of a retrospective Charlston Comorbidity index on all participants and the potential use of this as a covariate in analysis.
2) In the subgroup analysis overview, we have added a comparison of outcomes of patients from the two study sites Tromsø and Harstad and the number and type of comorbidities at discharge.
3) The primary endpoint analysis may not necessarily be a Poisson Regression analysis, but a comparison of rates of endpoints experienced by intervention group patients vs. control group patients.

8 References

1. Johansen JS, Havnes K, Halvorsen KH, Haustreis S, Skaue LW, Kamycheva E, et al. Interdisciplinary collaboration across secondary and primary care to improve medication safety in the elderly (IMMENSE study): study protocol for a randomised controlled trial. BMJ Open. 2018;8(1):e020106.
2. Gillespie U, Alassaad A, Henrohn D, Garmo H, Hammarlund-Udenaes M, Toss H, et al. A comprehensive pharmacist intervention to reduce morbidity in patients 80 years or older: a randomized controlled trial. Arch Intern Med. 2009;169(9):894-900.
3. Charlson Comorbidity Index (CCI) [cited 2020 20.04]. Available from: https://www.mdcalc.com/charlson-comorbidity-index-cci.
4. Pratt NL, Kerr M, Barratt JD, Kemp-Casey A, Kalisch Ellett LM, Ramsay E, et al. The validity of the Rx-Risk Comorbidity Index using medicines mapped to the Anatomical Therapeutic Chemical (ATC) Classification System. BMJ Open. 2018;8(4):e021122.

Appendix 1: Variables collected for use in primary and secondary analyses

Table A1: Variables that are and will be collected for the study participants.

Variable	Variable type	Definitions	Data source
Length of index hospital stay (actual)	Continuous	The number of days the patient was admitted to hospital during the index stay**. NB!** The patient may have been ready for discharge earlier, but because of no space in municipality he/she could not be sent out. These days are denoted and will be subtracted from the number shown in the patient registry.	National registry Study database*
Length of index hospital stay (when ready to be discharged)	Continuous	The number of days the patient was admitted to hospital during the index stay minus the number of days the patient was hospitalized after he/she was ready for discharge**. NB!** The patient may have been ready for discharge earlier, but because of no space in municipality he/she could not be sent out. These days are denoted and will be subtracted from the number shown in the patient registry.	National registry Study database*
Number of unplanned hospital admissions in the year preceding the index stay	Continuous	12 months' follow-up, 6 months before and after data for adjusting for secular trends	National registry
Number of deaths in the year preceding the index stay	Continuous	12 months' follow-up, 6 months before and after data for adjusting for secular trends	National registry
Number of unplanned visits to ED departments in the year preceding the index stay	Continuous	12 months' follow-up, 6 months before and after data for adjusting for secular trends	National registry
Living status	Categorical	1.home with home-care, 3. nursing home permanent living, 4. nursing home short term	Study database*
Responsible for administering their own medication on admission to index stay	Categorical	Yes No Partial	Study database*
Receiving multidose packed drugs at admission to index hospital stay	Categorical	Yes No	Study database*
Medications in regular use and use as needed at admission and discharge	Continuous	Name of medications (ATC level 5) in regular use exluding pro re nata drugs	Study database*
Charlson comorbidity index score at admission/discharge	Continuous	Score	Based on data in study database
Age	Continuous and Categorical	Years 70–79 80–89 90+	Study database* & from national registry
Sex	Categorical	Male 2. female	Study database* & from national registry
Study site	Categorical	Tromsø Harstad	Study database* & from randomization database
Able to self-provide informed consent or not.	Categorical	Yes No	Study database*

Educational status	Categorical	1. Grunnskole 2.frammansskole eller folkehøyskole 3. Yrkesfaglig videregående, Realskole, eller yrkesskole 4.Allmennfaglig videregående skole eller gymnas 5. Høyskole eller universitet under 4 år 6. Høyskole eller universitet over 4 år	Study database*
Receiving help from PSHT (patient centered health care team) at admission or discharge.	Categorical	Yes, No	Study database*
Kidney function (eGFR) at admissjon	Continuous	First value from index hospitalization.	Study database*
Help from the municipality	Continuous	Number of hours per week that the patient receives of home care services from the municipality	Collected from the municipalities at 1, 6 and 12 months after discharge.
Health-relate Quality of life	Continuous	EQ5D-VAS scale	Collected at baseline, at 1, 6 and 12 months.

* Data will be collected prospectively from patient journal and pharmacist work during the study period and denoted in a de-identified study database where patients are given a study ID number. The study database includes both intervention and control patients, and a code list is kept separate

Supplementary material 2

STABLE 1 BASELINE CHARACTERISTICS IN THE PER-PROTOCOL POPULATION (N = 442)

	Intervention group (n=221)		Control group (n=221)	
Age, mean years (SD)	83.3	(6.4)	83.0	(6.3)
Sex, female, n (%)	140	(63.3)	118	(53.4)
Study Site, n (%)				
Geriatric ward (study site 1)	181	(81.9)	182	(82.4)
General medicine ward (study site 2)	40	(18.1)	39	(17.6)
Ability to self-provide consent, n (%)	158	(71.5)	149	(67.4)
Marital status, n (%)				
Widow/widower	99	(44.8)	94	(42.5)
Married/live in partner	86	(38.9)	85	(38.5)
Single	23	(10.4)	25	(11.3)
Divorced/separated	11	(5.0)	14	(6.3)
Missing	2	(1.0)	3	(1.4)
Educational level, ISCED level n (%)				
Elementary school, level 1	102	(46.2)	106	(48.0)
Secondary education, level 2-3	79	(35.7)	74	(33.5)
Higher education (<4 years), level 5-6	21	(9.5)	17	(7.7)
Higher education (>4 years), level 7-9	11	(5.0)	10	(4.5)
Missing	8	(3.6)	14	(6.3)
Living status at admission, n (%)				
Home, no help from home care services	78	(35.3)	62	(28.1)
Home, with help from home care services	107	(48.4)	133	(60.2)
Nursing home, short term	19	(8.6)	11	(5.0)
Nursing home, permanent	17	(7.7)	15	(6.8)
Discharge to home, n (%)	136	(61.5)	126	(57.0)
Handling medications themselves, n (%)				
Yes	83	(37.6)	71	(32.1)
No	96	(43.4)	98	(44.3)
Partly	42	(19.0)	52	(23.5)
Missing				
Co-morbidity[b] (Median score,IQR)				
Charlson comorbidity index	2	(1-3)	2	(1-4)
Number of medications (ATC-codes) in use at hospital admission, Median (IQR)				
Total	8	(5-12)	9	(6-13)
Regular use	6	(4-9)	7	(4-10)
Use as needed	2	(0-3)	2	(0-3)
Medical history in admission notes, n (%)				
Hypertension	44	(19.9)	48	(21.7)
Atrial fibrillation	112	(50.7)	105	(47.5)
Asthma or COPD	63	(28.5)	62	(28.1)
Diabetes Mellitus	51	(23.1)	51	(23.1)
Heart failure	35	(15.8)	34	(15.4)
Dementia	31	(14.0)	32	(14.5)
Emergency medical visits one year before index hospital stay				
Emergency medical visits, n (% with one)	414	(67.9)	517	(72.4)
Emergency medical visits, median (IQR)	1	(0-3)	1	(0-3)

ATC; anatomical therapeutic chemical classification system, ; F; female, IRQ: interquartile range, ISCED; international standard classification of education, SD; standard deviation. a) educational level categorized by the international standard classification of education b) Co-morbidity based on diagnosis in admission and discharge papers.

sTable 2 Effect of the intervention on the primary endpoint (Rate of emergency medical visits one year after discharge) in the different subgroups of the ITT-population

Subgroup	Number of patients in subgroup (intervention/ control)	Intervention Number of events	Control Number of events	Incidence rate ratio (95 % CI) Intervention compared with control Crude	Adjusted[a]
Number of medications at admission					
0-5	120 (68/52)	104	68	1.09 (0.62-1.94)	1.10 (0.63-1.92)
6-10	185 (97/88)	211	167	1.26 (0.90-1.78)	1.36 (0.97-1.89)
>10	175 (79/96)	182	264	0.77 (0.55-1.09)	0.79 (0.59-1.08)
Age at inclusion, years					
70-79	139 (69/70)	136	140	1.07 (0.66-1.73)	1.01 (0.65-1.56)
80-89	264 (136/128)	268	293	0.93 (0.69-1.26)	1.05 (0.79-1.38)
≥90	77 (39/38)	93	66	0.84 (0.50-1.40)	0.95 (0.58-1.57)
Responsible for own medication at discharge, n					
yes	108 (57/51)	83	103	0.73 (0.46-1.15)	0.80 (0.51-1.26)
no	283 (142/141)	257	254	0.98 (0.72-1.33)	1.09 (0.82-1.46)
Partially	81 (43/38)	144	134	1.02 (0.64-1.62)	1.01 (0.68-1.50)
missing	8			-	-
Comorbidity, Charlson Comorbidity Index					
0-2	262 (140/122)	266	217	1.05 (0.77-1.43)	1.07 (0.81-1.42)
>2	218 (104/114)	231	282	0.91 (0.65-1.26)	1.01 (0.74-1.39)
Emergency medical visits in the year before index stay, n					
0-1	252 (132/120)	210	169	1.05 (0.75-1.47)	1.05 (0.75-1.47)
>1	228 (112/116)	287	330	0.92 (0.69-1.23)	0.98 (0.75-1.29)
Length of index hospital stay, days					
0-6	270 (145/125)	301	248	0.99 (0.74-1.34)	1.01 (0.77-1.32)
>6	210 (99/111)	196	251	0.93 (0.64-1.34)	1.07 (0.75-1.51)
Admitted from, n					
Home, no help from municipality	157 (88/69)	127	130	0.83 (0.55-1.24)	0.86 (0.59-1.26)
Home, with help from municipality	255 (116/139)	317	310	1.18 (0.88-1.59)	1.26 (0.96-1.65)
Nursing home	68 (40/28)	53	59	0.61 (0.30-1.24)	0.64 (0.32-1.28)
Ability to consent, n					
Yes	334 (174/160)	394	371	1.04 (0.79-1.36)	1.07 (0.84-1.36)
No	146 (70/76)	103	128	0.74 (0.47-1.67)	0.85 (0.55-1.33)
Study site, n					
Geriatric ward	389 (198/191)	411	402	0.97 (0.74-1.25)	1.02 (0.81-1.30)
General medicine ward	91 (46/45)	86	97	0.88 (0.52-1.51)	1.07 (0.65-1.78)

a) Adjusted for the number of emergency medical visits in the year before index hopitalization.

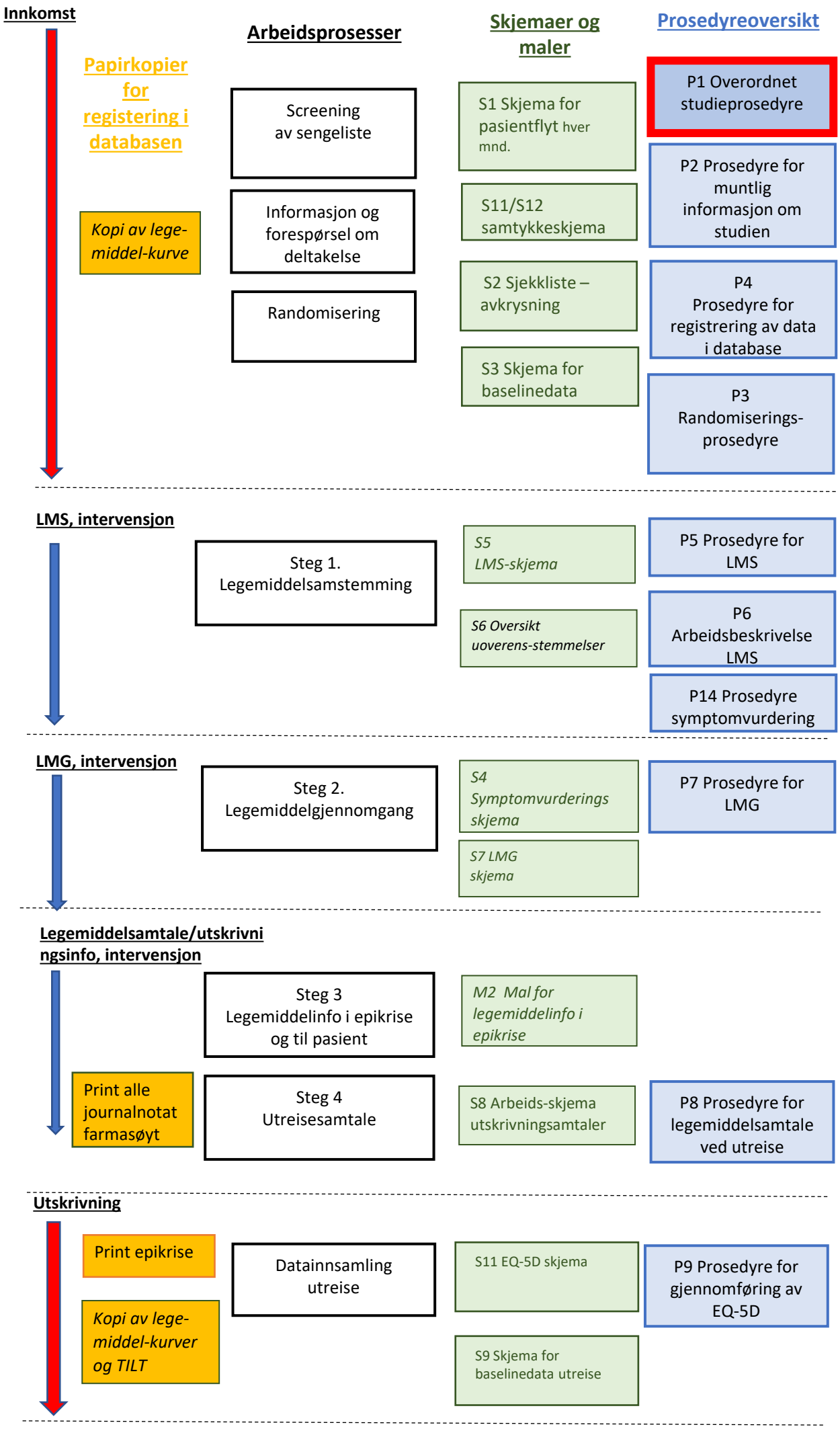
sTABLE 3 PRIMARY AND SECONDARY OUTCOMES IN THE PER-PROTOCOL POPULATION (N=442)

Primary outcome after 12 months	Intervention (n=221)		Control (n=221)		Crude	Adjusted[a]
	n, median (IQR)		**n, median (IQR)**		**Incidence rate ratio (95 % CI)**	
Emergency medical visits	434	1 (0-3)	472	1 (0-3)	0.90 (0.70-1.14)	0.97 (0.77-1.21)
ED-visits	245	1 (0-2)	263	1 (0-2)	0.89 (0.68-1.18)	0.94 (0.72-1.23)
Rehospitalisation	189	1 (0-1)	209	0 (0-1.5)	0.90 (0.67-1.21)	0.97 (0.74-1.27)
Secondary outcomes						
Days to first event	**median (%)**		**median (%)**		**Hazard rate (95 % CI)**	
Readmission	329	(50.7)	351	(47.5)	1.01 (0.78-1.32)	1.07 (0.82-1.40)
Emergency medical visit	143	(70.6)	108	(71.0)	0.89 (0.71-1.11)	0.92 (0.74-1.15)
	n (%)		**n (%)**		**Odds ratio (95 % CI)**	
Readmissions within 30 days	23	(10.4)	32	(14.5)	0.69 (0.39-1.22)	0.78 (0.43-1.41)
All-cause mortality within 12 months	40	(18.1)	45	(20.4)	0.86 (0.54-1.39)	0.90 (0.56-1.46)

IQR; Interquartile Range a) Adjusted for the number of emergency medical visits during 365 days prior to the index hospital stay.[a)]Adjusted for study site and the number of emergency medical visits one year before index hospital stay.

Appendix A

A flowchart over study procedures, forms and data collection in the IMMENSE study


Innkomst
Arbeidsprosesser
Skjemaer og maler
Prosedyreoversikt
Papirkopier for registering i databasen
Kopi av lege-middel-kurve
Screening av sengeliste
Informasjon og forespørsel om deltakelse
Randomisering
S1 Skjema for pasientflyt hver mnd.
S11/S12 samtykkeskjema
S2 Sjekkliste – avkrysning
S3 Skjema for baselinedata
P1 Overordnet studieprosedyre
P2 Prosedyre for muntlig informasjon om studien
P4 Prosedyre for registrering av data i database
P3 Randomiserings-prosedyre
LMS, intervensjon
Steg 1. Legemiddelsamstemming
S5 LMS-skjema
S6 Oversikt uoverens-stemmelser
P5 Prosedyre for LMS
P6 Arbeidsbeskrivelse LMS
P14 Prosedyre symptomvurdering
LMG, intervensjon
Steg 2. Legemiddelgjennomgang
S4 Symptomvurderings skjema
S7 LMG skjema
P7 Prosedyre for LMG
Legemiddelsamtale/utskrivningsinfo, intervensjon
Steg 3 Legemiddelinfo i epikrise og til pasient
M2 Mal for legemiddelinfo i epikrise
Print alle journalnotat farmasøyt
Steg 4 Utreisesamtale
S8 Arbeids-skjema utskrivningsamtaler
P8 Prosedyre for legemiddelsamtale ved utreise
Utskrivning
Print epikrise
Kopi av lege-middel-kurver og TILT
Datainnsamling utreise
S11 EQ-5D skjema
S9 Skjema for baselinedata utreise
P9 Prosedyre for gjennomføring av EQ-5D

Oppfølging fastlege og kommunehelsetjeneste , Intervensjon

Steg 5.
Samtale med fastlege og hjemmetjeneste

S10 Skjema for fastlegeoppføling

P11 Prosedyre for oppfølgings-samtale fastlege

P10 Prosedyre for melding av multidoseendring

Datainnsamling, 1 mnd

Innhente Livskvalitet og hjelp i hjemmet

S11 EQ-5D skjema

S12 Skjema for innhenting av data om omsorgsnivå

P9 Prosedyre for gjennomføring av EQ-5D

P12 Prosedyre for innhenting av data fra kommunehelsetje nesten

---

Datainnsamling, 3 mnd

Legemiddelliste primærhelsetje neste

Innhente legemiddelister

P13 Prosedyre for innhenting av data fra fastlege

Datainnsamling, 6 mnd

Innhente Livskvalitet og hjelp i hjemmet

S11 EQ-5D skjema

S12 Skjema for innhenting av data om omsorgsnivå

P9 Prosedyre for gjennomføring av EQ-5D

P12 Prosedyre for innhenting av data fra kommunehelsetje nesten

---

Datainnsamling, 12 mnd

Legemiddelliste primærhelsetje neste

Innhente livskvalitet, hjelp i hjemmet og legemiddellister

S11 EQ-5D skjema

S12 Skjema for innhenting av data om omsorgsnivå

P9 Prosedyre for gjennomføring av EQ-5D

P12 Prosedyre for innhenting av data fra kommunehelsetje nesten

P13 Prosedyre for innhenting av data fra fastlege

Appendix B

Appendix B – Paper I, Variables from NPR and NorPD

Variables included in the datasets from the Norwegian patient registry (NPR) and the Norwegian prescription database (NorPD). Files were merged based on the patients-ID number generated by NorPD for this study.

NPR **For every visit to secondary care in 2013, the following parameters are available in our dataset**	**NorPD** **The following parameters are available in our dataset for every prescription medication dispensed in a Norway pharmacy one year before or one year after the index hospital stay.**
Patients id. number	Patients id. Number
Patient county	Patients' year of birth
Patient age group	Patent sex
Geriatric ward (yes/no)	Patient name of the municipality of residence
Name of the geriatric ward	Patient year of death
Death (yes/no)	Prescriber id
The main reason for visit (ICD-code)	Prescriber year of birth
Discharge to a nursing home or other institution/hospital	Prescriber sex
Hospital stay or day visit	Date of dispense relative to index day from NPR file.
Admittance (days from index day)	Year of dispense
Discharge (days from index day)	ATC-code
Admittance (elective/ Non elective	Type of reimbursement
	Reimbursement code (ICD or ICPC)
	Mediation name
	Nordic article number (from pharmacy registry identifying the package sold)
	Drug units dispersed
	Number of DDD dispersed

Appendix C

Appendix C – Paper I, Syntax NORGEP-NH SPSS

Part A

1.Combination analgesic codein/paracetamol

```
DO IF N02AJ06=1.
COMPUTE Norgep_NH_1_før=1.
ELSE.
COMPUTE Norgep_NH_1_før=0.
END IF.
```

2. Tricyclic antidepressants (TCAs)

```
DO IF (N06AA04=1 | N06AA06=1 | N06AA09=1 | N06AA10=1 | N06AA12=1).
COMPUTE Norgep_NH_2_før=1.
ELSE.
COMPUTE Norgep_NH_2_før=0.
END IF.
```

3. Non-steroid anti-inflammatory drugs (NSAIDs)

```
DO IF
(M01AB05=1|M01AB55=1|M01AC01=1|M01AC06=1|M01AE01=1|M01AE02=1|M01AE03=1|M01
AE52 =1| M01AX01=1).
COMPUTE Norgep_NH_3_før=1.
ELSE.
COMPUTE Norgep_NH_3_før=0.
END IF.
```

4. First-generation antihistamines

```
DO IF (R06AB02=1|R06AD01=1|R06AD02=1|N05BB01=1).
COMPUTE Norgep_NH_4_før=1.
ELSE.
COMPUTE Norgep_NH_4_før=0.
END IF.
```

5. Diazepam

```
DO IF (N05BA01=1).
COMPUTE Norgep_NH_5_før=1.
ELSE.
COMPUTE Norgep_NH_5_før=0.
END IF.
```

6. Oxazepam: Dosage > 30 mg/day

*DDD = 50 mg if over 72 DDD dispensed in the 120 days time window criteria 6 was computed

```
COMPUTE Norgep_NH_6_før=atckode='N05BA04' & DDDfør_sum >= 72.
```

7. Zopiklone: Dosage > 5 mg/day

*Removed all Nordic article numbers corresponding to packages with 3.75 mg and 5 mg form the dataset when applying this criteria

```
DO IF (N05CF01=1).
COMPUTE Norgep_NH_7_før=1.
ELSE.
```

```
COMPUTE Norgep_NH_7_før=0.
END IF.
```

8. Nitrazepam

```
DO IF (N05CD02=1).
COMPUTE Norgep_NH_8_før=1.
ELSE.
COMPUTE Norgep_NH_8_før=0.
END IF.
```

9. Flunitrazepam

```
DO IF (N05CD03=1).
COMPUTE Norgep_NH_9_før=1.
ELSE.
COMPUTE Norgep_NH_9_før=0.
END IF.
```

10. Chlometiazole

```
DO IF (N05CM02=1).
COMPUTE Norgep_NH_10_før=1.
ELSE.
COMPUTE Norgep_NH_10_før=0.
END IF.
```

11. Regular use of hypnotics

* calculated regular use of hypnotics as dispensed more than 60 DDD in 120 days.

```
DO IF (N05CD02=1|N05CD03=1|N05CF01=1|N05CF02=1|N05CH01=1|N05CM02=1).
COMPUTE Norgep_NH_11_før=1.
ELSE.
COMPUTE Norgep_NH_11_før=0.
END IF.
```

PART B: Combinations to avoid

12. Warfarin + NSAIDs

```
DO IF (Norgep_NH_3_før=1 & B01AA03=1).
COMPUTE Norgep_NH_12_før=1.
ELSE.
COMPUTE Norgep_NH_12_før=0.
END IF.
```

13. Warfarin + SSRIs/SNRIs

```
DO IF (B01AA03=1 &
(N06AB03=1|N06AB04=1|N06AB05=1|N06AB06=1|N06AB08=1|N06AB10=1|N06AX16=1|N06AX
21=1)).
COMPUTE Norgep_NH_13_før=1.
ELSE.
COMPUTE Norgep_NH_13_før=0.
```

14. Warfarin+ ciprofloxacin/ofloxacin/erythromycin/ Clarithromycin

```
DO IF (B01AA03=1 & (J01MA01=1|J01MA02=1|J01FA01=1|J01FA09=1)).
COMPUTE Norgep_NH_14_før=1.
```

```
ELSE.
COMPUTE Norgep_NH_14_før=0.
END IF.
```

15. NSAIDs/coxibs + ACE-inhibitors/AT2-Antagonists

```
DO IF
((M01AB05=1|M01AB55=1|M01AC01=1|M01AC06=1|M01AE01=1|M01AE02=1|M01AE03=1|M01
AX01=1 |M01AH01=1|M01AH05=1))
&(C09AA02=1|C09AA03=1|C09AA05=1|C09BA02=1|C09BA03=1|C09CA01=1|C09CA02=1|C09C
A03=1|C09CA04=1|C09CA06=1|C09CA07=1
|C09DA01=1|C09DA03
        =1|C09DA04=1|C09DA06=1|C09DA07=1|C09DB01=1|C09DX01=1).
COMPUTE Norgep_NH_15_før=1.
ELSE.
COMPUTE Norgep_NH_15_før=0.
END IF.
```

16. NSAIDs/coxibs + diuretics

```
DO IF
(M01AB05=1|M01AB55=1|M01AC01=1|M01AC06=1|M01AE01=1|M01AE02=1|M01AE03=1|M01
AX01=1 |M01AH01=1|M01AH05=1) &
(C03AA03=1|C03AB01=1|C03CA01=1|C03CA02=1|C03DA01=1|C03EA01=1).
COMPUTE Norgep_NH_16_før=1.
ELSE.
COMPUTE Norgep_NH_16_før=0.
END IF.
```

17. NSAIDs/coxibs + glucocorticoids

```
DO IF
(M01AB05=1|M01AB55=1|M01AC01=1|M01AC06=1|M01AE01=1|M01AE02=1|M01AE03=1|M01
AX01=1 |M01AH01=1|M01AH05=1)  & (H02AB04=1|H02AB06=1|H02AB10=1).
COMPUTE Norgep_NH_17_før=1.
ELSE.
COMPUTE Norgep_NH_17_før=0.
END IF.
```

18. NSAIDs/coxibs + SSRI/SNRIs

```
DO IF
(M01AB05=1|M01AB55=1|M01AC01=1|M01AC06=1|M01AE01=1|M01AE02=1|M01AE03=1|M01
AX01=1 |M01AH01=1|M01AH05=1)
&
(N06AB03=1|N06AB04=1|N06AB05=1|N06AB06=1|N06AB08=1|N06AB10=1|N06AX16=1|N06AX
21=1).
COMPUTE Norgep_NH_18_før=1.
ELSE.
COMPUTE Norgep_NH_18_før=0.
END IF.
```

19. ACE-inhibitors/AT2-Antagonists + potassium or potassium-sparing diuretics

```
DO IF (A12BA01=1| A12BA02=1|C03DA01=1)
&(C09AA02=1|C09AA03=1|C09AA05=1|C09BA02=1|C09BA03=1|C09CA01=1|C09CA02=1|C09C
A03=1|C09CA04=1|C09CA06=1|C09CA07=1
|C09DA01=1|C09DA03
        =1|C09DA04=1|C09DA06=1|C09DA07=1|C09DB01=1|C09DX01=1).
```

```
COMPUTE Norgep_NH_19_før=1.
ELSE.
COMPUTE Norgep_NH_19_før=0.
END IF.
```

20. Beta blocking agents + cardioselective calcium antagonists

```
DO IF (C07AA05=1|C07AA07=1|C07AB02=1|C07AB03=1|C07AB07=1|C07AG02=1|C07BB07=1)
& (C08DA01=1| C08DB01=1).
COMPUTE Norgep_NH_20_før=1.
ELSE.
COMPUTE Norgep_NH_20_før=0.
END IF.
```

21. Erythromycin/clarithromycin + Statins

```
DO IF (C10AA01=1|C10AA02=1|C10AA03=1|C10AA04=1|C10AA05=1|C10AA07=1) &
(J01FA01=1|J01FA09=1).
COMPUTE Norgep_NH_21_før=1.
ELSE.
COMPUTE Norgep_NH_21_før=0.
END IF.
```

22.Bisphosponate + proton pump inhibitors

```
DO IF (M05BA04=1|M05BA06=1|M05BA07=1|M05BA08=1) &
(A02BC01=1|A02BC02=1|A02BC03=1|A02BC05=1).
COMPUTE Norgep_NH_22_før=1.
ELSE.
COMPUTE Norgep_NH_22_før=0.
END IF.
```

23. Concomitant use of 3 or more psychotropics

```
DO IF sum (N02AA01, N02AA05, N02AA55, N02AB02, N02AE01, N02AG02, N02AX02,
N02AJ06, N02AX06, N05AA01, N05AA02, N05AB03, N05AB04, N05AD01, N05AF01, N05AF03,
N05AF05, N05AH03, N05AH04, N05AN01, N05AX08, N05AX12, N05AX13,
N06AA04, N06AA06, N06AA09, N06AA10, N06AA12, N06AB03, N06AB04, N06AB05,
N06AB06, N06AB08, N06AB10, N06AX03, N06AX11, N06AX12, N06AX16, N06AX21,
N05BA01, N05BA04, N05BA12, N05CD02, N05CD03) >=3.
compute Norgep_NH_23_før=1.
else.
compute Norgep_NH_23_før=0.
end if.
```

24. Tramadol + SSRIs

```
DO IF ((N02AX02=1) &
(N06AB03=1|N06AB04=1|N06AB05=1|N06AB06=1|N06AB08=1|N06AB10=1)).
COMPUTE Norgep_NH_24_før=1.
ELSE.
COMPUTE Norgep_NH_24_før=0.
```

25. metoprolol + paroxetine/fluoxetine/bupropion

```
DO IF ((C07AB02=1) & (N06AB03=1| N06AB05=1| N06AX12=1)).
COMPUTE Norgep_NH_25_før=1.
ELSE.
COMPUTE Norgep_NH_25_før=0.
END IF.
```

26. Metformin + ACE-Inhibitors/AT2-antagonists + diuretics

```
DO IF (A10BA02=1|A10BD07 =1| A10BD08=1|A10BD11 =1) &
(C09AA02=1|C09AA03=1|C09AA05=1|C09BA02=1|C09BA03=1|C09CA01=1|C09CA02=1|C09CA
03=1|C09CA04=1|C09CA06=1|C09CA07=1
|C09DA01=1|C09DA03=1|C09DA04=1|C09DA06=1|C09DA07=1|C09DB01=1|C09DX01=1) &
(C03AA03=1|C03AB01=1|C03CA01=1|C03CA02=1|C03DA01=1|C03EA01=1).
COMPUTE Norgep_NH_26_før=1.
ELSE.
COMPUTE Norgep_NH_26_før =0.
END IF.
```

Appendix D

Appendix D – Paper II, IV, informed consent forms

UNIVERSITETSSYKEHUSET NORD-NORGE
DAVVI-NORGGA UNIVERSITEHTABUOHCCEVIESSU

Forespørsel om deltakelse i forskningsprosjekt - Pårørende

En ny tverrfaglig samarbeidsstruktur for å kvalitetssikre medisinbruk hos eldre pasienter

Bakgrunn og hensikt
Dette er et spørsmål til deg om å delta i en studie ved Universitetssykehuset i Nord Norge. Det er bare dersom du selv ønsker det eller dersom du ikke selv kan samtykke til egen deltakelse at vi kontakter dine nærmeste pårørende med denne forespørselen. Vi ønsker å undersøke effekten av en ny arbeidsstruktur hvor sykehusleger, farmasøyter, sykepleiere og fastleger samarbeider tverrfaglig om din behandling med medisiner. Målet er å unngå at du får flere sykehusinnleggelser eller legevaktsbesøk. Du forespørres om å delta fordi du er innlagt ved medisin A/B i Harstad eller geriatrisk avdeling i Tromsø i perioden hvor studien foregår. Universitetet i Tromsø er ansvarlige for studien. Universitetssykehuset Nord-Norge (UNN) er samarbeidspartner.

Hva innebærer studien?

Dersom du takker ja til å delta i studien vil du enten bli plassert i intervensjonsgruppen eller kontrollgruppen. Hverken prosjektlederne eller du selv kan påvirke hvilken gruppe du havner i da dette skjer ved tilfeldig trekning. Dersom du havner i intervensjonsgruppen vil du i tillegg til vanlig behandling, også møte en farmasøyt i avdelingen som vil snakke med deg om dine medisiner, samt vurdere disse i samarbeid med behandlingsansvarlig lege. Kontrollgruppen vil få behandling/omsorg ved avdelingen som vanlig. Vi kommer til å innhente informasjon om dine sykehusinnleggelser og legemiddelbruk hos sykehus, legevakt, fastlege og nasjonale kvalitets-registre (se nærmere beskrivelse nedenfor). Du/din(e) pårørende *kan* bli forespurt om å være med på intervju i forhold til erfaringer med den nye strukturen.

Mulige fordeler og ulemper
Dersom du trekkes ut til deltakelse i intervensjonsgruppen, vil en mulig fordel være at farmasøyten kartlegger om du har bivirkninger av de medisinene du bruker i dag, samt gjennomgå din medisinliste i forhold til om medisinene du bruker er hensiktsmessige for deg, i rett dose og at du har nok informasjon til å bruke medisinene riktig etter at du blir utskrevet. Farmasøyten vil også ringe fastlegen din og formidle eventuelle endringer i din medisinering muntlig i tillegg til skriftlig, samt diskutere dette med ham/henne.

Deltagelse i studien vil sannsynligvis ikke ha noen direkte ulemper for deg, men du vil muligens bli bedt om å besvare en noen ekstra spørsmål i avdelingen.

Hva skjer med informasjonen om deg?
Opplysningene om deg vil registreres avidentifisert. En kode vil knytte ditt navn til opplysninger om deg gjennom en navneliste. Når resultatene analyseres, vil alle opplysningene bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. Kun autorisert personell knyttet til prosjektet vil ha adgang til navnelisten og vil kunne finne tilbake til deg. Navnelisten som knytter deg til data vi har registrert vil slettes innen 31. desember 2023.

Hvilke data samles inn og kobles sammen?

For alle deltakere samles det inn informasjon om følgende ila sykehusoppholdet, samt ved de tidspunkter etter utskrivning fra sykehus som angitt under:
- Alder, kjønn, høyde, vekt, sivilstatus, røykestatus, morsmål, utdanningsnivå, fastlege, adresse og telefonnummer (fra pasientjournal og pasient/pårørende)
- Medisiner du bruker ved innleggelse og utskrivning (fra pasientjournal, kjernejournal, pasient, pårørende, kommunehelsetjeneste, apotek og/eller fastlege)
- Din medisinliste etter 3 og 12 mnd (fra fastlege/sykehjem)
- Dine sykdommer (fra pasientjournal)
- Målinger som f.eks. blodtrykk, puls og vekt (fra pasientjournal)
- Blodprøvesvar som kan ha betydning for din medisinbehandling (fra pasientjournal)
- Resultater av tester tatt i avdeling om hukommelse/demens/aktivitetsnivå (fra pasientjournal)
- Kommunalt hjelpebehov etter 1, 6 og 12 mnd (fra din bostedskommune)

Følgende informasjon registreres i tillegg for intervensjonsgruppen:
- Mulige problemer med dine medisiner som vi finner (fra sykehusopphold)
- Plan for din medisinbehandling og resultat av kommunikasjon med din fastlege

Etter utskrivning innhentes følgende informasjon om alle deltakere fra nasjonale registre, fastlege og kommune. Disse data innhentes for perioden 12 måneder før innleggelse og 12 måneder etter utskrivelse (totalt 24 måneder):
- Kontakt med fastlege eller legevakt (Helfo via Helsedirektoratet)
- Kontakt med sykehus, innleggelse eller kontakt med akuttmottaket (Norsk pasientregister)
- Hoftebrudd (Nasjonalt hoftebruddsregister)
- Hjerneslag (Norsk hjerneslagregister)
- Medisiner på resepter uthentet fra apotek (Reseptregisteret v/Folkehelseinstituttet)
- Død og årsak til død (Dødsårsakregisteret)

Hvis du blir innlagt på sykehuset igjen vil vi gå igjennom din journal for å undersøke om innleggelsen skyldes medisinbruk eller ikke.

Frivillig deltakelse
Det er frivillig å delta i studien. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke til å delta i studien. Dette vil ikke få konsekvenser for din videre behandling. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Om du nå sier ja til å delta, kan du senere trekke tilbake ditt samtykke uten at det påvirker din øvrige behandling. Dersom du senere ønsker å trekke deg eller har spørsmål til studien, se kontaktinformasjon nederst på arket.

Rett til innsyn og sletting av opplysninger om deg
Hvis du sier ja til å delta i studien, har du rett til å få innsyn i hvilke opplysninger som er registrert om deg. Du har videre rett til å få korrigert eventuelle feil i de opplysningene vi har registrert. Dersom du trekker deg fra studien, kan du kreve å få slettet innsamlede opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner.

Økonomi og forsikring
Du har normal pasientforsikring som ved alle sykehusbehandlinger. Studien er finansiert gjennom forskningsmidler fra Universitetet i Tromsø og Universitetssykehuset Nord-Norge. Det vil ikke gis noen form for kompensasjon eller dekning av utgifter utover det som normalt dekkes ved avtaler på sykehuset.

Informasjon om utfallet av studien
Alle deltakerne har rett til å få informasjon om utfallet/resultatet av studien. Hvis du skulle være interessert, se nederst på siden for kontaktpersoner. Du vil bli orientert så raskt som mulig dersom ny informasjon blir tilgjengelig som kan påvirke din villighet til å delta i studien.

Samtykke til deltakelse i studien

_____ er villig til å delta i studien, en ny tverrfaglig samarbeidsstruktur for å kvalitetssikre medisinbruk hos eldre pasienter:

_____/_____
Navn pårørende BLOKKBOKSTAV Relasjon til deltaker

_____/_____
Signatur pårørende Dato

Telefon (brukes til evt. kontakt etter sykehusopphold): _____

Jeg bekrefter å ha gitt informasjon om studien

(Signert, rolle i studien, dato)

Forespørsel om deltakelse i forskningsprosjekt

En ny tverrfaglig samarbeidsstruktur for å kvalitetssikre medisinbruk hos eldre pasienter

Bakgrunn og hensikt
Dette er et spørsmål til deg om å delta i en studie ved Universitetssykehuset i Nord Norge. Vi ønsker å undersøke effekten av en ny arbeidsstruktur hvor sykehusleger, farmasøyter, sykepleiere og fastleger samarbeider tverrfaglig om din behandling med medisiner. Målet er å unngå at du får flere sykehusinnleggelser eller legevaktbesøk. Du forespørres om å delta fordi du er innlagt ved medisinsk A/B i Harstad eller geriatrisk avdeling i Tromsø i perioden hvor studien foregår. Universitetet i Tromsø er ansvarlige for studien. Universitetssykehuset Nord-Norge (UNN) er samarbeidspartner.

Hva innebærer studien?

Dersom du takker ja til å delta i studien vil du enten bli plassert i intervensjonsgruppen eller kontrollgruppen. Hverken prosjektlederne eller du selv kan påvirke hvilken gruppe du havner i da dette skjer ved tilfeldig trekning. Dersom du havner i intervensjonsgruppen vil du i tillegg til vanlig behandling, også møte en farmasøyt i avdelingen som vil snakke med deg om dine medisiner, samt vurdere disse i samarbeid med behandlingsansvarlig lege. Kontrollgruppen vil få behandling/omsorg ved avdelingen som vanlig. Du *kan* bli forespurt om å være med på intervju i forhold til dine erfaringer med den nye strukturen. Du vil bli kontaktet per telefon etter 1, 6 og 12 måneder etter utskrivning for at vi skal følge hvordan det går med deg og samle data. Vi kommer også til å innhente informasjon om dine sykehusinnleggelser og legemiddelbruk hos sykehus, legevakt, fastlege og nasjonale kvalitets-registre (se nærmere beskrivelse nedenfor).

Mulige fordeler og ulemper
Dersom du trekkes ut til deltakelse i intervensjonsgruppen, vil en mulig fordel være at farmasøyten kartlegger om du har bivirkninger av de medisinene du bruker i dag, samt gjennomgå din medisinliste i forhold til om medisinene du bruker er hensiktsmessige for deg, i rett dose og at du har nok informasjon til å bruke medisinene riktig etter at du blir utskrevet. Farmasøyten vil også ringe fastlegen din og formidle eventuelle endringer i din medisinering muntlig i tillegg til skriftlig, samt diskutere dette med ham/henne.

Deltagelse i studien vil sannsynligvis ikke ha noen direkte ulemper for deg, men du vil bli bedt om å besvare en noen ekstra spørsmål i avdelingen. Uansett hvilken gruppe du havner i vil vi ta kontakt med deg per telefon etter 1,6 og 12 mnd.

Hva skjer med informasjonen om deg?
Opplysningene om deg vil registreres avidentifisert. En kode vil knytte ditt navn til opplysninger om deg gjennom en navneliste. Når resultatene analyseres, vil alle opplysningene bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. Kun autorisert personell knyttet til prosjektet vil ha adgang til navnelisten og vil kunne finne tilbake til deg. Navnelisten som knytter deg til data vi har registrert vil slettes innen 31. desember 2023.

Hvilke data samles inn og kobles sammen?

For alle deltakere samles det inn informasjon om følgende ila sykehusoppholdet, samt ved de tidspunkter etter utskrivning fra sykehus som angitt under:

- Alder, kjønn, høyde, vekt, sivilstatus, røykestatus, morsmål, utdanningsnivå, fastlege, adresse og telefonnummer (fra pasientjournal og pasient/pårørende)
- Medisiner du bruker ved innleggelse og utskrivning (fra pasientjournal, kjernejournal, pasient, pårørende, kommunehelsetjeneste, apotek og/eller fastlege)
- Din medisinliste etter 3 og 12 mnd (fra fastlege/sykehjem)
- Dine sykdommer (fra pasientjournal)
- Målinger som f.eks. blodtrykk, puls og vekt (fra pasientjournal)
- Blodprøvesvar som kan ha betydning for din medisinbehandling (fra pasientjournal)
- Resultater av tester tatt i avdeling om hukommelse/demens/aktivitetsnivå (fra pasientjournal)
- Egenvurdering av livskvalitet etter 1, 6 og 12 mnd (per telefon med samtykkekompetent deltaker)
- Kommunalt hjelpebehov etter 1, 6 og 12 mnd (fra din bostedskommune)

Følgende informasjon registreres i tillegg for intervensjonsgruppen:

- Mulige problemer med dine medisiner som vi finner (fra sykehusopphold)
- Plan for din medisinbehandling og resultat av kommunikasjon med din fastlege

Etter utskrivning innhentes følgende informasjon om alle deltakere fra nasjonale registre, fastlege og kommune. Disse data innhentes for perioden 12 måneder før innleggelse og 12 måneder etter utskrivelse (totalt 24 måneder):

- Kontakt med fastlege eller legevakt (Helfo via Helsedirektoratet)
- Kontakt med sykehus, innleggelse eller kontakt med akuttmottaket (Norsk pasientregister)
- Hoftebrudd (Nasjonalt hoftebruddsregister)
- Hjerneslag (Norsk hjerneslagregister)
- Medisiner på resepter uthentet fra apotek (Reseptregisteret v/Folkehelseinstituttet)
- Død og årsak til død (Dødsårsakregisteret)

Hvis du blir innlagt på sykehuset igjen vil vi gå igjennom din journal for å undersøke om innleggelsen skyldes medisinbruk eller ikke.

Frivillig deltakelse
Det er frivillig å delta i studien. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke til å delta i studien. Dette vil ikke få konsekvenser for din videre behandling. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Om du nå sier ja til å delta, kan du senere trekke tilbake ditt samtykke uten at det påvirker din øvrige behandling. Dersom du senere ønsker å trekke deg eller har spørsmål til studien, se kontaktinformasjon nederst på arket.

Rett til innsyn og sletting av opplysninger om deg
Hvis du sier ja til å delta i studien, har du rett til å få innsyn i hvilke opplysninger som er registrert om deg. Du har videre rett til å få korrigert eventuelle feil i de opplysningene vi har registrert. Dersom du trekker deg fra studien, kan du kreve å få slettet innsamlede opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner.

Økonomi og forsikring
Du har normal pasientforsikring som ved alle sykehusbehandlinger. Studien er finansiert gjennom forskningsmidler fra Universitetet i Tromsø og Universitetssykehuset Nord-Norge. Det vil ikke gis noen form for kompensasjon eller dekning av utgifter utover det som normalt dekkes ved avtaler på sykehuset.

Informasjon om utfallet av studien
Alle deltakerne har rett til å få informasjon om utfallet/resultatet av studien. Hvis du skulle være interessert, se nederst på siden for kontaktpersoner. Du vil bli orientert så raskt som mulig dersom ny informasjon blir tilgjengelig som kan påvirke din villighet til å delta i studien.

Samtykke til deltakelse i studien

Jeg er villig til å delta i studien, en ny tverrfaglig samarbeidsstruktur for å kvalitetssikre medisinbruk hos eldre pasienter:

(Navn BLOKKBOKSTAVER , Signatur av studiedeltaker, dato)

Telefon (brukes til kontakt etter sykehusopphold): _____

Jeg bekrefter å ha gitt informasjon om studien

(Signert, rolle i studien, dato)