Factors of concern regarding drug-related patient safety in emergency department

- A summary of results from a randomized controlled trial and observational studies

Dissertation for the degree of *Philosophiae Doctor*

Lisbeth Damlien Nymoen

Department of Pharmacy, Faculty of Mathematics and Natural Science, University of Oslo, Norway

Diakonhjemmet Hospital Pharmacy AS

Oslo 2022

Diakonhjemmet Hospital pharmacy

Diakonhjemmet Hospital

Series of dissertations submitted to the
Faculty of Mathematics and Natural Sciences, University of Oslo
No. 2551

ISSN 1501-7710

Print production: Graphics Center, University of Oslo.

To Malene, Matias, and Marius

Contents

Scientific environment

The studies presented in the four papers included in this dissertation were conducted as a cooperation between Diakonhjemmet Hospital Pharmacy, Diakonhjemmet Hospital and the University of Oslo, Oslo, Norway.

Supervisors:

Associate Professor II Kirsten K. Viktil, main supervisor, cand.pharm., PhD
Diakonhjemmet Hospital Pharmacy AS & Section of Pharmacology and Pharmaceutical Biosciences, Department of Pharmacy, University of Oslo

Head of Cardiology and Senior Consultant Erik Øie, co-supervisor, MD, PhD
Department of Internal Medicine, Diakonhjemmet Hospital

Professor Espen Molden, co-supervisor, cand.pharm., PhD
Center for Psykopharmacology, Diakonhjemmet Hospital & Section of Pharmacology and Pharmaceutical Biosciences, Department of Pharmacy, University of Oslo

Acknowledgements

Malene 6 years: my mom likes to do research on drugs, but I look forward to her "book" is finished…

I am grateful for the opportunity to conduct this PhD project, and the journey as a PhD-student have given me valuable new perspectives. I want to express my gratitude to the people making the PhD project and the work with this dissertation possible, both professionally, economically and personally.

First and foremost, I am deeply grateful to my main supervisor **Kirsten K. Viktil**. I would not have been able to do this project and completed this dissertation without you. Thank you for all productive discussions and all your support, both professional and personal. As one of the pioneers within clinical pharmacy in Norway, you have always inspired me, and you have paved the way for future generations of clinical pharmacists. Thank you for cheering for me when I wanted to pursue a PhD, for prioritizing me when I needed help, and for always reminding me to celebrate milestones during the PhD period.

I would express my sincere gratitude to my co-supervisor **Erik Øie**, despite your busy schedule you always took the time to answer my questions, both big and small. Thank you for believing in the project and providing me with your valuable physician perspective in every stage of the studies, during the writing of the papers and the dissertation, and through contribution in the expert panel assessments.

A sincere and heartfelt thank you to my co-supervisor **Espen Molden.** Thank you for believing in the project and for your support. Your extended experience with research and your insightful comments in funding applications and during the writing of papers has been valuable. Thank you for always looking at things differently and expanding my perspectives.

Further, I would express my sincere thankfulness to:

All participants in the studies, including both patients and physicians for making it possible to conduct the research.

Diakonhjemmet Hospital Pharmacy AS for the work experience as a clinical pharmacist, for the opportunity to be a PhD student, and for funding the PhD project, and **The Hospital Pharmacy Board** for supporting the PhD project.

Diakonhjemmet Foundation and **Diakonhjemmet Hospital Fund for research, innovation, and professional development** for funding the PhD.

The Norwegian Pharmaceutical Society (NFS) for travel grants and the Mentor Program.

The Faculty of Mathematics and Natural Sciences at the University of Oslo for giving me the opportunity to conduct my PhD.

Staff at the Emergency Department, Diakonhjemmet Hospital for the warm welcoming. It felt safe to work evening shifts in the emergency department together with you. **Lasse Andreassen** which paved the way for our first study in the emergency department, and **Nina Davidsen** for trading your emergency nurse activities with medication reconciliation for several weeks to contribute in the data collection and being a co-author on paper I. **Ole Kristian Roald** for believing in the project when we proposed a continuance of the emergency department research, and for constructive comments during writing of funding applications. **Aasmund Godø** for your valuable physician perspective in two rounds of expert panel assessments and being a co-author on paper I and III. **Tord Kjesbu** for supporting our research in the emergency department.

All my wonderful **colleagues** at Diakonhjemmet Hospital Pharmacy AS for always sharing your knowledge, for your support, and for always caring. **Ragnhild Holtskog** for making it possible for me to be a PhD student, I am forever grateful that you believed in me and for your support and cheering through this period. **Trude E. Flatebø** for your contribution as study pharmacist, in expert team assessment, as co-author in paper II and III, and for supporting and friendly conversations when I needed them through the ups and downs of the PhD journey. **Merethe Nilsen** for your contribution as study pharmacist, in expert team assessment, and as co-author in paper I and III. **Ann-Christin Riddarsporre** and **Tonje Thingstad Johansen** for your contribution as study pharmacists**. Kristine Olsen and Jasmina Zogaj** for our friendship developed through our years together at the hospital pharmacy and for making every workday better with your presence.

Elin C. Lehnbom, co-author in paper IV, for your constructive comments and input, for introducing us to the WOMBAT-method and for training us in the methodology.

For statistical assistance and guidance **Tron A. Moger**, co-author in paper I and II, **Scott R. Walter**, co-author in paper IV, and **Andrew Henry Reiner** for valuable support during the preparation of outcome data files for paper II and III.

Liv Hopen, for your input as patient representative during the designing of study II and III.

Marianne Lea for interesting and inspiring discussions, and further for sharing your Epidata knowledge, your experiences from dissertation writing, and for answering all my big and small questions. Also, thank you for critical input on my dissertation.

Liv Mathiesen, for all pleasant meetings in the research group of clinical pharmacy the recent years, and for input on funding applications.

Master students **Malin Björk,** co-author in paper III, **Therese Tran**, co-author in paper IV**,** and **Ingrid Kinne Tunestveit**, co-author in paper IV, for your valuable contributions.

PhD-student colleagues during my PhD period for research discussions and inspiration.

Tove Kalsrud which were my mentor (NFS Mentor Program) during a decisive year of my career, but sadly passed away fall 2019. You challenged me and my mindset when I did not know what direction I wanted for my career. Thank you for nurturing the PhD idea!

Skarnesjentene and the Supersvigerinnes for reminding me that a social life is important even during a PhD.

My parents, Solveig and Øystein, for always believing in me, for teaching me that hard work pays off, and for all your loving support.

The rest of my family for your support and cheering.

Marius, Malene, and Matias, my dear family**.** Marius, thank you for anchoring me whenever I was overwhelmed, for being there through ups and downs, and taking one for the team (numerous times). Thank you for being you through this process, this would not have been possible without you. Malene and Matias, thank you for forcing me out of the PhD bubble with your laughs, songs, and jokes, and for making me realize what life is really about. To all three of you, thank you for our wonderful life together. I love you all! And now Malene, I have finally finished my "book".

Synopsis of the dissertation

This synopsis sets the scene for the dissertation, defines the scope, and aims, and serves as an introduction to the problem areas addressed. Topics covered in this section is broadly discussed throughout the dissertation and in the included papers.

Scope and aim

In an overall perspective, challenges regarding drug therapy affects patient safety in all stages throughout the healthcare service, i.e., at hospital admission, during a hospital stay, at discharge, and in the primary healthcare setting. The research project presented in this dissertation originated from drug-related challenges at admission to a Norwegian emergency department (ED), and thus focus on the hospital admission-phase.

Medication discrepancies (MDs) and drug-related problems (DRPs) are common among patients admitted to EDs. In addition, it has been revealed recent years that drug-related ED visits are a considerable concern. The following topics and questions thus provided the basis for the dissertation and study aims:

- For decades researchers have investigated prevalence of MDs between different sources to patients' drug lists. Resulting in numerous studies reporting consistent results: Drug lists registered at hospital admission are often not reflecting patients' actual drug use. Why are MDs still a problem at hospital admission? Patients' drug lists are traditionally obtained and registered in the ED, and in Norway and several other countries this task is assigned to physicians. Can ED physicians' prioritization between different tasks be a contributing factor to the occurrence of MDs?
- Medication reconciliation (MR) and medication review is methods broadly implemented and used in hospital departments for identifying MDs and DRPs, respectively. Can these methods be tailored to be efficient and feasible in the ED setting? Further, can implementation of such methods in the ED setting impact clinical outcomes for ED patients?
- Drug-related hospital admissions (DRHAs) are common and has clinical consequences for the patients and economic consequences for the healthcare system. But what is known about drug-related *ED visits*?

The overall aim of the research project and this dissertation was to study factors affecting drug-related patient safety in the ED, by investigating drug information flow, DRPs, and drug-related admissions. Furthermore, in a randomized controlled trial (RCT), investigate if a pharmacist-led intervention comprising ED medication review could improve patients' clinical and post-discharge outcomes.

Included studies – aim and design

Four studies with different perspectives on drug-related patient safety in the ED were conducted to achieve the overall aim:

- The first study, presented in paper I, investigated the frequency of clinically relevant MDs at admission to the ED with a cross-sectional study design. Further, characteristics of patients with clinically relevant MDs were identified to develop a prioritizing model. This study also tested a redesigned working model for conducting MR in the ED.
- In the second study, presented in paper II, the tested working model from the first study were broadened. The impact of a pharmacist-led intervention, consisting of MR and medication review, on clinical outcomes was investigated with a RCT in the ED setting.
- The third study, presented in paper III, investigated the prevalence and risk factors of drug-related ED visits in the intervention group from the RCT through a retrospective cohort study design.
- The perspective in the fourth study, presented in paper IV, was turned to gather knowledge regarding ED physicians working patterns, with specific focus on the time spent on drug-related activities. This was investigated with a time-motion study design.

Main results

The main findings from these studies underlined that both clinically relevant MDs and drug-related ED visits are critical concerns when patients are admitted to the ED, as this affects 62% and 20% of ED patients, respectively. It was revealed that obtaining drug lists at admission is a fragmented process for ED physicians, on which they spend an average of 4 minutes per hour. Furthermore, documentation regarding drug-related ED visits was low among physicians. The studies revealed that integrating clinical pharmacists in the interdisciplinary team of the ED improves the quality of the registered drug list and can increase recognition of drug-related ED visits. The presented prioritizing model for MR and identified risk factors for drug-related ED visits is valuable when identifying high risk patients in need of a thorough evaluation of their drug list. The pharmacist-led intervention

investigated in the RCT, did not impact clinical outcomes. However, this study provided valuable information regarding how to tailor the working models for MR and medication review additionally to the ED setting.

Conclusion

The four conducted studies have added new knowledge regarding drug information flow, drug-related ED admissions, and tailoring of pharmacists-led ED MR and medication review interventions. This dissertation challenges the existing procedures where physicians are assigned the task of drug history taking at admission to the ED. Furthermore, increased awareness, tailored interventions, and willingness to take action are necessary to address the identified factors of concern regarding drug-related patient safety for patients admitted to the ED.

List of papers

Paper I

Damlien L, Davidsen N, Nilsen M, Godø A, Moger TA, Viktil KK. Drug safety at admission to emergency department: an innovative model for PRIOritizing patients for MEdication Reconciliation (PRIOMER). *European Journal of Emergency Medicine.* 2017 Oct;24(5):333-339. Epub 2015 Dec.

Paper II

Nymoen LD, Flatebø TE, Moger TA, Øie E, Molden E, Viktil KK. Impact of systematic medication review in emergency department on patients' post-discharge outcomes -a randomized controlled clinical trial. *Under review PLOS ONE, minor revisions*

Paper III

Nymoen LD, Björk M, Flatebø TE, Nilsen M, Godø A, Øie E, Viktil KK. Drug-related emergency department visits: prevalence and risk factors. *Internal and Emergency Medicine*. 2022 Feb 7. Epub ahead of print.

Paper IV

Nymoen LD, Tran T, Walter SR, Lehnbom EC, Tunestveit IK, Øie E, Viktil KK. Emergency department physicians' distribution of time in the fast paced-workflow-a novel time-motion study of drug-related activities. *International Journal of Clinical Pharmacy*. 2022 Apr;44(2):448-458. Epub 2021 Dec 23.

Abbreviations

ATC	Anatomical Therapeutical Chemical
CI	Confidence interval
DRHA	Drug-related hospital admission -*explanation of the term, page 22*
DRP	Drug-related problem -*explanation of the term, page 20*
ED	Emergency department
GP	General practitioner
HR	Hazard ratio
ICD-10	International statistical Classification of Diseases and related health problems, 10th revision
IMM	Integrated Medicines Management
IRR	Inter-rater reliability
LOS	Length of stay
MD	Medication discrepancy -*explanation of the term, page 21*
MR	Medication reconciliation -*explanation of the term, page 23*
NPR	Norwegian Patient Registry
OR	Odds ratio
PCNE	Pharmaceutical Care Network Europe
RCT	Randomized controlled trial
WHO	World Health Organization

Other key terms used in this dissertation:

Adverse drug event -*explanation of the term, page 20*

Adverse drug reaction -*explanation of the term, page 20*

Adverse effect -*explanation of the term, page 20*

Drug history taking -*explanation of the term, page 16*

Medication error -*explanation of the term, page 20*

Medication review -*explanation of the term, page 24*

Non-adherence -*explanation of the term, page 40*

1 Background

1.1 Emergency Department

The organizing of EDs are different across countries, and occasionally even within countries (1). Steptoe et al. aimed to create a universal understanding of what is meant by the term *ED* (1). Two criteria which must be fulfilled for a facility to be defined as an ED was provided; *1) the provision of immediate, often stabilizing, care for patients with emergent medical needs, and 2) provides a base level of availability and accessibility (i.e., available 24 hours per day, 7 days per week, 365 days per year) with no restriction on who can access that care* (1). In Norway, as in several other countries the EDs are hospital-based, meaning located in acute care hospitals. Thus, in this dissertation ED-activities will be discussed based on a hospital-based ED structure.

The main purpose of a hospital-based ED is to prioritize patients related to the acuteness of their symptoms, and further to examine and diagnose patients, initiate time-critical treatment, and determine the adequate level of care for each patient (2-4), i.e., admission to a hospital department, transferred to another hospital, or directly discharge from the ED. A hospital-based ED thus serves as a gatekeeper for hospital admissions.

An ED is different from a hospital department. As a result of the gatekeeper role, patients with a broad variety of symptoms and complaints present to the ED. Hospital departments are on the other side more specialized and treat narrower patient groups e.g., a cardiological departments treats patients with cardiovascular diseases, and an orthopedic department handles fractures and related complaints. Further, the length of stay (LOS) distinguishes EDs from hospital departments, LOS in EDs are counted in minutes or hours (5), whereas LOS at hospital departments are counted in days (6).

1.1.1 The Norwegian healthcare system

Similar to the other Nordic countries, the main actors of the Norwegian healthcare service are public and funded predominantly by taxation (7). The pre-hospital organization in the Norwegian healthcare system has a different structure than the healthcare systems in other countries (8, 9) (Figure 1). Most inhabitants in Norway are assigned to a general practitioner (GP) (“fastlege”) and all municipalities are obliged to provide emergency services outside the GPs opening hours through the municipal emergency clinics (“legevakt”). GPs and

the municipal emergency clinics have a gatekeeper function and handle less severe conditions. Patients with more severe conditions where an ED visit is necessary, need a referral from a GP, a physician at the municipal emergency clinic, a nursing home physician, or are transported directly by the emergency medical services (9). In 2014, two thirds of acute admissions to Norwegian hospitals were referred by a GP or a municipal emergency clinic physician. The rest were direct admissions of different kinds, e.g., patients admitted from nursing homes, hospitals out-patient clinics, or directly admitted by ambulance services (10, 11).

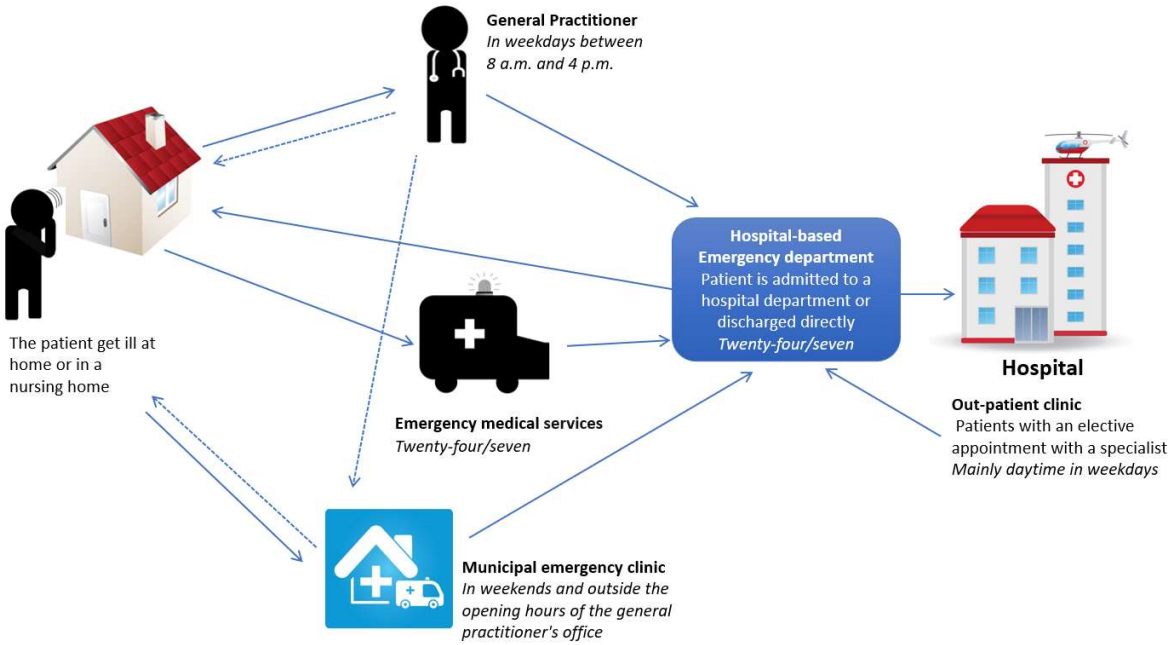


Figure 1. Patient pathways in the Norwegian healthcare system. Patients need a referral from general practitioner, physician at the municipal emergency clinic or transportation by the emergency medical service to be admitted to a hospitals' emergency department. Patients can also be referred from physicians at the hospital out-patient clinic to the emergency department.

1.1.2 Patient population

According to estimates from 2013 the annual number of patients presenting to EDs in Norway was 180 visits per 1000 citizens (12). Denmark had a similar ED admission rate at 196 visits per 1000 citizens (13). Further, corresponding annual estimated numbers for the United Kingdom (UK), Australia and United States of America (USA) was >400 visits per 1000 citizens (13). Sweden has a similar organization of their healthcare system as the latter countries (12), and therefore most likely has a higher ED admission rate compared with Norway and Denmark. The discrepancy is mainly explained by the pre-hospital organization of the healthcare systems in Norway and Denmark, where primary healthcare personnel handle patients with less severe conditions (12).

Studies have reported that the comprehensive pre-hospital organization of the healthcare system in Norway (Figure 1), leads to a selected patient population presenting to Norwegian EDs (8, 9). Compared with EDs in other countries, a higher percentage of high-level acute patients (based on triage, Figure 3) are referred to Norwegian EDs, and a higher percentage of patients are hospitalized after the ED-stay in Norway (8). Approximately 50% of patients admitted to the ED in a Norwegian study were older than 65 years (8), indicating that Norwegian ED patients is older than ED patients included in studies from other countries (14-16).

According to the World Health Organization (WHO) the number of hospital discharge per 100 citizens has been stable in most countries the last 30 years (17). With a growing world population this indicates an increase in absolute numbers of hospital admissions, and most likely also ED visits. In 2018, Norwegian hospitals handled over 1.6 million adult patients admitted to hospital departments (18). However, due to the variability in organization of EDs between and within countries, annual numbers of ED visits are not routinely reported, thus international overview statistics are not available.

1.1.3 Physician's role

Physicians' main tasks in the ED is to diagnose and initiate acute treatment of admitted patients, and to determine the adequate level of care for each patient (2). To elucidate the patients' presented symptoms, obtaining information regarding patients' medical history and drug history is essential. Further, to inform the next level of care (i.e., personnel at hospital department or healthcare personnel in the primary healthcare) regarding conducted examinations and initiated treatment, documentation in patient record is an important task for ED physicians. To ensure safe and efficient treatment of patients, ED physicians must communicate with ED colleagues (19, 20). Due to the fast-paced workflow and the continuous patient flow to the ED, physicians are forced to distribute their time to ensure that all admitted patients receive adequate emergency care. Figure 2 is a graphical depiction of key events ED physicians and other personnel in the ED are involved in during a patient stay in a Norwegian ED, i.e., standard care.

Several countries have a tradition for specialised emergency medicine physicians working in the ED (21). There are few emergency medicine specialists in Norway as this physician speciality was first established here in 2017 (21). Therefore, most patients who are admitted

to a Norwegian ED do not meet an emergency medicine physician but a resident in e.g., internal medicine, surgery or orthopedic surgery. In Norway, the physician referring the patient to the hospitals' ED sets a tentative referral diagnosis after assessing the patient's symptoms and conducting an initial examination. The specialty of the resident who patients are assigned to see in the ED, thus depends on the pre-hospital tentative referral reason/ main complaint (8, 9).

1.1.4 Drug history taking

At arrival to the ED, patients' drug use prior to the admission is obtained through drug history taking. A good drug history should comprise currently prescribed drugs, currently used over-the counter drugs, and herbal or alternative drugs (22, 23). The following information should be obtained for each drug: the name of the drug, formulation (e.g. modified-release tablets), dosage, route of administration (e.g. oral, transdermal, by inhalation), and dosage frequency (22), altogether this information constitutes the patient's current *drug list.* In addition, information regarding recently terminated treatment, previous adverse drug reactions including hypersensitivity reactions, and adherence to therapy should be obtained through the drug history taking (22). When obtained, the drug history is registered in the hospital's patient record. If the patient is admitted to a hospital department following the ED visit, the current drug list is also register in the medication chart (Figure 2).

The obtained drug history and registered current drug list is basis for further drug treatment during the ED visit and potential hospital stay. Drug history taking can be time consuming and challenging, thus some countries have implemented personnel, such as nurses or pharmacists to focus specifically on conducting this task in the ED (24-28). In Norway, and several other countries, responsibility for drug history taking is assigned to the ED physicians.

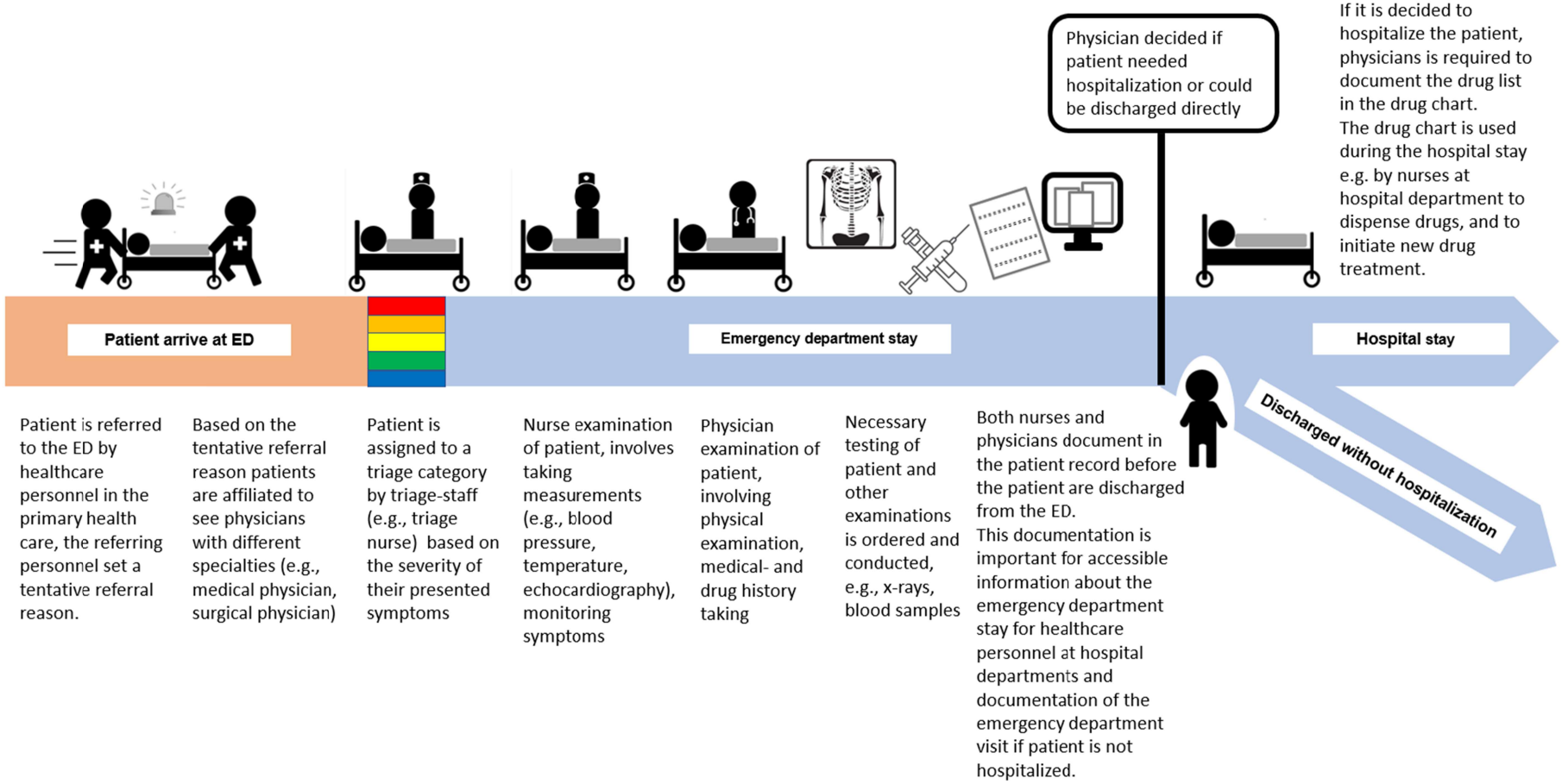


Figure 2. Key events during the fast-paced workflow in Norwegian emergency departments (ED), standard care.

1.1.5 The fast-paced workflow

The volume of patient admissions to an ED cannot be precisely predicted, and the need for emergency services can therefore occasionally exceed available resources for patient care (29), referred to as ED crowding (29, 30). Crowding is an increasing challenge in EDs worldwide (9, 31, 32). Systematic reviews have summarized consequences for patients during ED crowding; increased mortality, delayed assessment and care, increased LOS in the ED and hospital, risk of readmission, and exposure to errors (among these adverse drug events) (33, 34).

Asplin et al. have presented a commonly accepted conceptual framework for understanding the factors leading to ED crowding: the input – throughput – output model (35). The input component describes factors who influence the patient volume presenting to the ED. The throughput component describes internal ED processes, and factors which impact LOS is highlighted, e.g., effective ED triage and initial physician evaluation, and further diagnostic work up and treatment. Finally, the output component describes the accumulation of admitted patients, mostly dependent on the inability to move patients from the ED to a hospital department, e.g., because the in-hospital capacity is exceeded (35).

According to Asplin et al. (35) an effective ED triage is an essential part in the first phase of the throughput component to prevent ED crowding. Most EDs use validated triage systems to prioritize patients at arrival, for instance Manchester Triage System (30, 36) (Figure 3). The prioritizing of patients ensures that patients are seen by an ED physician in order of severity of their presented symptoms rather than order of arrival to the ED (37).

Priority	Colour	Triage category	Target time to be seen by physician
1	Red	Immidiate	0
2	Orange	Very Urgent	10
3	Yellow	Urgent	60
4	Green	Standard	120
5	Blue	Not Urgent	240

Figure 3. Triage categories used in Manchester Triage System (36).

ED LOS is not a direct measurement of ED crowding, though identified as an important indicator (38), and this is also implied in Asplin et al.'s throughput component (35). ED crowding is related to the capacity of the ED; hence a local threshold must be defined to

measure ED crowding. ED LOS is often available through the hospitals' patient record system, and therefore is a more accessible measure. ED LOS is used as a tool to monitor emergency care quality, and several countries have set a 4-hour time target for ED LOS (5). This time target mandated that 98% of admitted ED patients, should be assessed, treated, and discharged/ transfer from the ED to the adequate level of care, within four hours (5, 39).

1.2 Drug-related errors and harm in emergency department

Drugs are essential to manage symptoms, slow disease progression or to prevent the development of future illnesses in many conditions. However, drugs also have a risk of causing harm. According to a recent report from the Norwegian Directorate of Health, drug-related injury is the most frequent cause of patient harm during hospital stays (40). High frequency of medication errors and patient harm is a considerable challenge also in other countries. A recent publication from UK (41) reported that approximately 66 million medication errors annually cause patients moderate or severe harm. Furthermore, a study investigating a random selection of all deaths within three Swedish counties, linking death certificates to relevant case records (hospitals, and/or primary care centers, and medicolegal files), found that 3.1% of deaths were caused by fatal adverse drug reactions (42).

Drug-related errors and harm can affect patients in all healthcare levels. However, over several decades transitions of care have been identified as a key risk event regarding drug-related patient safety (43, 44). WHO refers to transitions of care as *the various points in the health care system where a patient moves to, or returns from, for the purposes of receiving health care* (43). Admission to an ED is one example of a transition of care where patients are at increased risk of drug-related errors and harm (44-47).

Terms describing drug-related errors, harm, and concerns

In the literature, terminology used regarding drug-related errors, harm, and concerns is heterogenous and is often used interchangeably (48, 49). In addition, to the ambiguous terminology, there are numerous definitions and classifications for each term used in prior studies (49), and some of the terms are also overlapping. The following statements regarding different terms should not be interpreted as definitions, rather as explanation of terms used in this dissertation.

Medication errors

A failure in the treatment process that leads to, or has the potential to lead to, harm to the patient (50). Hence, the term medication errors does not only cover harm or potential harm caused by drugs (51), because failures occurring during all stages in the treatment process are included (the process of prescribing, ordering, delivering, and administrating the drug (52)).

Adverse drug events

The term has been described differently over the last decades. However a recent report from WHO (44) supports this description: *Any injury resulting from medical interventions related to a drug. This includes both adverse drug reactions in which no error occurred and complications resulting from medication errors* (52). Adverse drug events caused by medication errors are generally considered to be preventable (53). It has been argued that the adverse drug events term is superfluous, due to the overlapping scope with medication errors and adverse drug reactions (54). However, the adverse drug events term is frequently used in prior studies aiming to investigate a broader range of drug-related concerns leading to patient harm, i.e., not only adverse drug reactions.

Adverse drug reactions

There is less dispute regarding the definition of adverse drug reactions, and the most frequently used is the definition provided by WHO: *A response to a drug which is noxious and unintended and that occurs at doses used in humans for prophylaxis, diagnosis or therapy of diseases, or for the modification of physiological function* (43). According to this definition, there is an established causality between a patient's response and a drug used at normal doses (49).

Adverse effects

The term refer to the same phenomenon as adverse drug reaction (54). However, adverse effects are either suspected or attributed. Hence, the causality between a drug and an adverse effect described in a patient is not always definite (54, 55).

1.2.1 Drug-related problems

The early work by Hepler and Strand (56) regarding pharmaceutical care has formed the basis for later classifications of DRPs (57, 58). A commonly used definition of the DRP term is *an event or circumstance involving drug therapy that actually or potentially interferes with*

desired health outcomes (57). The DRP term comprises both processes that may result in harm (medication errors and potential harm) and observed harm (49), such as adverse drug reactions/adverse effects and adverse drug events. Identifying and solving DRPs can therefore lead to interventions targeting actual patient harm, such as manifested adverse drug reactions, and non-adherence leading to disease progression. Further, identifying and solving DRPs can also prevent harm that has not yet manifested, for instance through deprescribing where there is no valid indication, and handling drug-drug interactions before the patient get symptoms from an adverse drug reaction.

Examples of DRPs are unnecessary drug treatment, sub-optimal dosing, drug-drug interaction, adverse drug reactions and need for additional drug treatment (58). An advantage of the existing DRP classifications is that they are patient-centric, which is valuable for identifying interventions that can prevent potential DRPs (49). However, this have led to some overlap of categories in DRP classifications. For instance, co-administration of citalopram and tramadol causing serotonin syndrome could be classified as both an adverse drug reaction and a drug-drug interaction (49).

DRPs have been associated with increased patient mortality and morbidity, and also increased healthcare service costs, due to increased LOS and DRHAs (59-63). A systematic review (64) summarized the most frequently reported risk factors associated with DRPs: polypharmacy, elderly patients (defined as over 65 years), female gender, poor renal function and the presence of multiple comorbidities. Further, risk of DRPs was linked to prescription of certain drugs or classes of drugs, among other thrombolytics/anticoagulants, cardiovascular agents, central nervous system agents and corticosteroids. These risk factors is in line with another systematic review summarizing risk factors for adverse drug events during hospital stay (65), underlining the overlapping and similarity of the terms.

1.2.2 Incorrect drug lists and medication discrepancies

The Institute for Healthcare Improvement states that poor communication regarding patients' drug treatment at transition of care is the cause of 50% of all medication errors and 20% of all adverse drug reactions in hospitals (23). When comparing patients' actual drug use before admission with the drug list registered by physicians at ED admission, prior studies has been revealed that over 60% of patients are registered with an incorrect drug list (14, 66-68). MD

are a frequently used term to describe *any difference between the medication use history and the admission medication orders* (44, 47).

Examples of MDs are omission of a regular drug the patient has used, addition of a drug the patient has not used, and dosage discrepancies. Further, MDs may be intentional, undocumented intentional or unintentional (44, 47), where the latter two have negative effects on patient safety and quality of care (69-73). Prior studies have reported that unintended MDs can result in medication errors with the potential to cause patient harm if not identified and corrected (74, 75). Further, unintended MDs are mainly considered preventable and in DRP classifications-systems MDs are listed as an own category of concern (57, 58).

Up to 27% of hospital prescribing errors have been linked to inaccurate or incomplete drug lists obtained by physicians in the ED (74). A Norwegian multi-centre study found that 80% of in-hospital patients had one or more MDs (72), and approximately 70% of the identified MDs were clinically relevant, i.e., of importance for the patient treatment. Increasing age, increasing number of used drugs, and surgical referral reason have been identified as risk factors for MDs at admission to the ED (76, 77).

1.2.3 Drug-related emergency department visits and drug-related hospital admissions

DRHAs caused by patients' drug use are well studied and reported to be common (14, 62, 63, 78-80). DRHAs have both clinical consequences for the patients and economic consequences for the healthcare system and society (81-83). Advancing age, comorbidity and increasing number of used drugs have been associated with a higher risk of DRHAs (62, 63, 78, 80). Due to the increasing worldwide challenge with ED crowding, there has been a growing interest in investigating drug-related ED visits during the recent decade (14, 78-80). Drug-related ED visits have been associated with a higher hospital admission rate compared with non-drug-related ED visits (14, 78, 80). Furthermore, studies have revealed that 57-70% of drug-related ED visits may be preventable (16, 78, 84).

There is, however, no universal consensus regarding the definition of a drug-related ED visit or DRHA. The reported prevalence in prior studies therefore varies widely between 1.3 and 41.3% (14-16, 62, 63, 78-80, 85, 86). The reported prevalence from prior studies is highly influenced by the applied definition, the method used for detection and the investigated patient population. Regarding definitions, studies investigating drug-related ED visits/

DRHAs solely associated with adverse drug reactions (15, 62) report a lower prevalence compared with studies investigating ED visits/ hospital admissions related to adverse drug events or DRPs (85, 87-89). Further, in the matter of detection methods, prospective studies are found to report higher prevalence compared with retrospective studies (81, 90). Finally, the included patient population has great impact on the reported prevalence. For instance, studies investigating older multimorbid patient in hospital departments (86, 91, 92) report higher prevalence compared with studies investigating more heterogenous populations admitted to the ED (14, 78, 80).

Identifying drug-related ED visits/ DRHAs is challenging. Prior studies investigating this issue have used a range of methods, for instance retrospective classifications based on coding in patient records (15, 16), pharmacists prospectively classifying drug-related ED visits/ DRHAs according to sets of criteria (14, 78, 80), and assessments by expert panels (93, 94). Warlé-van Herwaarden et al. developed the Quick Assessment of Drug-Related Admissions over Time (QUADRAT) system to identify DRHAs more efficiently (95, 96). One disadvantage of the QUADRAT risk assessment tool is that the tool only examines adverse drug events due to overuse (97), i.e., adverse drug events due to prescription or use of more drugs that are clinically needed. Hence, when using the QUADRAT-tool, non-adherence and need for additional drug treatment is not included as possible causes of DRHAs (97).

An additional concern regarding drug-related ED visits is the growing body of evidence suggesting that ED physicians do not recognize drug-related ED visits in the fast-paced workflow (14, 80, 98). If ED visits caused by drug-related issues are not identified during the stay in the ED, physicians might end up misdiagnosing and treating the symptoms instead of the actual problem (14). Hence, identifying patients with a drug-related referral reason early in the admission-process is found crucial to the patient safety (14, 84, 99).

1.3 Actions to improve safety of drug therapy

1.3.1 Medication reconciliation

Medication reconciliation (MR) is a process recognized world-wide to prevent incorrect drug lists and MDs during transition of care (45, 100, 101). Despite the widespread use of MR in healthcare, there is not an established universal definition of the process. According to the

WHO an MR is *the formal process in which health care professionals partner with patients to ensure accurate and complete medication information transfer at interfaces of care* (101). Even though there is wide agreement regarding the essence of the MR procedure; *to obtain the best possible medication history* (45, 102), definitions vary regarding the scope and specific tasks included. Penm et al. published a consensus definition of MR in 2019: *The process of creating the most accurate list possible of all medications a patient is taking and comparing that list against the prescriber's orders. In addition, the patient's allergies, history of side effects from medications and medication aids are listed with the goal of providing correct medication to the patient at all transition points within the health care system* (102). When MR is conducted in the ED, it is often performed before medication orders are written. In these cases the MR definition provided by WHO (101) is most suitable, and the process can be referred to as drug history taking rather than MR (24, 25), however, these terms are used interchangeably.

Prior systematic reviews have concluded that pharmacist-led MR programs at hospital transitions efficiently identifies MDs (45, 103-106). Decrease in adverse drug event-related hospital revisits, all-cause readmissions and ED revisits has been proposed as clinical outcomes of pharmacist-led MR programs (103, 106). Prior studies have also investigated pharmacy technicians (107) and nurses (108) performing MR, and concluded that MDs are efficiently identified by these professions.

According to the Pharmaceutical Care Network Europe (PCNE), a correct drug history is basis when conducting medication reviews, hence an MR is an essential first step of a medication review (109). The MR process has been reported to be time consuming and resource demanding (66), and a systematic overview of systematic reviews (110) concluded that more research was needed to determine the most efficient procedure to conduct MR.

1.3.2 Medication review

According to the PCNE, a medication review is defined as *a structured evaluation of a patient's medicines with the aim of optimising medicines use and improving health outcomes. This entails detecting drug-related problems and recommending interventions* (109). Further, PCNE classifies medication reviews into different levels considering information sources available (109):

- *Simple review:* based solely on the patient's medication history (type 1)

- *Intermediate review:* in addition to the patient's medication history, this review also includes a patient interview (type 2a) or clinical data (type 2b)
- *Advanced review:* includes the patient's medication history, a patient interview and clinical data (type 3)

Several prior studies investigating the impact of pharmacist-led interventions involving medication review have reported reduction in ED revisits and hospital readmissions (93, 111-114). There are also several studies reporting no impact on clinical outcomes (115-117). Hence, systematic reviews on the subject conclude ambiguously. A Cochrane review found that medication review may reduce ED contacts, but found no evidence that medication review reduces mortality or hospital readmissions (118). Another systematic review and meta-analysis concluded that medication review had a positive effect on most drug-related outcomes, but minimal effect on clinical outcomes, and no effect on quality of life (119). Several systematic reviews have however, supported the impact of pharmacist-led medication reviews, reporting positive effects such as optimized medication use (120-122), reduced costs (122), reduction in drug-related readmissions and all cause ED revisits (123). The impact of medication review performed in the ED on clinical outcomes is scarcely investigated (124).

Conducting advanced medication reviews as described by PCNE (109), requires identification of DRPs using implicit criteria. Thus, combining knowledge of the individual patient's symptoms and health status with knowledge of pharmacology and pharmacotherapy to identify DRPs. Personnel conducting medication review must therefore have adequate knowledge regarding all these areas. In addition, identifying DRPs through implicit criteria can be time consuming and resource demanding. To simplify the process, lists of inappropriate drugs and common prescribing omissions has been developed. These lists are referred to as explicit criteria (125), and examples of such lists is Beers-criteria (126, 127) and START/STOPP criteria (128, 129). However, studies have reported that only applying explicit criteria during medication review is inferior to identifying DRPs through implicit criteria with regards to actually optimizing patients' drug treatment (125, 130). Primary studies included in prior systematic reviews investigating impact of medication review comprise both studies utilizing advanced medication review identifying DRPs, for instance Gillespie et al. (111), and studies applying explicit criteria, for instance Gallagher et al. (131). This diversity in prior studies medication review methods can contribute to explain the ambiguously conclusion regarding clinical impact of conducting medication review.

1.3.3 Integrated Medicines Management

The Integrated Medicines Management (IMM)-model (114) was developed by pharmacists in Northern Ireland to ensure quality and safety of drug treatment at an individual level during hospitalizations (132). The IMM-model is a working model for clinical pharmacists and the overall aim of the introduction was to maximize health and achieve the best outcome for the individual patient through optimal use of drugs (114). The IMM-model comprises procedures at three steps during a hospital stay: 1) MR at admission, 2) medication review during the hospital stay and 3) MR and information both to the patient and to the next level of care, at discharge (114). Hence, in comparison with conducting separate medication review, the IMM-model represents a more continuous, seamless process where the patient is followed up during the entire hospital stay (109).

In prior studies, implementation of the IMM-model has been reported to reduce LOS and prolong time to readmission (114), and further to reduce drug-related readmissions and all cause ED revisits (111).

1.3.4 Pharmacists in emergency department

The extent of clinical pharmacy services in the ED has developed internationally during the last 20 years (24, 26, 28, 133). In the UK, pharmacy services in EDs have shifted during these years, from stock drug supply and prescription dispensing towards pharmaceutical care oriented service to optimize drug use for the individual patient (24). Australian ED pharmacist has also focused their service towards performing patient centric activities in traditional areas of practice, such as drug history taking, MR, medication review, discharge medication counselling, and clinical consultations (134). In the USA, residency programs specific to emergency medicine pharmacy are established (25, 135), thus, pharmacists are trained specifically to work in the ED. In addition to the traditional pharmacist activities the emergency medicine pharmacist service also includes rapid bedside response for acutely unwell patients and participation in cardiopulmonary resuscitation responses (25). Hence, there is variety in the ED pharmacy service models both between countries and even within countries (24, 26, 133, 134). Drug history taking/ MR is nevertheless reported to be an important task for ED pharmacists in many countries (24-28, 134).

In Norway, integration of clinical pharmacists in direct patient care, and especially in EDs has progressed more slowly compared with other countries, and the majority of hospital

departments do not yet have access to clinical pharmacy services (136, 137). The IMM-model was chosen as the working model for all clinical pharmacists conducting patient-centric tasks in Norwegian hospitals (138). The clinical pharmacists working in Norwegian ED mainly conduct MR according to the procedure described in IMM, however, the methodology has not been systematically adapted to the ED setting. Further, no nationwide, standardized workflow for ED pharmacists has been established in Norway (139).

Prior studies have reported that implementing pharmacists in ED care has led to a reduction of medication errors (140-143) and reduced delay of care (144). With regards to drug history taking, prior studies have reported that pharmacists obtain more accurate drug histories, than other professional groups, e.g., physicians, in the ED setting (77, 145-148). A study by Mogensen et al. (149) conducted in a Danish ED concluded that 25% of all included patients could benefit from a medication review by a pharmacist during the ED stay. Mogensen et al. revealed that 47% of the recommendations from ED pharmacists considered serious DRPs, which could lead to increased duration of treatment or permanent patient harm if not revealed and solved. The study also revealed that these serious DRPs had not been recognized by the ED physicians, and that they were especially prevalent among the elderly patients (149).

Research related to the impact of ED pharmacists' activities on clinical outcomes is scarce. One prior retrospective cohort study reported that implementing a clinical pharmacy specialist, which conducted MR and medication review, in an ED for Seniors, did not improve clinical outcomes (150). This study was later disputed by Awad et al. (151), which argued that the study had investigated a to narrow ED pharmacist role, and that clinical pharmacists are essential to the care of patients in the ED.

1.3.5 Norwegian patient safety initiatives

MR was one of several focus areas in the Norwegian Patient Safety *Campaign* initiated in 2011 (152). Through the campaign-period healthcare personnel were encouraged to perform MR at all transitions of care. In the final report from the Norwegian Patient Safety Campaign, the authors concluded that the MR focus areas needed additional monitoring to be fully integrated and that common electronic patient records for primary and secondary healthcare could contribute to solve many of the problems related to MR (152). Hence, MR was also one of the focus areas of the Norwegian Patient Safety *Program* continuing the Patient Safety initiative from 2014-2018. A final evaluation report of the Norwegian Patient Safety Program

revealed that the MR focus area was one of the areas with lowest implementation of actions throughout the program-period (153). From 2019, the patient safety work in Norway has been founded in the National Action Plan for Patient Safety and Quality Improvement (154), and MR and medication reviews are underlined as important actions to improve patient safety with regards to drug treatment.

The use of electronical support tools and shared electronical databases to improve healthcare service and patient safety has increased drastically the last decades. Electronical prescription databases or shared drug records have been reported to be essential with regards to improve the drug information flow in transitions of care (153, 155). In Norway, electronical prescription was introduced in 2013, and the Prescription Intermediary ("Reseptformidleren") were the first nationwide, shared electronic system between primary and secondary healthcare in Norway (156). This database facilitated an overview of patients' prescribed drugs, available for all prescribing physicians and dispensing pharmacies. The Prescription Intermediary is primarily a database for prescribing and dispensing drugs to the patient. Until January 2019 healthcare personnel had to obtain oral consent from the patient to use the Prescription Intermediary as a source to the patients' drug list in emergency settings e.g., at hospital admission. The legislation was changed January 2019, requiring patients to actively block access if they did not consent to healthcare personnel accessing their prescription information. The Summary care record ("Kjernejournal") were available for all Norwegian citizens at the end of 2017, which includes a short summary of information needed in emergency care, e.g., information about critical adverse drug reactions and overview of prescribed drugs (157). Access to the Summary care record through the hospitals' patient record systems was, however, not nationally implemented until 2021. Both the Prescription Intermediary and the Summary care record represents easily accessible sources to information regarding patients' prescribed drugs. The drug information available in the Summary care record is automatically updated based on prescription information in the Prescription Intermediary.

2 Knowledge gaps

2.1 Working model and prioritizing model for medication reconciliation in emergency department

To increase patient safety in the ED regarding MDs and incorrect drug lists, it is important to standardize the drug history taking procedure, for instance by implementing specially assigned personnel using the methodology of MR. Due to the fast-paced workflow in the ED, it is important to tailor a time-efficient working model for MR adapted to the ED setting. Pharmacist-led MR and drug history taking has been implemented in EDs in some countries (24, 27, 28, 158). There is, however, no consensus regarding the most efficient procedure to conduct MR (110), and procedures for personnel specifically assigned to conduct MR in Norwegian EDs are not developed.

Due to the constant patient flow entering the ED and the limited resources assigned specifically to conduct MR/ drug history taking (158), prioritization is necessary. Identifying patients with high risk of clinically relevant MDs occurring at admission is key to an adequate prioritization for ED MR. Some prior studies have used literature-based criteria as risk factors for MDs (77, 159). Many different patient characteristics are proposed, but only a few are justified through calculated correlation with clinically relevant MDs (76, 160). A prioritizing model adapted to the clinical ED setting, for the purpose of identifying patients at high risk of clinically relevant MDs early during the admission process is not presented in prior studies.

2.2 Pharmacist-led interventions in emergency department

The previous RCTs investigating pharmacist-led interventions have included in-hospital patients (111, 113-115, 161, 162). The interventions in these prior studies has either concentrated on hospital discharge (113, 162), or demanded massive pharmacist resources due to follow-up such as following the patient during the entire hospital stay and/or contacting the patients, by phone after discharge (111, 114, 115, 161). As hospital resources in the real-world setting is limited, studies investigating more pragmatic and more implementable and sustainable interventions are necessary. In addition, LOS in hospital has decreased worldwide the last decades (6). Therefore, investigating interventions conducted during the ED stay, i.e., early during the hospital admission is important. The impact of pharmacists-led medication review interventions conducted during the ED stay on clinical outcomes are scarcely investigated.

2.3 Drug-related emergency department visits

In majority of the prior studies investigating drug-related ED visits, the ED visits were prospectively classified as drug-related or not (14, 78-80, 88, 89). The reported prevalence in these studies varies between 8.3-30.6%, the diversity can be explained by differences in the applied definitions, and age-diversity in study-populations. One prior study classified drug-related ED visits retrospectively, according to coding in patient records and reported a prevalence of 4.5% (87). Only one prior study by Nickel et al. have used a combination of prospective and retrospective methods to identify drug-related ED visits (85). Nickel et al. only included ED patients admitted due to non-specific complaints, such as *generalized weakness* or *general deterioration*, and reported prevalence of drug-related ED visits to be 12.2% (85). No prior studies have investigating drug-related ED visits in a general ED population, using a combination of prospective and retrospective methods. Also, prevalence of drug-related visits to Norwegian EDs has not previously been investigated. As the Norwegian healthcare system has a different structure than healthcare systems in other countries, international studies are not necessarily generalizable.

2.4 Emergency department physicians' working patterns and distribution of time

Essential drug-related tasks, among other obtaining and documenting patients drug lists are assigned to physicians at ED admission in several countries (67, 107, 145, 146). Thus, it is important to investigate physicians' working patterns, to highlight where workflow redesign is needed to improve patient safety regarding for instance MDs (163, 164). Work tasks of physicians in hospital departments have been investigated in several prior studies (20, 165-168). However, work tasks performed by ED physicians are more scarcely investigated (19, 169-171). These previous studies of ED physicians have focused on LOS, communication patterns, interruptions, multitasking, and time dedicated to direct patient care. There is a lack of studies focusing on what drug-related tasks ED physicians conduct and their distribution of time between drug-related and non-drug-related tasks.

3 Aims

The overall aim of this dissertation was to study factors affecting drug-related patient safety in the emergency department (ED), by investigating drug information flow, drug-related problems, and drug-related admissions. Furthermore, in a randomized controlled trial, investigate if a pharmacist-led intervention comprising ED medication review could improve patients' clinical and post-discharge outcomes.

The specific aims of the studies were:

Study I, presented in paper I:

- To investigate the prevalence of clinically relevant medication discrepancies at admission to the ED
- Develop a clinical prioritizing model, which can identify patients at high risk of clinically relevant medication discrepancies during the ED stay
- To investigate how medication reconciliation methodology can be tailored to be efficient in the fast-paced workflow of the ED

Study II, presented in paper II:

- To investigate the impact of pharmacist-led ED medication reviews on patients' clinical and post-discharge outcomes compared with standard care

Study III, presented in paper III:

- To investigate the prevalence of drug-related ED visits, with a combination of prospective and retrospective methods
- To identify patient characteristics and drug-groups associated with drug-related ED visits

Study IV, presented in paper IV:

- To quantify how ED physicians distributed their time between various work task categories, with particular focus on the time spent on drug-related tasks

4 Methods

4.1 Overview of study design and participants

All studies presented in this dissertation investigate participants included in the ED at Diakonhjemmet Hospital, Oslo, Norway. Studies I, II and III included patients admitted to the ED. In addition, study I included a selection of ED physicians. Study IV included solely ED physicians. Table 1 presents an overview of data collection periods, included participants, utilized study design and inclusion/ exclusion criteria.

Table 1. Overview of data collection periods, included participants, study designs and inclusion/exclusion criteria.

Study	Data collection period	Included participants	Study design	Number of participants included in analysis	Inclusion criteria	Exclusion criteria
I	January 13-April 11, 2014	Patients	Observational cross-section study	Prioritizing model development: 156 Prioritizing model testing: 120	All patients ≥18 admitted to the emergency department	
		Physicians	Questionnaire	19	Working shifts in the emergency department during data collection period	Previously answered the survey
II	April 24, 2017-May 16 2018	Patients	Randomized controlled trial	Inclusion stay analysis: 799 ITT follow-up analysis: 789 PP follow-up analysis: 662	Patients ≥18 admitted to the emergency department Capable and willing to provide written consent	Previously included Control group: 1) Physicians at the ED requested an assessment from a clinical pharmacist 2) Project pharmacist revealed obvious drug related problem of major clinical relevance during inclusion and had to intervene
III	November 20, 2017-February 11, 2019	Patients	Retrospective cohort study	402	Allocated to intervention group in RCT and reviewed by interdisciplinary team retrospectively	
IV	October 16, 2018- January 8, 2019	Physicians	Continuous observation time-motion study	31	Working shifts in the emergency department at pre-set data collection hours	Physicians already observed for 2 observation sessions

ITT: Intention-to-treat, PP: per-protocol

4.2 Study setting

According to description of EDs given by Steptoe et al.(1), the ED at Diakonhjemmet Hospital, is a hospital-based, contiguous ED with triage to service, full-time, adult ED (1, 172), hence an ED located in an acute hospital where medical and surgical emergencies are treated in one area. Further, patients are assessed by physicians who treat emergencies related to their specialty (not emergency medicine specialists), and the ED provides emergency care to adults, 24 h per day, 7 days per week, 365 days per year (172).

During the data collection of study I (2014), the ED comprised 11 beds and a waiting room. The average LOS in the ED was 2.8 hours, and approximately 13000 patients were referred annually. During the data collection of study II and III (2017-2018), the ED had expanded to comprised 13 beds and a waiting room. The average LOS in the ED was 3.2 hours, and the patient flow had increased to approximately 13500 patients referred annually.

During all presented studies patients with both surgical (gastrointestinal surgical or orthopedic) and medical referral reasons arrived at the ED. Similar to EDs in other Norwegian hospitals (8, 9) patients with medical referral reasons represents 73% of the referred patients, and patients with surgical referral reason represents 27% of the referred patients. According to summary statistics from Diakonhjemmet Hospital (2017-2018) were 76% of patients who arrived at the ED admitted to a hospital department after the ED stay, 24% were directly discharged from the ED.

The staff permanently affiliated to the ED during all studies consists of a senior consultant (specialist in Internal Medicine), a secretary and nurses. Many of the nurses were specialized in emergency nursing. The physician staff, beside the senior consultant, consisted of interns and residents from different specialities, rostered to cover shifts in the ED. The interns and residents were affiliated with the Department of Internal Medicine (medical physicians), or the Department of Surgery (surgical physicians). During the data collection period of study IV, 4-7 physicians were present in the ED at all times, 3-4 medical physicians, 1-2 surgical physicians, and the senior consultant (in day shifts). However, due to the aim of the study it was decided to exclude the senior consultant who normally did not take drug histories.

In 2014, when study I was performed the ED were covered by a 0.25 full-time equivalent pharmacist position (approximately 9.5 hours per week) delivered by Diakonhjemmet Hospital Pharmacy. During the data collection periods approximately 50-70 hours per week

(on weekdays) were covered by study pharmacists and a study nurse conducting MR. I 2017-2018, when study II and III was performed the ED were covered by a 0.5 full-time equivalent pharmacist position (approximately 19 hours per week). During the data collection periods these resources were used to deliver study pharmacists. In addition, extra pharmacists resources that were needed to include the the predetermined target number of patients was delivered.

4.3 Description of study teams

In study I, six clinical pharmacists and one emergency nurse were responsible for conducting MR and data collection. All clinical pharmacists had standardized training in MR and had practiced as clinical pharmacists for several years prior to the study. The emergency nurse was educated and trained in the MR methodology before the data collection started. The expert panel classifying MDs according to clinical relevance in this study consisted of two clinical pharmacists which participated in the data collection, and one independent senior consultant.

In studies II and III, three clinical pharmacists, conducted the intervention and participated in data collection. The three study pharmacists had all practiced as clinical pharmacists for at least five years prior to the study. The expert panel assessing clinically relevance of the identified DRPs (study II) and drug-related ED visits (study III) consisted of two senior consultant not involved in the data collection and three experienced clinical pharmacists. One of the clinical pharmacists participated in the data collection, the two others were not involved in the data collection.

In study IV, an experience clinical pharmacist and one master student in pharmacy conducted the observations. A statistician familiar with time-motion data calculated inter-rater reliability (IRR) and assisted in statistical analysis of outcome data. The discreet categories (Table 4) for work tasks used in data collection was evaluated by an experienced clinical pharmacist and a senior consultant.

4.4 Characteristics of participants

Table 2 presents an overview of characteristics registered for included participants in the four studies. The questionnaire in study I was responded to anonymous, thus no characteristics was registered regarding the responding physicians.

Table 2. Overview of participant characteristics variables in the included studies.

Characteristics variable	*Information regarding*	*Source of information*	*Paper I*	*Paper II*	*Paper III*	*Paper IV*
Date of birth (age was calculated)	Patients	Patient record	x	x	x	
Sex	Patients	Patient record	x	x	x	
*Department affiliation**	Patients	Patient record	x	x	x	
Living situation before ED admission	Patients	Patient record	x	x	x	
Who referred the patient to the ED	Patients	Patient record	x	x	x	
Number of admissions to DH last 12 months before inclusion	Patients	Patient record	x	x	x	
Assigned triage category at admission	Patients	Patient record	x	x	x	
Number of drugs registered by physicians at admission	Patients	Patient record	x	x		
Number of drugs registered through medication reconciliation	Patients	Patient record	x	x	x	
All drugs listed in documented reconciled drug list	Patients	Patient record	x		x	
If the patient brought a drug list to the ED	Patients	Medication reconciliation	x	x		
Who were responsible for drug administration before admission	Patients	Medication reconciliation	x	x	x	
Results from relevant laboratory tests	Patients	Patient record		x	x	
Patient was admitted to hospital or discharge directly from ED	Patients	Patient record		x	x	
Documented discharge diagnoses	Patients	Patient record		x	x	
Date and time for admission to the inclusion ED stay	Patients	Patient record	x	x		
Date and time for discharge from the inclusion ED stay	Patients	Patient record		x		
Date and time for discharge from hospital after the inclusion ED stay	Patients	Patient record		x		
Date if patients died during hospital stay	Patients	Patient record		x		
*Experience level***	Physicians	Observed physicians				x
*Department affiliation**	Physicians	Hospital system				x
Number of patients treated by the observed physicians per observation session	Physicians	Observers' registration				x

DH: Diakonhjemmet Hospital, ED: Emergency department
* Affiliation to either Department of Internal Medicine or Department of Surgery
** Categorized as inexperienced: interns and junior residents or experienced: senior residents

Types of diagnoses

Information regarding patients' *medical histories* (e.g., chronical conditions, recent or prior diseases) is often deficient at hospital admission. The medical histories registered in hospitals' patient records are often based on an arbitrary selection of diagnoses registered during earlier hospital stays (both at the same hospital and discharge notes from other hospitals), information from GPs and information from the patient. No source with complete overview of patients' medical histories is available in Norway. In study I, medical history (retrieved from the hospital's patient record) was included as a variable. However, the variable was categorized before used in analyses (≥ 3 registered diagnoses- yes/ no, ≥ 5 registered diagnoses -yes/ no). In studies II and III, information regarding patients' medical histories was

used to identify DRPs (such as untreated conditions (need of additional drug), or unnecessary/ inappropriate drugs), however, not registered for analysis purpose.

Tentative referral reason(s) set by the healthcare personnel referring the patient to the hospitals' ED and *discharge diagnose(s),* set by physicians in hospital and documented by the physician writing the discharge note, was collected from the hospital's patient record in study II and III. Both tentative referral reasons and discharge diagnoses reflects conditions of which the patient are referred and treated, during a particular ED visit or hospital stay. Hence, these variables do not reflect the patients' total diagnosis-burden.

4.5 Pharmacist-led medication reconciliation and medication review

4.5.1 Medication reconciliation in study I

In study I, MR was conducted according to the procedure described in the IMM model (114). The MR consisted of a standardized patient interview, including use of a checklist with specific questions regarding drugs often omitted, e.g., eyedrops, inhalation drugs, contraceptives, drugs not taken daily. If the patient received assistance with taking drugs before the ED visit, the supporting person/personnel was contacted to be interviewed. In addition, sources providing information on prescribed drugs were used to verify current drug use and the respective dosages and brand names, e.g., drug lists from GPs, drug list of patients with multidose drug dispensing, and prior discharge notes from Diakonhjemmet Hospital or other hospitals. Patients' current drug lists obtained through MR was documented in the hospital's patient record. The study presented in paper I consisted of three data collection periods.

In the first two data collection periods, MR was conducted according to the traditional working model (Figure 4), to be able to identify MDs.

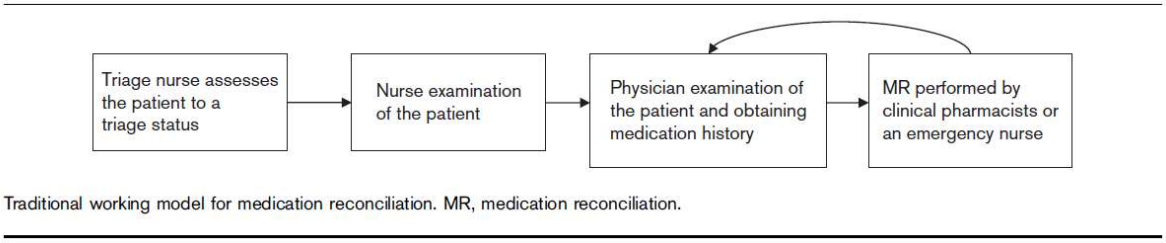


Figure 4. **Original medication reconciliation (MR) working model.** Used in the first two data collection periods of study I. Reproduction of Figure 1 in paper I.

Before the third data collection period the MR working model was redesigned based on experience from the two first data collection periods (Figure 5). In the third data collection period, MR was conducted according to the redesigned working model.

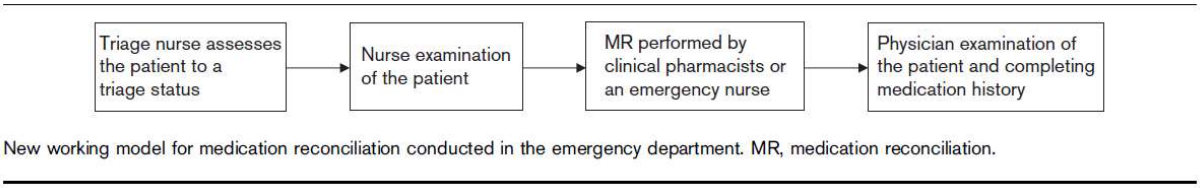


Figure 5. **Redesigned medication reconciliation (MR) working model.** Tested in the third data collection period of study I. Reproduction of Figure 2 in paper I.

Questionnaire regarding drug history taking and the redesigned medication reconciliation working model

A semi-structured questionnaire with 11 main questions was developed to investigate ED physicians' perspectives regarding sources used during drug history taking, workflow in the ED with regards to drug information, with and without MR. The questionnaire comprised a mixture of multiple choice and rating scale questions, one open ended question was also included. In relation to five of the questions, a comment box was included, allowing the physicians to comment their answers. The questionnaire was presented as a two-sided paper-scheme and was responded to anonymously. The questionnaire was handed out to ED physicians present during the last week of the third data collection period of study I (June 10-20, 2014).

4.5.2 Medication discrepancies in study I

MDs were only identified during the two first data collection periods, through comparing the drug history documented by ED physicians with the drug list obtained through MR. All discrepancies were registered and categorized in nine categories:

- Omission of as needed drug
- Prescribed drug patient had not used
- Prescribed higher dose than patient had used
- Prescribed lower dose than patient had used
- Wrong time for dosage
- Wrong formulation
- Omission of dosage/strength
- Omission of supplement/herbal preparation

Classification of clinically relevant medication discrepancies

An expert panel graded all MDs for a selection of patients (Figure 8) included in the two first data collection periods. The expert panel received a de-identified list of all identified MDs, and first graded all MDs individually. Further, two consensus meetings were arranged. The MDs were graded according to the significance of the discrepancy, the grading scale was an adjusted version of Scullin and colleagues' intervention grading (114):

(1) no impact on health outcomes
(2) minor impact on health outcomes
(3) potentially significant impact on health outcomes
(4) potentially severe impact on health outcomes
(5) potentially life-saving impact on health outcomes.

4.5.3 Medication reconciliation and medication review in study II

Medication reconciliation

MR was performed by the same procedure as in study I. In addition to the available sources providing information on drug prescribing in study I, the Prescription Intermediary was available during study II (the Summary care record was not available). MR was preferably conducted according to the redesigned working model from study I (Figure 5). Due to the critically illness of some patients, and occasional ED crowding, the MR was not completed before ED physicians' consultation for all included intervention group patients. The ED physician in charge of the patient was alerted orally when the MR was conducted, and the patient's reconciled current drug list and other relevant drug history was documented by study pharmacists in the hospital's patient record.

Medication review

Following the MR, a systematic advanced medication review (109) was conducted. All drugs in the patients' reconciled current drug list and recent drug history were assessed according to predefined DRP categories (Table 3), based on a validated DRP classification tool (58). The medication review was conducted by interviewing patients and assessing initial examinations by ED nurse as well as laboratory tests results. Furthermore, computer resources were utilized (e.g., interaction databases, summary of product characteristics for drugs, medical databases

and treatment guidelines) and referral letters from GPs and municipal emergency were reviewed.

The identified DRPs (both actual and potential) and possible actions to manage or solve the problems were orally communicated to the ED physician in charge of the patient, as well as documented by the study pharmacists in the hospital's patient record.

Table 3. Description of drug-related problem categories. All drugs documented in the patients' current drug list and recent drug history were assessed according to these categories during medication review. The utilized drug-related problem categorization is based on a validated DRP classification tool (58). Adjusted reproduction of S3 Appendix in paper II.

Drug-related problems categories	Detailed description
Drug monitoring	Therapeutic drug monitoring or laboratory monitoring was needed, regarding e.g., digoxin, warfarin, levothyroxine, antidiabetics, statins
Adherence issues (non-adherence)	Intentionally, or unintentionally deviation between patient's actual drug use and usage intended by the prescribing physician. With respect to type of drug, dose, or scheme
Adverse effects	A negative or harmful patient outcome, or changed laboratory values that seems to be associated with drug treatment (55)
Drug-interactions	Clinically relevant drug-interactions (both drug-drug interactions and drug-supplements/herbal preparations interactions were included)
Need for additional drug	Deviation between the patients' listed earlier diagnoses and the received treatment, regards to established national/international guidelines
Non-optimal drug therapy	Adjustments in the patient's drug therapy (included both dose adjustments, formulation alternations and temporarily stopping drug therapy) are needed due to established national/international guidelines or due to: - the acute situation - reduced organ function (kidney failure, reduced liver function etc.) - absolute/relative contraindications
Unnecessary drug	Drug treatment without indication according to guidelines
Drug-related ED visit	Considering all the above-mentioned categories, clinical pharmacists assessed if the current ED visit could be connected to one or more of the drugs used by the patient at admission

4.5.4 Drug-related problems and medication discrepancies in study II

Drug-related problems

An expert panel classified all identified DRPs according to the following: clinically relevant to identify in the ED, clinically relevant to identify during the hospital stay, or not clinically relevant during the ED/ hospital stay. A clinically relevant DRP was defined as a DRP which should be identified to improve the standard of care, prevent major organ failure, prevent adverse effects, or be potentially lifesaving (114). Hence, the DRPs classified as clinically relevant were issues of importance for the patient treatment. All DRPs were first assessed and

classified by each member of the expert team individually. Further, six consensus meetings were arranged.

Acceptance of pharmacists' recommendations regarding identified DRP was investigated through comparing changes in the patients' drug lists during hospital stay, with DRPs identified by study pharmacists. Changes during hospital stay were revealed though retrospectively assessment of differences between the drug list registered by physicians in the admission notes and the drug lists registered by physicians in the discharge notes.

Medication discrepancies

Due to the MR methodology used in study II, MDs for the intervention group patients were identified retrospectively. The drug list documented by ED physicians at admission was compared with the drug list obtained through MR. The preferred physician drug list for comparison was the drug list documented in the medication chart. If the patient was not hospitalized the medication chart was often not written, in which the drug list documented by physicians in the admission note was used. If there were no drug list in the medication chart or admission note, the discharge note was checked.

The drug list of each patient was classified according to the following categories regarding what type of MDs was identified through the retrospective assessment:

- The drug list has major MDs issues (omission of one or more regular drug, incorrect strength/frequency/count of unit's information related to one or more regular drug)
- The drug list has minor MDs issues (omission of as needed drugs, incorrect strength/frequency/count of unit's information related to as needed drugs)
- The drug list has no MDs
- No drug list is registered for the patient during inclusion stay (meaning there were no drug list registered in medication chart, admission note or discharge note)

The intervention MR was deemed not successful if there were no documented drug list by physicians at admissions, or if the physicians drug list had major MD issues. This formed the basis for excluding patients in the *per-protocol* analysis presented in paper II.

4.6 Data on unplanned contacts with hospital and mortality

The Norwegian Patient Registry (NPR) provided data on unplanned contacts with hospital and dates for patients' death after discharge from the inclusion stay, used in analysis of outcome measures in study II. NPR comprises data on all patient treatment conducted by the secondary healthcare system in Norway (173). Visits to the municipal emergency clinics and GPs are not included.

NPR delivered information on a personally identifiable level. Hence, to be able to harvest data from the register, patients need to have a Norwegian personal identification number. In study II, we included 10 patients without a Norwegian personal identification number (foreign citizens). Follow-up data from NPR for these patients are therefore missing.

We used data on unplanned contacts with somatic hospitals (both acute outpatient clinic visits and hospital admissions). As NPR is based on data reported from Norwegian hospitals, how ED visits are reported vary between hospitals. Some hospitals report ED visits as a part of the hospital stay if patients are admitted, and outpatient clinic visits if patients are directly discharge from ED. Other hospitals strictly report ED visits as acute outpatient clinic visits. This led to an uncertainty in the isolated ED-visit data. Hence, it was decided to merge ED-revisits and hospital readmission in "unplanned contact with hospital" in analysis of outcome measures in study II.

4.7 Drug-related emergency department visits

Classification of drug-related emergency department visits

In study III, an expert panel assessed the relationship between the patients' drug use and ED visits for all intervention group patients. A drug-related ED visit was defined as an ED visit directly (probably) or indirectly (possibly) associated with the patient's drug use prior to the visit.

A standardized de-identified patient scheme was created for each patient. The schemes included demographic data and results from completed laboratory tests. Further, the schemes included tentative referral reasons and the final diagnoses. Finally, the patient's reconciled current drug list, other recent drug history, and DRPs identified through intervention medication review were registered on the schemes. The template for the standardized de-identified patient scheme can be found in supplementary material of paper III.

The expert panel classified each ED visit according to a modified version of criteria for causality by the WHO Uppsala Monitoring Centre (174). It was assumed that the "certain" causality term utilized by WHO Uppsala Monitoring Centre would not be fulfilled in the included clinical cases. Nevertheless, it was decided to differentiate between "probable" and "possible" drug-related ED visits, hence these terms were adopted. The "unlikely" term was renamed "not drug-related" to simplify the interpretation, however covered the same assessment criteria. To cover the "Conditional / Unclassified" term, an unresolved category was introduced, which could be used by the expert panel if information essential to conclude were missing. Hence, the classification categories used by the expert panel were:

- *probably drug-related* (direct association between patients' drug use and ED visit)
- *possibly drug-related* (indirect association between patients' drug use and ED visit)
- *not drug-related* (no association between patients' drug use and ED visit)
- *unresolved* (information missing to determine association)

All patient schemes were first assessed and classified by each member of the expert panel, individually, using implicit criteria inspired by Hallas and colleagues' criteria for contribution (175). Further, six consensus meetings were arranged.

Documentation of drug-related emergency department visits

Physicians' documentation of drug-related ED visits and hospital stay were assessed though retrospective investigation of the discharge notes written by physicians treating intervention group patients during ED visit/hospital stay. It was registered that the treating physician considered the ED visit/hospital admission drug-related if the physician explicitly stated (either through a description in text or a drug-related diagnosis code) in the discharge note that drugs could be the cause of the visit/admission.

Pharmacists' documentation of suspected drug-related ED visits and hospital stay were assessed though retrospective investigation of the note written in the patient record by pharmacists after intervention medication review performance. It was registered that the pharmacist suspected the ED visit/hospital admission to be drug-related if the pharmacist had stated this in the patient record note.

4.8 Physicians' working patterns

4.8.1 Discrete Observation categories

In study IV, continuous direct observations of ED physicians were performed. As no previous time-motion study of ED physicians had defined drug-related tasks separately, it was decided to conceptualize discrete categories tailored to investigate the study aim. A pre-study period was conducted where two observers observed different ED physicians for a total of 10 hours. During the pre-study period all conducted activities were recorded in plain text, including tasks conducted (*what)*, the locations physicians were in when conducting the task (*where*), how tasks were conducted (*how*), and other persons involved in the conducted tasks (*who*). The recorded text was further grouped in discrete categories and structured under four dimensions (*what, where, how and who*) in line with earlier studies (176, 177). Categories in all dimensions were tested and evaluated during a pilot study, to ensure that all physician activities were covered by the conceptualized categories. The pilot study included a total of 16 observation hours of different ED physicians. Between observation hours continuous evaluation regarding the appropriateness of the categories was conducted, and changes were made when necessary.

The task categories for the *what* dimension (Table 4) were reviewed by an experience clinical pharmacist and a senior consultant, before data collection started. Figure 6 shows a screenshot from the Work Observation Method By Activity Timing (WOMBAT) software (167, 178) of the final discrete data collection categories used during data collection. Detailed overview and description of categories within *where, how* and *who* dimensions is presented in supplementary material of paper IV.

IRR testing was conducted before data collection to test the observers' agreement on the final data collection categories (all dimensions, and timestamping). The IRR testing was performed through the following procedure: The two observers followed the same physician for 30 minutes and independently recorded data with the final data collection categories on Samsung Galaxy 8 tablets running version 2 of the licensed WOMBAT software (167, 178). The IRR observation data were analyzed after the 30 minutes session using a multivariate chance-adjusted agreement method (the iota score, a multivariate generalization of Cohen's kappa (179, 180)) applied to the data in the format of one second time windows. The iota score before data collection was 0.781, indicating substantial agreement between observers (181),

which was considered satisfying to initiate the data collection. It was decided to conduct additional IRR testing during the data collection period to limit observer bias. Two IRR tests were conducted during data collection, with achieved iota scores of 0.622 and 0.867. Hence substantial agreement was maintained during the entire data collection period. The average iota score for the whole data collection period was 0.760.

Table 4. Work task categories (*What*), subcategories, definitions, and examples. Drug-related: all conversations, reading or writing that included information about the patients' drugs or drug use. Non-drug-related: all other conversations, activities, reading and writing. Where, how and with whom the observed physicians conducted tasks presented in the table, was specified by categories in *where, how* and *who* dimensions in the WOMBAT-tool (Appendix I of paper IV). The table is a reproduction of table 1 in paper IV.

Task category	Subcategories	Definition	Examples
Examination/ Treatment		**Direct, physical examination/treatment of the patient** [a]	Examination of patient Taking samples (e.g., fecal occult blood test, arterial blood gas) Relocating shoulder, suture a wound Monitoring patients' symptoms
Gather information	***Drug-related***	**Gather drug-related information related to patients/ patient treatment**	Physician obtained information about patients' medication history by talking directly or by telephone to patients, next of kin, other hospitals, reading on computer or paper referral letters.
	Non-drug-related	**Gather non-drug-related information related to patients/ patient treatment**	Physician obtained information about patients' medical history by talking directly or by telephone to patients, next of kin, other hospitals, reading on computer or paper referral letters.
Documentation	***Drug-related***	**Documentation of drug-related patient information**	Physician documented drug-related information on paper or on computer Prescribing drugs in medical chart/ Prescription Intermediary
	Non-drug-related	**Documentation of non-drug-related patient information**	Physician documented non-drug-related information on paper or on computer
Professional communication	***Drug-related***	**Professional communication with other healthcare personnel/ patients/ next of kin about drug-related matters relevant to patients' treatment**	Physician communicated direct or via telephone with other healthcare personnel about patient drug-related treatment Physician informed patient, next of kin about further drug-treatment
	Non-drug-related	**Professional communication with other healthcare personnel/ patients/ next of kin about non-drug-related matters relevant to patients' treatment**	Physician communicated direct or via telephone with other healthcare personnel about patient-related matters Physician informed patient, next of kin about further non- drug-related treatment
Social	***Professional***	**Professionally relevant activities or communication not directly linked to patient treatment/ information**	Digital courses Reading procedures (not directly regarding patient treatment) Send professional e-mail
	Non-professional	**Social activities or communication (not professionally relevant)**	Personal phone calls/ texting/ e-mailing Bathroom breaks Meal break
Unknown		**Activities that could not be observed**	Physician treated a patient in an infection isolated room (droplet- or airborne infections)
Hygiene		**Activities to prevent communicable diseases**	Physician washed/ disinfected hands
Movement		**Movement between locations (*Where*)**	Physician walked between locations (*where categories)*
Outside emergency department		**Activities conducted outside the defined area of the emergency department**	Physician were called on to assist patient on hospital department (left the emergency department)

[a] *During observation time physicians did not administer drugs to patients, hence only non-drug-related treatment and examination were recorded.*

Figure 6. Screenshot of the WOMBAT data collection tool with four dimensions. During direct observation of emergency department physicians, data were systematically registered in predefined discrete categories organised under four dimensions: *WHAT, WHERE, HOW, AND WHO*. The data were automatically time-stamped by the WOMBAT software i.e., recording the exact time for the start of the task and recording the time until a new task was started (either due to finishing the task or getting interrupted). The figure is also presented in Appendix 1 in paper IV.

4.8.2 Observation sessions

Summary statistics from Diakonhjemmet Hospital revealed that 80% of patients admitted to the ED arrive between 9:00 am to 9:00 pm. A previous time-motion study found that physicians night-time activities deviate from day-time activities (20). Hence, investigating physicians between 9:00 am to 9:00 pm were believed to give an estimation of how most patients are treated during the ED stay. A pre-set timetable for observation sessions was used to make sure the data collection covered weekdays/weekends and day/evening shifts (9:00 am to 9:00 pm).

Previous time-motion studies have indicated that observation sessions should be time limited to minimize observer fatigue (176, 178). Based on prior time-motion studies (20, 176) and experiences from the pilot-period, it was decided that each observation session in study IV should last for two hours.

Consecutively after inclusion, the included physician was continuously observed for one session, where observers recorded all activities which were automatically time-stamped by the WOMBAT software. Interruptions, defined as stopping the current task to respond to an external stimulus (e.g., a telephone call), and multitasking, defined as performing two (or more) tasks simultaneously, was also recorded in the WOMBAT software. The observation sessions were independent of the LOS for patients treated by the observed physicians. The observation sessions were ended two hours after the observation start, regardless of what task the observed physician conducted at that time. Each physician was observed for a maximum of two sessions.

Patients were not observed in this study, however the number of patients treated by the observed physicians was registered by the observers during each session. Patients were classified as “new” or “follow-up”. Patients were classified as new when no one had taken their medical history, prior to when the observed physician met the patient. Hence, the observed physician performed a thorough examination of the patient and had a conversation with patients/next of kin to obtain the medical and drug history. Further, the patients were classified as follow-up if a medical history, including a drug history, had already been obtained when the observed physician met the patient. Hence, the physicians only conducted one or few examinations of the patients and/or only a few questions were asked.

5 Data processing and statistical considerations

5.1 Data processing

Research databases for data processing of data in study I and III were developed in Microsoft Office Excel. All data were manually punched into these databases. Database for study I was imported to SPSS Statistics 20 (IBM Corporation, Armonk, New York, USA) for statical analyses, whereas database for study III was imported to STATA SE version 16 for statistical analyses.

To process data from study II a research database was developed, using EpiData (EpiData manager and EpiData entry client 4.4.3.1 r691, EpiData Association, Denmark). All data was manually punched into the database. Another researcher assured the quality of the data punching by the following pre-defined protocol:

- *Critical variables* were controlled in every 4th patient. If errors were revealed in more than 5% of the variables in the selected patients, all patients should be controlled.
- *All variables* were controlled for 10 randomly selected patients per 200 punched patients (hence, totally 40 patients). If errors were revealed in more than 10% of the variables in the 10 selected patients, all 200 punched patients should be controlled.

When the database quality was considered satisfactory, data were imported to STATA SE version 16 for statistical analyses of demographic data and inclusion stay outcomes. NPR data were received formatted as a Microsoft Office Excel file. These data were imported to STATA SE version 16, and the file was filtered for relevant unplanned contacts for each included patient (all unplanned contacts after inclusion stay discharge, and within end of follow-up; 12 months from inclusion stay discharge). Relevant data from the NPR datafile were merged with the data punched in EpiData in STATA SE version 16 for statistical analyses of follow-up outcomes.

Data from study IV were generated automatically from the WOMBAT-software version 2 into a Microsoft Office Excel file. Data was imported to IBM SPSS software, version 25 for statistical analysis of number of tasks and demographic data. Data was further transformed to "longform"-format with SAS system for Windows, version 9.4 to be able to analyze time-data

considering any overlap in time due to multitasking. Analyses were carried out in SAS system for Windows with assistance from Scott R. Walter.

Organizing diagnosis and drug data

Majority of discharge diagnoses were coded according to International statistical classification of diseases and related health problems, 10th revision (ICD-10) (182) in discharge notes written by physicians. If ICD-10 codes were missing, symptoms/diagnoses described in text in the discharge note was converted to ICD-10 codes using an decision support tool for ICD-10 codes (183). Discharge diagnoses were analyzed on chapter level in study II, due to high diversity in single diagnosis data.

Tentative referral reasons are presented as text at referral to the ED, hence not coded according to ICD-10 (182). In study III, similar symptoms/tentative diagnoses were grouped together before analyses to reduce diversity in data. In study II, all tentative referral reasons were converted to ICD-10 codes using an decision support tool for ICD-10 codes (183). Tentative referral reasons were analyzed on chapter level in study II, due to high diversity in single diagnosis data.

Patients drug lists was used in analyses in study III. All drugs listed in patients' reconciled drug lists were classified according to the Anatomical Therapeutic Chemical (ATC)-classification (184, 185). In study III, drugs were analyzed at ATC-classification 3rd level, to reduce diversity in data.

5.2 Randomization and blinding

To determine the prevalence of clinically relevant MDs in study I, every second (sequence decided after data collection) of the 312 included patients in the second data collection period were assessed by the expert panel regarding clinically relevant MDs.

In study II, patients were randomized to intervention- or control-group (1:1) after inclusion. Department of Biostatistics and Epidemiology at Oslo University Hospital was responsible for the randomization procedure. This department had no contact with patients, study pharmacists or ED personnel. A random number generator program was used for randomization sequencing with a permuted block design. The study pharmacists were blinded to block size, which was randomly varied. Allocation information was packed by staff at Diakonhjemmet

Hospital Pharmacy not involved in the study, in sequentially numbered, opaque, sealed envelopes and delivered to study pharmacists. Envelopes were assigned and opened in numbered sequence. Hence, at randomization the study pharmacists assigned the envelope with the lowest number to the individual included patient, thereafter the envelope was opened, and allocation was revealed. It was neither feasible to blind patients nor study pharmacists to the allocation. ED and other hospital staff could not be blinded regarding which of the patients belonged to the intervention group, because study pharmacists documented their findings in the hospital's patient record. Affiliates at the ED and hospital were, however, unable to distinguish between patients randomized to the control group and patients not participating in the study. NPR providing outcome data, were blinded to group allocation.

The population in study III, was the patients randomized to the intervention group in study II. The expert panel was blinded regarding whether the patient was hospitalized or discharged directly after the ED visit. In addition, the expert panel was blinded regarding the documentation of drug-related ED visit and hospital stay conducted by physicians and study pharmacists.

In study IV, information regarding the study aims and method was given in brief information lectures to both medical and surgical physicians, as well as ED nurses before study start. It was decided to give these lectures to prevent interruption of observers during observation sessions. All physicians present in the ED at the pre-set observation session time were eligible for inclusion. The observers randomized (by draw) which of the available physicians to observe. First a draw of affiliation (3:1, medical or surgical, due to the skewed distribution of physicians present in the ED), further a draw of experience level (1:1, experienced or inexperienced).

5.3 Sample size

No sample size calculation was conducted in study I. Patients included in developing and testing the prioritizing model, were consecutively included in two periods of 15 inclusion days (9:00 am to 8:00 pm).

The sample size calculation for study II (RCT) was based on an expected readmission frequency of 50% during 12 months following inclusion (114), which is also in line with Norwegian readmission frequency (information from South-Eastern Norway Regional Health

Authority). The sample size was calculated based on a superiority study design, and a 10% reduction in unplanned contacts with hospital was defined as a clinically relevant effect of the intervention. This estimate was considered realistic according to a prior study (111) and accounting for our general population. Accordingly, it was calculated that 385 patients would have to be included in each group, with significance level of 5% and study power of 80%. To compensate for dropouts, it was decided to include 400 patients in each project group, i.e., a total of 800 patients.

No separate sample size calculation was conducted for study III. Sample size was determined by the included number of intervention group patients in the RCT (study II).

In study IV, the number of observation hours (sample size of concern in time-motion studies) was selected based on previous time-motion studies (19, 20, 165, 176). According to the aim of this study, 90 hours of observations were considered sufficient to accurately describe physicians work pattern.

5.4 Statistical considerations

In results from study I, II and III patient demographics are given as median and interquartile ranges (IQRs) for continuous variables, due to the skewed distribution of these variables. Regarding categorical variables, number of patients in each group and percentage are reported (group specific percentage when comparing groups). In these three papers Mann-Whitney/ Wilcoxen rank sum-test was used to compare demographics of patient groups regarding continuous variables. For categorical variables, Pearson-Chi^2 were applied. P values less than 0.05 were considered statistically significant in all studies presented in this dissertation.

Study I

During identification of characteristics associated with clinically relevant MDs, development, and testing of the prioritizing model, MDs graded 1 or 2 were classified as not clinically relevant, and MDs graded 3, 4 or 5 were classified as clinically relevant. Continuous variables (e.g., age, number of medications) were categorized to be suitable for further statistical analyses and development of the prioritizing model.

Patient characteristics variables which were accessible at admission to the ED and associated with clinically relevant MDs, were included in a logistic regression model. The performance of the model built on data from the second study period was tested on data from the first study

period. A receiver operating characteristic curve analysis and estimate of the area under the curve was applied. As the model was built on clinically relevant MDs, false negatives were seen as more severe than false-positive classifications; therefore, we chose a cut-off that yielded a high sensitivity from the receiver operating characteristic curve analysis.

Study II

Pearson's chi-square test was applied to determine proportion of patients with unplanned contact with hospital during follow-up time (primary outcome), significance level was set to 0.05. Logistic regression was applied to determine odds ratio with 95% confidence interval (CI). The Kaplan-Meier estimator was used to estimate the survival function regarding time to next unplanned contact with hospital (event). Kaplan-Meier curves and log-rank test were applied to present a visual representation and test difference between groups, respectively. Cox proportional hazards model was utilized to determine hazard ratios and 95% CI. Negative binomial regression was utilized to compare mean length of stay and number of unplanned hospital events within 12 months after inclusion stay discharge, in the latter individual patient-time in study was applied as exposure variable. Mann-Whitney U test was applied to compare median length of stay. For the secondary outcomes comparative analyses were explorative.

In sensitivity analyses on the primary and secondary outcomes, death was included as competing risk in the outcome measures (both death during hospital stay and within 12 months from inclusion stay discharge) (S4 Appendix for paper II). The sensitivity analyses revealed that results did not change. To clarify interpretation of the outcome measures it was therefore decided to excluded patients who died during hospital stay from both *inclusion stay analyses* and *follow-up analyses.* Further, in the primary outcome and survival analysis death within 12 months from inclusion stay discharge was censored. However, in the negative binomial regression, time of death within 12 months from inclusion stay discharge was accounted for through the exposure variable.

Intention-to-treat analyses was conducted on all patients with follow-up data allocated to intervention or control group.

In *per-protocol analyses,* patients where the intervention MR was deemed not successful was excluded, i.e.:

1) patients where no drugs were documented by physicians in the hospital's patient record

2) patients where the drug list documented by physicians at admission had major MD issues

All control group patients with follow-up data were included in per-protocol analysis.

Study III

In comparative analysis, probably and possibly drug-related ED visits were treated as one group: drug-related ED visits. Patients not classified (Unresolved/No consensus reached) were not included in the comparative statistics. Logistic regression was used to determine odds ratios of drug-related ED visits, 95% CI. The relative frequency of ATC3-groups was calculated as follows: how often a drug from the specified ATC-3 group was involved in drug-related ED visits divided by number of times drugs from that specific ATC-3 group was used.

Study IV

Proportions of total observation time were defined as the time spent on each task category, accounting for any multitasking, divided by the total observation time. Proportions specific for physician groups and specific drug-related and non-drug-related time were calculated similarly, although the denominators were group specific (considering any overlap in time due to multitasking). As the field of analyzing proportions of continuous time measures are scarcely investigated, a bootstrapping approach was used to generate 95% CI for the proportions and interruption rates. Monte Carlo testing was applied for comparing drug-related task time between different physician groups: medical vs. surgical physicians, experienced vs. inexperienced physicians. Both bootstrapping and Monte Carlo testing were chosen to avoid the reliance on parametric assumptions which were not met by this data.

By using iota score compared with traditional Cohens'/ Fleiss kappa in time-motion studies enables the comparison of all dimensions, including the timestamping, simultaneously (179). However, because the iota analysis includes more variables simultaneously it results in lower scores compared to the scores computed with traditional Cohens'/Fleiss kappa. The average Fleiss kappa score on the *what* dimension during the three IRR-validations were 0.81, indicating almost perfect agreement (181). Nevertheless, it was considered important that all dimensions and timestamping were compared and therefore iota scores were the chosen strategy.

6 Ethical considerations

All studies presented in this dissertation were approved by the Regional Committee for Medical and Health Research Ethics (REK) (Study I: 09.10.13, 2013/1586/ REK south-eastern C, also approved by the Privacy Ombudsman at Oslo University Hospital 17.12.13, 2013/14419. Study II and III: 10.09.15, 2015/1356/ REK south-eastern A, Study IV: 08.08.18, amendment to 2015/1356/ REK south-eastern A). Protocols for all studies were also approved by the Research Committee at Diakonhjemmet Hospital. Ethical principles described in the Declaration of Helsinki was applied in all four studies. studies presented in paper II and III was registered in ClinicalTrials.gov, Identifier: NCT03123640 in April 2017.

Patients admitted to the ED is in a vulnerable position and is often critically ill. The basic pillar of all the studies described in this dissertation was therefore, not to delay lifesaving and necessary acute treatment. However, it is important to identify how standard care can be improved regarding safety of drug treatment and transfer of drug information, also in the acute setting in the ED. Investigating patients in a real-world setting creates the most realistic picture of what stages in standard care that are possible and beneficial to redesign. In the studies involving patients (I, II and III) it was considered that the potential benefit with regards to preventing unintended MDs and identifying DRPs outweighed the potential burden for included patients.

All participant data (both patient data (studies I, II and III), and characteristics data regarding included physicians in study IV) were handled confidentially. Paper data collection schemes were stored in a locked cabinet only accessible to authorized study personnel, and not taken out of the hospital. Study databases was developed without participant names or personal identification numbers, only a code list connected the participant to his or her data, the code list was stored in a locked cabinet separate from other data. The study databases were stored at the hospitals password-secured research server.

In study I, REK concluded that written informed consent was not necessary to include patients. It was assumed that conducting MR had few or no negative effects for the included patients, therefore it was decided to include patients to this study without written informed consent and regardless of their ability to provide such consents.

In studies II and III, REK concluded that written informed content had to be obtained from the patients themselves. In the original protocol for it was proposed that next of kin to severely ill

patients could provide a temporarily written consent until the patients were in a condition where they could consent themselves, this proposal was not approved by REK. Hence, in these studies patients was included if they were capable and willing to provide written informed consent. Unconscious and severely cognitive impaired patients were not included e.g., severe intoxications and patients with advanced dementia. It was considered that the additional questions related to the performance of the intervention could cause a burden to intervention group patients. Therefore, patients were informed briefly about the study and the intervention content before they were asked to participate. An information leaflet was presented to all patients willing to consider inclusion, before they were finally included. The information leaflet comprised a description of the study (including what information about the patient that was registered and stored) and stated that participating in the study was voluntary and that the patient could withdraw from the study at any point without giving a reason. Key points of this information were also given orally.

It was decided that patients allocated to the control group should receive standard care without pharmacist intervention during the ED visit, this decision was based on the following considerations. Even though, MR had been proven efficient in identifying unintended MDs in prior studies, the effect on clinical outcomes were inconclusive. Further, the intervention utilized in the RCT (study II) had not been investigated in prior RCTs in the ED setting. Hence, it was a true uncertainty regarding the effect of the intervention on clinical outcomes before study start. In addition, most patients admitted to Norwegian EDs does not receive a pharmacist-led medication review during their ED visits, as this is not part of standard care. Without MR, the information basis regarding drug lists in the control group patients would be uncertain. However, if MR and/ or medication review was conducted in the control group, this may have forced study pharmacists to intervene regarding identified MDs and DRP due to ethical considerations. This would have made it challenging to investigate the impact of the intervention due to spill-over effects. Clinical pharmacists had been present in the ED at Diakonhjemmet Hospital conducting MR before initiation of studies II and III. It was therefore, of ethical concerns, decided to implement a statement in the inclusion procedure that control group patients should be excluded after randomization if;

1) Physicians in the ED requested an assessment from a pharmacist regarding the control group patient
2) Study pharmacist revealed obvious DRPs of major clinical relevance during inclusion of the control group patient and had to intervene.

In study IV, REK concluded written informed consent was not necessary to include physicians. However, observing physicians in a fast-paced workflow raised some ethical issues regarding the relationship between the observed physician and the treated ED patient, and further the relationship between the observed physician and the observer. We considered it important to have an honest and open interaction with the physicians regarding the study aim. Hence, it was decided to only include physicians willing to provide written informed consent. An information leaflet was presented to physicians before inclusion. The information leaflet described the study (including what information about the physician that was registered and stored), and that the physician could withdraw from the study at any point without giving a reason. To reduce observations' impact on the relationship between included physicians and treated patients, the physicians were instructed to inform the patients that the observers were only observing the physicians' working patterns. In addition, it was made clear to the patients that they at any point could demand the observers to leave the room without giving a reason.

7 Results

In this section main results and conclusions of the four studies included in this dissertation is presented. Further detailed results are presented in each paper. Patient flow charts for studies I, II and III is also presented.

7.1 Study I

A total of 276 patients were included in analyses (156 patients to build the prioritization model, and 120 patients to test the prioritization model). The median age of these patients was 69 (IQR =28, range 17-96), and 52% were women. Further, a redesign of MR methodology adjusted to the fast-paced workflow in the ED was presented (Figure 5).

Main findings:

- The number of documented regular medications per patient varied significantly ($p< 0.01$) between the drug list documented by physicians (median 4, IQR 6) and drug list documented through MR (median 6, IQR 6)
- 62% of the patients had one or more clinically relevant MD
- Risk factors associated with clinically relevant MDs which were included in the prioritizing model: sex (woman), age (≥60), one or more admission to hospital in the last 12 months, and tentative referral reasons: surgical, malfunction, or cancer
- Sensitivity of the prioritizing model was 0.761 and specificity was 0.642 (erroneously reported to 0.358 in paper I). Indicating that the prioritizing model both had high precision in identifying high-risk patients and ruling out low-risk patients.
- Of 35 available physicians, 27 received the questionnaire. Of these 19 (70%) physicians completed the questionnaire.
    - Self-reported time spent on drug history taking was: 0-5 minutes for 8 physicians (42%), 6-10 minutes for 10 (53%) physicians and 11-20 minutes for 1 (5%) physician.
    - If MR was performed before the physician had taken their drug history, 58% of the ED physicians reported that they spent less time on drug history taking, the remaining 42% reported no effect on their time spent (self-reported time use 0-5 minutes).

Conclusion

Clinically relevant MDs are a major concern with regards to drug-related patient safety in the ED. By using MR methodology in the ED setting, these MDs can be identified and corrected. This study found that it is beneficial to adjust the MR methodology to the ED setting, and a working model redesign was presented and tested. A novel and clinically implementable prioritizing model were developed based on the identified risk characteristics, combined with clinical experience from the ED setting regarding what characteristics were available early during a patients ED stay.

7.2 Study II

A total of 807 patients were included to investigate whether pharmacist-led medication review conducted in the ED setting could impact clinical outcomes and post-discharge outcomes. Median age of the study-population was 69 years (IQR 27, range 19-99), 57% of the patients were aged over 65 years. Further, 70% of patients had a medical referral reason and 30% had a surgical, and 52% were men.

Inclusion stay analysis included 799 patients (399 intervention group patients and 400 control group patients. Follow-up analysis (including analysis on primary outcome) comprised 789 patients (394 intervention and 395 control).

Main findings:

- Primary intention-to-treat analysis revealed that there was no significant difference in proportion of patients with an unplanned contact with hospital within 12 months after inclusion stay discharge between groups (51% of intervention group patients vs. 53% of control group patients, p=0.55).
- Number of regular drugs documented by physicians at admission was median 3 (IQR 6, range 0-16), number of drugs documented by study pharmacists after intervention MR was median 4 (IQR 6, range 0-19). Hence, study pharmacists documented a higher number of regular drugs compared with physicians for the intervention group patients at admission (p<0.01).
- Regarding secondary outcome, median time until next unplanned contact with hospital within 12 months follow-up, intention-to-treat analysis revealed that the intervention prolonged median time with 22 days compared with standard care (p=0.755, HR 0.97, 95%CI 0.80, 1.18) (Figure 7A). Per-protocol analysis revealed that the intervention

prolonged median time with more than 57 days compared with standard care (p=0.38, HR 0.91, 95%CI 0.73, 1.13) (Figure 7B).

- Regarding the DRPs identified during the ED stay, 74% were found clinically relevant to identify during the ED visit (23%) or hospital stay (51%). Physicians implemented the pharmacists' recommendations for 45% of the clinically relevant DRPs.

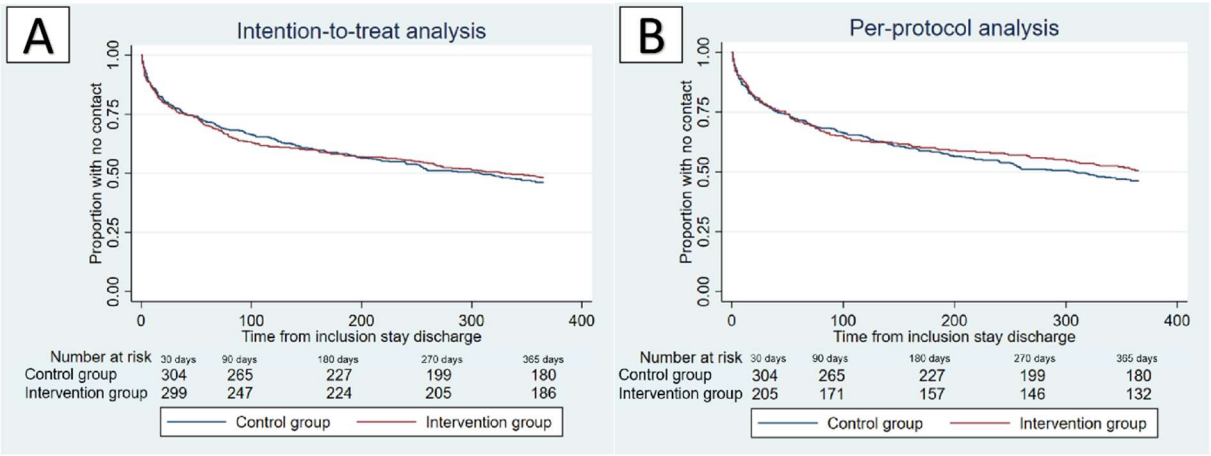


Figure 7. Time to next unplanned contact with hospital (ED-visit or hospital admission).
(A) Intention-to-treat analysis of patients with follow-up data, intervention group (n=394) vs. control group (n=395) **(B) Per-protocol analysis** of patients with follow-up data, intervention group (n=267) vs. control group (n=395). Reproduction of Figure 3 in paper II.

Conclusion

As currently designed, the intervention did not significantly influence clinical- or post-discharge outcomes. It was revealed that pharmacists documented a higher number of the patients' regular drugs compared with physicians at admission. Hence, if pharmacists are implemented in a more efficient way in the interdisciplinary team of the ED, for instance by documenting their findings directly in the medication chart, this can improve the drug-related information flow at transition of care. This study also revealed that majority of DRPs identified through ED medication review were of importance for the patient treatment, hence has the potential to improve drug-related patient safety. If medication review methodology is redesigned to focus on acute DRPs in the ED, and a referral system is developed for follow-up of in-hospital DRPs, physicians' implementation of the pharmacists' recommendations may increase.

7.3 Study III

A total of 402 patients randomized to the intervention group in study II was included to investigate the prevalence of drug-related ED visits and associated risk factors. The study population had median age 67 years (IQR 27, range 19-96), and according to the reconciled drug list used median 4 regular drugs (IQR 6, range 0-19).

Main findings:

- In total, 79 (20%) patients had a drug-related ED visits, of these 22% was *probably* drug-related and 79% was *possibly* drug-related.
- Identified risk factors: increasing age, increasing number of regular drugs, medical referral reason in general (compared to surgical), and specifically *Hemorrhage or anemia*, and *Dizziness, syncope, or tendency to fall*
- Adverse effects and non-adherence were the most common causes of drug-related ED visits, registered as cause in 72% and 17% of the drug-related ED visits, respectively.
- Antithrombotic agents were the drug group most frequently involved in drug-related ED visits, whilst immunosuppressants had the highest relative frequency.
- Physicians treating the patients documented only 11% of the identified drug-related ED visit as drug-related in the discharge notes.

Conclusion

Drug-related ED visits are a major concern regarding drug-related patient safety in ED, as only a minor part of the identified drug-related ED visits was documented by physicians. The associated risk factors can be used to identify patients in need of additional attention regarding their drug list during the ED visit. Further, the risk factors can be used as alert signs by healthcare providers in primary healthcare to identify patients where a systematic medication review is needed, and thus maybe prevent future drug-related ED visits.

7.4 Study IV

During the total observation time of 91.4 hours, 31 ED physicians were observed to investigating ED physicians working patterns.

Main findings:

- ED physicians spent majority of their time gathering information (36.5%), communicating (26%), and documenting (24%)
- In total, 18% (95% CI 17%, 19%) of the physicians' time were spent on drug-related tasks
- On average, physicians spent 7.8 minutes (95% CI 7.2, 8.6) per hour to obtain and document patients' drug lists at admission. This time was distributed on several fragmented tasks:
    - 1.7 minute was spent talking to patient/next of kin
    - 2.0 minutes were spent gathering information on computer or paper
    - 4.0 minutes were spent on documentation (on paper and computer)
- Physicians multitasked for 17% (95% CI 15, 21) of the drug-related task time and 10% (95% CI 9, 11) of the non-drug-related task time ($p<0.01$).
- In total, physicians were interrupted 4.0 (95% CI 3.6, 4.4) times per hour. Interruption rate during drug-related task time were 4.3 (95% CI 3.0, 5.2) times per hour ($p = 0.81$, compared to the interruption rate for non-drug-related task time).

Conclusion:

The findings from this study illustrates that ED physicians are required to conduct numerous essential tasks and distributes a minor proportion of their time on drug-related tasks. Gathering information in general were the most time-consuming task overall, and also the most time-consuming drug-related task. The results reveal that physicians use multiple sources to obtain and document drug lists at admissions, and that the process is fragmented. Reliable, easily accessible sources to patients medical and drug history is highly needed to improve drug-related patient safety with regards to drug information flow during transitions of care. Compared to prior studies performing MR in ED setting, the ED physicians in our study spent less time obtaining and documenting drug lists.

7.5 Patient flow charts of Study I, II and III

Study I

In total, 57.9% of patients admitted to the ED were included in the two first data collection periods. MR was finalized in 87.0% of the included patients. In 13% of the included patients, MR could not be finalized (12% due to no drug list documented by physicians before patients left the ED, and 1% due to lack of drug information).

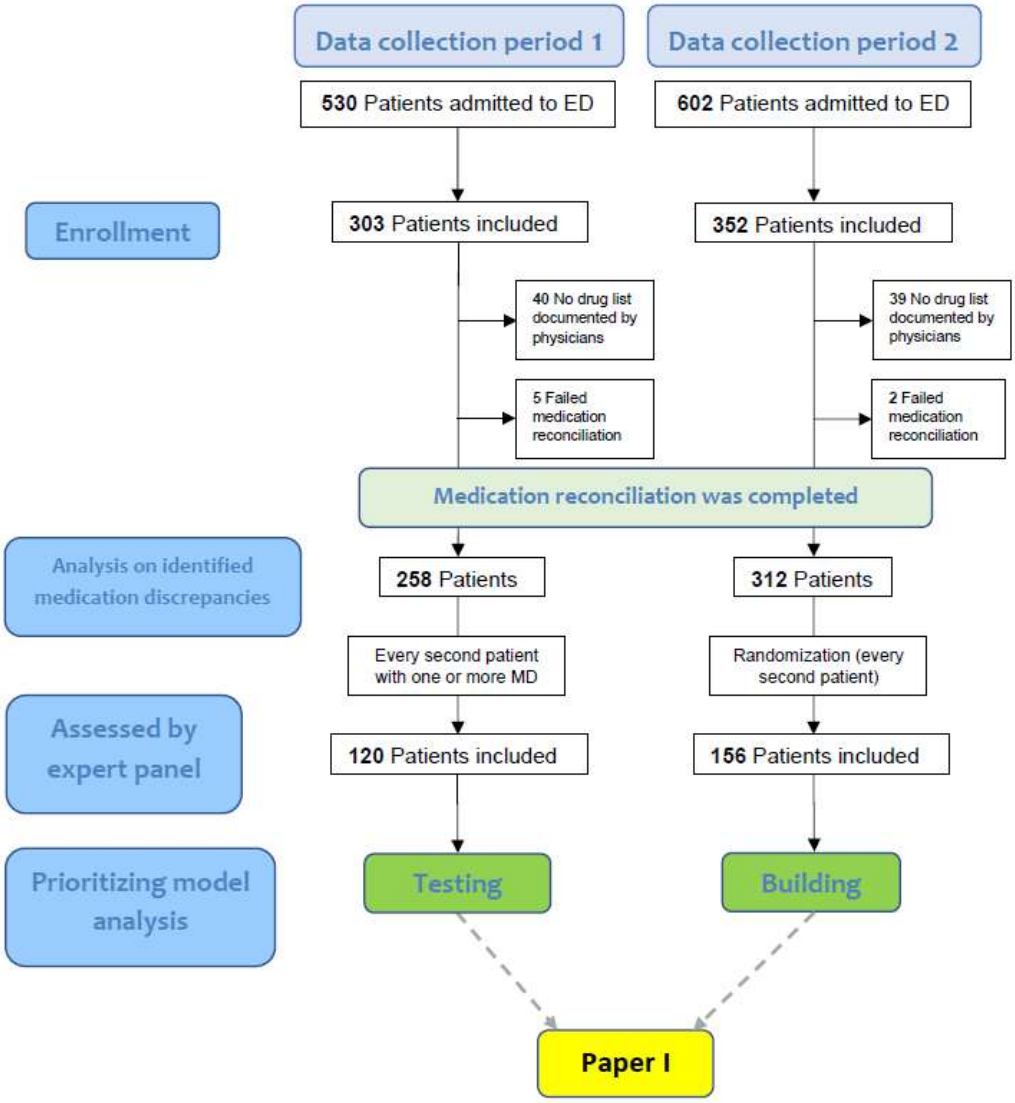


Figure 8. Patient flow chart for patients included in study I.

Study II and III

Approximately 1900 patients were admitted to the ED during data collection, 43.7% of these patients were assessed for eligibility for inclusion. The remaining patients were not assessed due to ED crowding which exceeded study pharmacists' capacity.

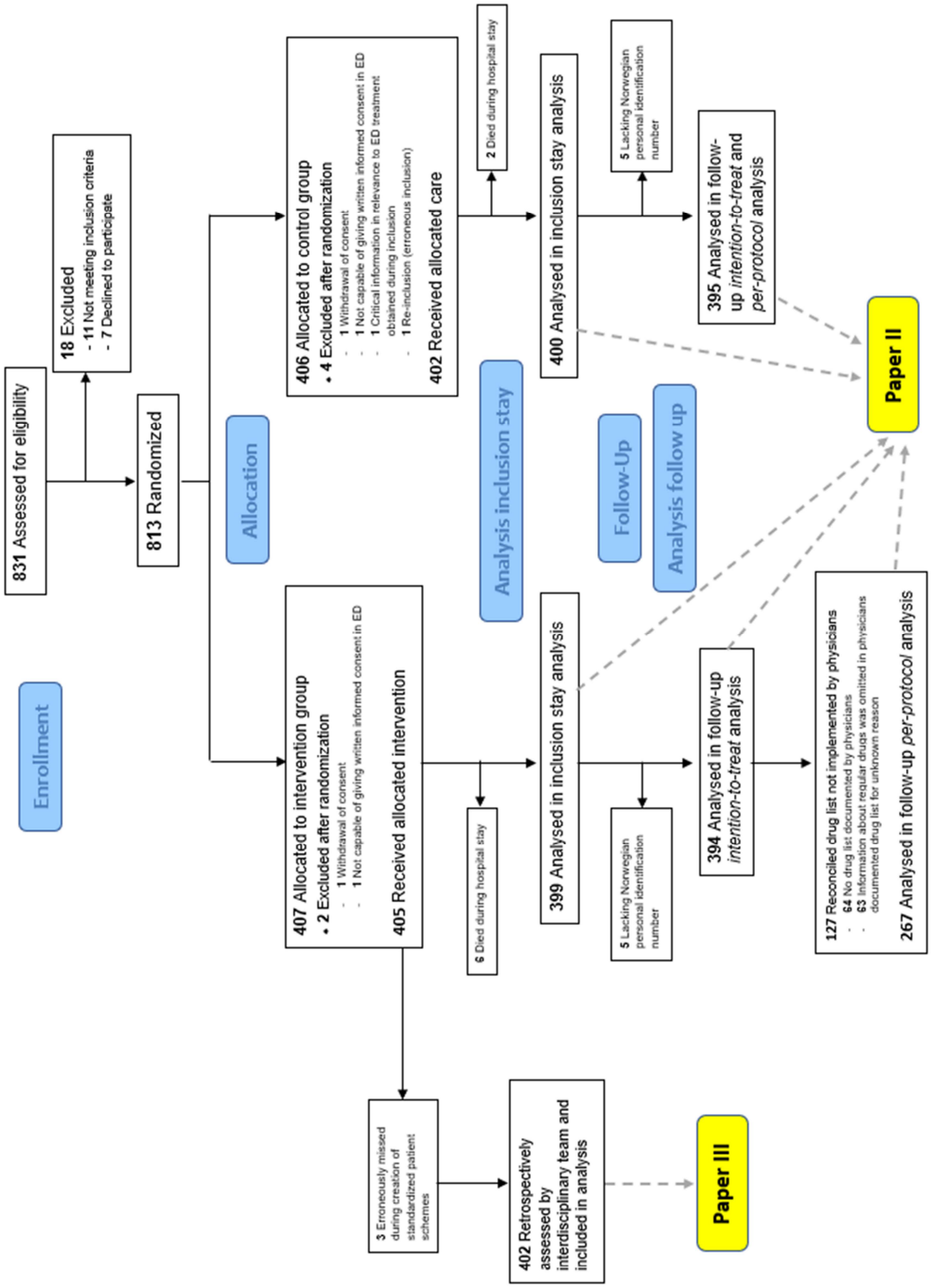


Figure 9. Patient flow chart for patients included in the studies presented in paper II and III.

8 Discussion

8.1 Methodological considerations

8.1.1 Study setting

Most patients admitted to hospital receive their first consultation during the ED stay. The ED setting is also where the drug history traditionally is obtained, and further drug treatment during the ED visit and potential hospital stay is based on the drug history obtained in the ED. It is reported that up to 27% of hospital prescribing errors have been linked to inaccurate or incomplete ED drug lists (74). Hence, MDs which occur during the ED stay can stick with the patient during the entire hospital stay. This highlights the importance of obtaining a correct and complete drug list during the ED stay. Patients' signs and symptoms are assessed by ED physicians, and a decision regarding hospitalization or direct discharge is made. If ED visits caused by patients' drug treatment are not identified during the ED stay, physicians might end up misdiagnosing and treating the symptoms instead of the actual problem (14). The ED has a time-pressured work environment with frequent interruptions, there is often lack of essential information about patients medical history and drug history, and communication methods/ preconditions can be poor (186). It is therefore crucial to study factors affecting drug-related patient safety in the ED setting to be able to identify what stages in standard care which are possible and beneficial to redesign. Additionally, since LOS in hospitals is decreasing worldwide (187), investigating interventions conducted during the ED stay i.e., early during the hospital admission is important. Thus, the ED setting was chosen as study setting for the project presented in this dissertation.

The nature of the ED setting, however, result in a more challenging study setting compared to other clinical settings, e.g., in-hospital, outpatient clinic and primary healthcare. Average LOS in the investigated ED was 3.2 hours in 2018. Hence, all patients included for studies I, II and III were available for pharmacists-led interventions for a relatively short amount of time. In addition, due to the fast-paced workflow, the possibility for dialogue with ED physicians regarding for instance identified DRPs was also limited.

8.1.2 Study design

Determining prevalence of clinically relevant MDs and drug-related ED visits were aims in studies I and III, respectively. In addition, revealing prevalence was essential for identifying patient specific risk factors and development of the prioritizing model (study I). An observational study design is adequate to investigate research questions regarding prevalence (188, 189) and were therefore chosen for these studies.

The aim in study II was to investigate the impact of a pharmacist-led intervention on clinical outcomes for patients admitted to the ED. A RCT was chosen as study design, as this provides the best evidence on effectiveness of an intervention (189). As no prior RCTs investigating impact of pharmacists-led intervention in the ED setting were published, it was decided to include all patients admitted to the ED.

In study IV, ED physicians' working patterns and distribution of time between various work tasks were the scope. A time-motion study in the form of direct, continuous observations is the favored design for such purpose(163). It was determined to use the validated time-motion method WOMBAT (167, 178), which is based on direct, continuous observations. WOMBAT is specifically developed and validated to provide a reliable method for investigating the complexity of clinical working patterns (178).

An expert panel was used to retrospectively classify clinical relevance of the prospectively identified intervention findings (study I and II) and to determine association between patients' drug use and reason for ED visits (study III). This combination of a prospective intervention with a retrospective expert panel assessment was chosen because prospective and retrospective methods of classification both have limitations when used in an isolated fashion (62, 90). In study III, the retrospective assessment balanced the prospectively available information by also assessing patients' final discharge diagnoses and additional laboratory tests results from the hospital stay.

8.1.3 Selection bias

Study I

Study I included 58% of patients admitted to the ED during the first two data collection periods (Figure 8). Comparative analyses were conducted to investigate potential differences

between included and not included patients. There were no significant differences in age, sex, tentative referral reason or who referred the patients. However, significant difference was revealed in distribution of triage-status ($p<0.001$) and department allocation of referral reason ($p=0.032$). Regarding triage status, no patients with triage 1 (red) were included. In exchange a higher proportion of patients with triage 2 (orange) was included, compared with proportion among patients not included. It is noteworthy that the triage status was unknown for a higher proportion of the non-included population (due to retrospective data collection for these patients), compared with the included population. Thus, the distribution of the triage variable was thus uncertain in the non-included population. Further, the included population comprised a higher proportion of patient with medical referral reasons, and a lower proportion of patients with surgical referral reasons compared with the non-included population. Only the variables refer to in this section were available with regards to the non-included population. Hence, selection bias regarding other variables cannot be rejected.

Due to restrictions in expert panel capacity, 48% of the patients where MR was completed were comprised in prioritizing model development (building and testing). The prevalence of clinically relevant MDs was determined based on the study population in the second period of data collection. Selecting every second patients to assessment by the expert panel is not a robust randomization method and may have introduced additional selection bias.

Studies II and III

As the patient population in studies II and III had the same origin, selection bias issues are similar in these two studies.

The inclusion procedure comprised a brief information session and required written informed consent. Hence, the most severely ill patients could conceivable have declined to participate in the study to a larger degree than others or was not eligible for inclusion. This is supported by patients with triage category 1 (red) being underrepresented in the study population, only one patient with triage category 1 (red) was included. Underrepresentation of the most severely ill patients may also explain why fewer patients in the study population (68%) was admitted to a hospital department after their ED visit, compared to annual summary statistics from the ED at Diakonhjemmet Hospital (73%). Annually, a total of 97% of patients with triage 1 is admitted to a hospital department after the ED visit, compared to 17-89% of patients with other triage categories (triage 2-5).

Of patients admitted to the ED during data collection shifts, 44% were assessed regarding eligibility for inclusion (Figure 9). To limit selection bias, study pharmacists had no specific criteria for which patients to include in case of ED crowding. Summary statistics from Diakonhjemmet Hospital for the period from 2017 to 2018 reveal that 57% of patients admitted to the ED were aged over 65 years, 73% of patients were referred with a medical referral reason, and 27% with a surgical referral reason. Hence, both the annual age-distribution and distribution regarding allocation of referral reason were similar to the study population. According to patient data security guidelines we were not permitted to record patient demographics for the non-included population, selection bias regarding other variables can therefore not be ruled out.

Study IV

Due to the roster-based affiliation of physicians to the ED, the proportion of physicians enrolled from the total number of available physicians was not calculated. To reduce selection bias, observers randomized which of the available physicians to include before each observation session, and each included physician was maximum observed for two sessions. Further, the pre-set observation session timetable was designed to comprise different hours and days (weekdays/weekends between 9:00 am to 9:00 pm). Data collection duration was approximately 3 months, which also reduced the potential selection bias as the physician staff in the ED was frequently altered due to the roster-based affiliation.

8.1.4 Expert panel assessments

It has been argued that using expert opinions or global introspection (such as WHO UMC classification) in causality assessment result in poor reproducibility and inter- and intra-rater agreements (190, 191). Causality assessment algorithms, such as Naranjo and colleagues' method (192), have frequently been used in prior research regarding DRHAs (62) and drug-related ED visits (14, 16, 78, 79). It is argued that use of algorithms provides higher inter-rater agreement, due to the fixed framework for the causality assessment (190). A study comparing causality assessment methods, revealed that algorithms have a high specificity, but low sensitivity compared with expert opinions (193). These results indicate that algorithms have substantial rate of false negatives relative to true positives, which could lead to underestimating prevalence. In addition, most available causality assessment algorithm are developed to assess adverse drug reactions caused by one drug, and usually leave no room for

the user to include additional information in the assessment (190). In our study III, we investigated drug-related ED visits which could be caused by problems related to one or more drugs, the fixed framework of the algorithms was therefore considered as a limitation. The expert panel approach was chosen because assessment in an expert panel is quite similar to clinical diagnosis and thus closer to the clinical practice than some of the available algorithms (190). Because none of the panel members had prior experience with causality assessment, it was also considered an advantage that the expert panel assessment was straightforward and easier to operate than algorithms. The implicit criteria used by the expert panel during assessments were inspired by elements of Hallas and colleagues' algorithm (175), which included criteria for the rating of contribution in dose-related therapeutic failure.

Prior studies have reported that between 57.3 and 70.7% of drug-related ED visits may be preventable (16, 78, 84). Preventability of the identified drug-related ED visits in study III was not investigated, as the assessment of preventability would have introduced an additional subjective aspect to this study. In prior studies, ED visits caused by non-compliance, suboptimal dosing and need for additional drug treatment were most frequently found preventable (16, 78). Our study found that after adverse effects, non-adherence and suboptimal dosing were the most frequent DRPs leading to ED visits. Indicating that a proportion of the drug-related ED visits identified in our study could have been prevented.
To reduce bias regarding group decision making all expert panel assessments (studies I, II and III) was conducted in two steps:

1) All expert panel members first assessed and classified all MDs/DRPs/ED visits individually
2) All members participated in consensus meetings

To reduce shared-information bias within the group all members of the expert panel received the same information, both with regards to the included patients, and the assessment procedure. However, we had to trust in the members of the expert panels to share profession-related knowledge with the other panel members during the consensus meetings. To reduce "groupthink" (194) during the consensus meetings, consensus discussion regarding each patient was started with each member of the expert panel presenting their individual classification. However, there were not conducted analyses to investigate if specific panel members had more impact on consensus compared to the others.

In study I, the expert panel had three members, one chief physician, and two clinical pharmacists. The two pharmacists also conducted MR in this study, this dual role may have influenced the proportion of MDs being assessed as clinically relevant in this study. The pharmacists could have been more attached to the assessed MDs and may have had additional information in some of the cases. In studies II and III, the expert panel consisted of three clinical pharmacists and two chief physicians. One of the clinical pharmacists was also involved in performing the intervention in the ED. The bias related to the dual role of one of the panel members were assessed as limited. The composition of the team with more than one representant from each profession were considered a strength and believed to balance both inter-professional and inter-individual differences of opinion.

As several consensus meetings were held with the same expert panels, we cannot rule out that members over time adjusted their individual classifications, to fit with prior group consensus. No analyses were conducted to investigate this issue. Further, as each patient was assessed individually in the order of inclusion number, we cannot be sure that similar patient cases were classified similarly by the expert team over time.

8.1.5 The intervention in the RCT

The intervention used in study II, involved two main components, a MR and a medication review. These components comprised patient interviews, identification of DRPs and further identification of possible actions to manage or solve the problems, documentation of findings in the hospital's patient record, and communication with the physician responsible for the patient. Even though our intervention was composite it may not be classified as a complex intervention (195) due to the short time aspect of clinical follow-up. However, some of the suggestions related to designing complex interventions are applicable also to our intervention.

Craig et al. state that complex interventions may work best if tailored to local circumstances rather than being completely standardized (195). The MR working model was redesigned to fit the ED setting in study I, and further used in study II. The medication review methodology used in study II, was however not tailored, as this methodology was not investigated in ED setting before the initiation of our study. Recent published work has revealed that physicians' acceptance of pharmacists' recommendations are low in ED setting (196, 197) compared with in-hospital setting (111, 198, 199), and low acceptance of pharmacist recommendations has recently been identified as a threat to the success of medication review interventions (197,

200). Tailoring the medication review methodology to the ED setting before conducting study II (the RCT) would have been beneficial.

Another concern studying the effect of complex interventions is whether the intervention is delivered as planned (195, 201). The data collection scheme was piloted in the ED setting and written procedures were developed regarding data collection, inclusion- and randomization procedure, and the intervention deliverance. The intervention was delivered by three experienced clinical pharmacists which were instructed in all the procedures. It can be argued that the number of involved pharmacists is too low to state that we investigated the effect of the intervention and not the individual pharmacists. However, we believe that the written procedures contributed to standardize the intervention deliverance.

8.1.6 Outcomes in the RCT

The conclusions in prior systematic reviews and meta-analyses investigating impact of medication review on clinical outcomes (118, 122, 123, 202, 203) have been limited by the heterogeneity of the reported outcomes in prior RCTs (204). Beuscart et al. published a *core outcome set* with recommended outcomes for studies investigating impact of medication review-interventions in multi-morbid older patients (over 65 years) with polypharmacy (204). None of the outcomes included by Beuscart et al. were "hard" outcomes, meaning objective measures, possible to measure with a high degree of precision (205, 206). As the core outcome set (204) was published during our data collection, the chosen outcomes in study II, including the primary outcome, do not coincide with the recommended outcomes (204).

Readmission within 30 days of discharge is widely used as a quality indicator in healthcare (207, 208). This outcome is possible to measure with a high degree of precision, thus are frequently used as an outcome in healthcare-related research (209). The unplanned readmissions are the most relevant to measure, and this is also the focus in the healthcare quality indicator (207). Planned readmissions can be a sign of high-quality care with close follow-up of patients with chronic conditions. An unplanned readmission is more complex, and can be the result of e.g., preliminary discharge (210) or inadequate collaboration between the primary and secondary healthcare (211). Unplanned readmissions are also considered possible to influence with different interventions, hence to some degree preventable (212). Similar to prior RCTs investigating impact of in-hospital pharmacists-led medication review on clinical outcomes (111, 112, 116, 161), unplanned contacts with hospital were chosen as

the primary outcomes in study II. Originally, we planned to analyze the primary outcome divided into proportion of patient with an unplanned ED visit and proportion of patients with an unplanned readmission. However, due to the uncertainty regarding coding of the ED visits in the NPR data, it was decided to analyze unplanned contacts with hospital as one outcome. It was considered important to include both the readmissions and the acute ED visits in the outcome, because the unplanned ED visits also stress the healthcare service, and these patients also require adequate healthcare. This decision resulted in a more conservative outcome, which may have affected the results. Long-term follow-up (i.e., at least up to a year) have been proposed necessary to provide more definite evidence for the impact of medication review on clinically important outcomes (118). Hence, in study II it was decided to follow patients for 12 months after inclusion stay discharge.

ED LOS is frequently used as a tool to monitor emergency care quality (5). Reducing LOS in hospital is a policy aim for many healthcare systems and is thought to indicate efficiency in hospital treatment (213). ED LOS and LOS in hospital are therefore easily accessible outcomes. According to Asplin et al. (35), diagnostic work up and treatment decisions occupies the majority of the ED LOS. In study II, it was hypothesized that the intervention could increase the accessibility of drug information at transition of care, and thus decrease ED LOS. It was also though that an assessment of patients' drug lists and identification of DRPs early during the ED stay could improve documentation and communication regarding this during the hospital stay, and thus decrease LOS in hospital. However, ED LOS and LOS in hospital are complex outcomes affected by numerous factors. ED LOS has been found to be influenced by efficient use of triage systems, nurse and physician staffing, efficiency and use of diagnostic testing (e.g., laboratory, radiology), accessibility of medical information, the quality of the documentation and communication systems in the ED, and in-hospital capacity (35). Additionally, a recent study found that ED LOS were influence by remaining time until physicians shift ends (214). Physicians spent less time to discharge a patient from the ED (either to hospital department or home) late in their shift compared to early during their shift(214). LOS in hospital has been reported influenced by patients' age and history of previous admission, patients' condition, type of treatment given during hospital stay, number of hospital beds (215, 216). In Norway, LOS in hospital is also influenced by capacity in the municipal managed healthcare. Patients LOS in hospital can be prolonged awaiting free nursing home beds. After initiating the Health Care Interaction reform ("Samhandlingsreformen"), a collaboration reform between secondary healthcare and

municipally-managed home care service and nursing homes, this issue is increasing (217). Considering all factors influencing ED LOS and LOS in hospital this may not be optimal outcomes for the intervention investigated in our study, especially since the intervention only targeted a small piece in a large puzzle.

The population included in our RCT, differs from the multi-morbid older patient group of which were the scope of the developed core outcome set (204). However, comparing our groups regarding some of the outcomes listed in the core outcome set, such as overuse of drugs, underuse of drugs, potentially inappropriate drugs and clinically significant drug-drug interactions, could have provided more information regarding the effects of the conducted intervention on optimalization of patients' drug therapy. The only clinical post-discharge outcome included in the core outcome set were DRHAs, which is an outcome measure with potential to increase patient safety. A recent systematic review focusing on drug-related hospital *readmissions* (218), concluded that 21% of hospital *readmissions* were drug-related. Further, it was stated that 69% of these *readmissions* were preventable. However, without a standardized definition of DRHAs, it can be challenging to measure this outcome in RCTs, and further to compare impact between studies (62, 219).

Study II was designed as a hybrid RCT approach with elements from both active data collection combined with outcome measures harvested from routinely collected data, e.g., NPR data and LOS (220). A recent meta-research study revealed that RCTs using routinely collected data for outcome ascertainment show smaller treatment benefits compared with traditional RCTs not using routinely collected data (220). The hypothesis presented by Mc Cord et al. to explain this finding was that *trials using routinely collected data might be more pragmatic than traditional trials. In addition, the trials using routinely collected data reflect a more natural care settings with less eagerness to artificially increase treatment adherence.*

8.1.7 Logistic regression

In studies I and III, logistic regression was applied to identify risk factors. In both studies the dependent variable in the logistic regression was determined through expert panel assessment, which can be a limitation. To reduce the uncertainty of the assessments the dependent variable in both studies was dichotomized before logistic regression analysis. All available clinical variables were investigated regarding correlation with the dependent variable in both studies. However, we cannot rule out that some associated variables may have been omitted, due to

limitation of information; for instance, specific information about drug-groups in study I, and triage, number and types of earlier diagnoses in study III.

We expected some of the variables to be correlated, such as age, number of used drugs and number of earlier diagnoses (the latter only included in study I). In the prioritizing model built in study I it was considered important that all variables included in the regression model were easily accessible early during the ED stay. Hence, number of used drugs and number of earlier diagnoses were therefore ruled out. It was not revealed any interactions between the variables included in the final prioritizing model.

In study III, the aim was to identify risk factors, and all variables were analyzed separately to determine the odds ratio of drug-related ED visits. No attempt to build a prioritizing model was done in this study. Thus, both age and number of used regular drugs were listed as risk factors. Hospitalization rate was checked for correlation with age, because this could contribute to explain the finding. However, the results were consistent even after adjusting for age, and our data could not determine whether this result represented an association, a causation, or both.

8.1.8 The questionnaire

The questionnaire used in study I was not validated, and some of the questions may have triggered a recall bias. For instance: *What sources do you usually use when taking the drug history?* Followed by a list of 17 pre-set answer options. Further, the questions regarding physicians' time use on drug history taking were ambiguous regarding what should be involved in the time-estimate. The formulation of the question was: *How much time do you use when taking a drug history, including time to clarify questions regarding what drugs patients have been using before admission?* with 5 pre-set answer options (0-5 minutes, 6-10 minutes, 11-20 minutes, 21-30 minutes, and >30 minutes). Whether physicians included only the information gathering part of the drug history taking or also the documentation part is unknown. Self-reported time spent on activities has also been reported to be of limited value, when estimating the mean time per activity (221), because of perceptual differences between participants of what constitutes an activity.

Of the eligible physicians, 77.1% received the questionnaire, 70.4% of these completed the questionnaire. Hence, only 54.3% of the eligible physicians completed the questionnaire. We

therefore cannot rule out response bias. In addition, the physicians received the questionnaire directly from a pharmacist or an ED nurse involved in conducting MR in study I. This may have led to a higher response rate from physicians' who initially were positive to MR in the ED.

Based on several weaknesses and high risk of potential bias, it was decided not to heavily emphasize the results from this questionnaire in the final paper I.

8.1.9 Time-motion studies

According to the Enhancing the QUAlity and Transparency Of health Research (EQUATOR) network there is currently no specific reporting guideline available in their database tailored for time-motion studies (personal communication S. Kirtley, EQUATOR Knowledge and Information Manager, 30 July 2020). Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)-statement (222) for observation studies can be utilized. However, the STROBE-statement does not completely cover the complexity of the time-motion design. To standardize designing and reporting of time-motion studies, researchers is encouraged to adopt Zheng's methodological reporting checklist (STAMP) (223) to describe the details of the implementation of the method (163). Study IV was designed and reported according to STAMP, also considering the applicable recommendations in the STROBE-statement.

One of the strengths with our time-motion study is the continuous observation approach enabling us to record physicians' working patterns in real time. This approach provided highly detailed data regarding conducted task and time consumption, linked to location, tool and other involved personnel data. Using the WOMBAT-method, applied with the WOMBAT-software (167, 178), simplified a complex data collection, as we were able to collect majority of the data simultaneously. However, the continuous observation method restricted the observation session time due to risk of observer fatigue. We were not able to observer physicians through full shifts, which may have affected the results. Work sampling and is another approach utilized in prior time-motion studies investigating the distribution of staff work activities (19, 163). In work sampling, it is registered if a task is performed at a given time-point, and further repeating the measure at predefined fixed or random time intervals during the observation. Hence, work sampling relies on the repetitive nature of work and assumes the probabilistic generalization of the sampling results to describe how workers spend their time (163). Work sampling enables observers to observe more participants simultaneously and is also argued to reduce the Hawthorn effect (19). However, it is a

concern that work sampling may not provide an acceptably precise approximation of the time distribution that would be obtained by continuous observation time-motion studies (163, 221). It has been broadly reported that the nature of clinical working patterns are unpredictable (164). Thus, complex frameworks and continuous observations is the favored design of time-motion studies (163), and were therefore chosen for our study IV.

Erroneous recordings could be changed during data collection in our study IV, if corrected before two other tasks had been recorded. Only a few obvious erroneous recordings were corrected in the final database directly harvested from the WOMBAT-software. Majority of these corrected recordings were marked by the observers during data collection, by writing down time of error, the erroneous recording, and what recording was correct. On average 160 single tasks with range between 81-233 (not accounting for multitasking) were recorded in each observation session (two hours). Hence, the collected data were highly detailed, and we cannot ensure that all erroneous recordings were corrected. However, the performed IRR testing revealed substantial agreement between the two observers, which strengthens our findings.

Like all direct observation studies, time-motion studies include risk of observers' presence interfering with working patterns of the observed participant (i.e., the Hawthorne effect (224)). Subjects might feel disturbed, and sometimes an improvement in performance can be evidenced by the presence of an external observer (163, 224). The information lectures regarding the study aim and method given to physicians before study start, may have enhanced the Hawthorne effect. However, these lectures were necessary to prevent interruptions of observers during observation sessions. To reduce the potential Hawthorne effect, the observation session procedure was explained to the included physicians before observation session start. As far as possible, the observers did not talk to the observed physicians during the observation session. If physicians started to explain what they were doing, the observation procedure was shortly reiterated. These short conversations were recorded as "non-drug-related professional communication with others" and might have influence this discreet category.

8.1.10 Retrospective assessment of outcomes

Acceptance of pharmacists' recommendations in study II was calculated through comparing identified DRPs with changes during the hospital stay. This is not an optimal approach as we

cannot be certain that the changes were conducted because of the pharmacists' recommendations. Optimally we should have registered if the ED physicians accepted the recommendation or not immediately. However, in the fast-paced workflow there was little room for discussion with physicians. The chosen approach can only indicate what pharmacists' recommendations were in line with the chosen changes during hospital stay. The presented acceptance rate can thus both represent real acceptance of the pharmacists' recommendations and/or changes physicians themselves considered relevant and these changes coincidentally matched the recommendations made by study pharmacists.

Further, physicians' documentation of drug-related ED visits was determined by retrospectively reviewing discharge notes, therefore we cannot conclude regarding physicians' recognition of drug-related ED visits. Only recording documented cases, may have underestimated the recognition compared with studies where physicians' have been asked at the end of their shift if they considered admissions to be drug-related or not (14). However, if the next link in the healthcare chain should follow-up on drug-related events leading to an ED visit, documentation in discharge notes is the safest communication form. Our registration of documented drug-related events represents the information passed on to the next link in the healthcare chain.

8.1.11 Validity

Internal validity

Our prioritizing model (study I) was internally validated. However, according to a recent systematic review (225), our event frequency may have been too low to suggest that the validation was adequately powered. In the systematic review, an event frequency >100 is suggested as adequate. Sensitivity and specificity of our prioritizing model were calculated, and were acceptable compared to both prior and post published risk assessment tools (225).

The lack of specific inclusion criteria resulted in inclusion of heterogenous populations in studies II and III, and this may threaten the internal validity of the RCT data (study II). Before our RCT was initiated pharmacist-led medication review interventions in ED setting was not investigated. The literature therefore gave no obvious indications of patient groups which could benefit from such interventions. In addition, to determine prevalence of drug-related ED visits it was necessary to include a real-world population. Introducing specific inclusion criteria could have increased the internal validity of the RCT data (study II). However, this

would have reduced the external validity of data in both study II and study III. The internal validity of the data from the RCT (study II) was, however, strengthened by a well-conducted randomization procedure where study pharmacists were not able to predict group allocation. Further, three experienced clinical pharmacists served as study pharmacists and followed standardized study procedures developed for all study elements considered critical (inclusion and randomization, intervention conduction and registration of data). Finally, chosen outcomes were objective measures and possible to measure with a high degree of precision for majority of included patients (foreign patients excluded). According to our intention-to treat analysis in the RCT (study II) it can be argued that the low implementation of study pharmacists' findings threatens the internal validity, thus an additional per-protocol analysis where provided. However, the calculated sample size was not reached in per-protocol intervention group patients, leading to uncertainty regarding the calculated results.

The determination of clinically relevant MDs (study I), DRPs (study II) and drug-related ED visits (study III) can be biased as discussed in the methodological considerations section in this dissertation. However, the prevalence and identified risk factors presented in studies I and III were in line with prior studies, which supports the validity of the classifications from the expert panel assessments. In addition, in study III, the combination of obtained information from the prospective intervention with the retrospective expert panel assessment provided a more robust methodology compared to previous studies and strengthens the face-validity of the results in this study.

In study IV, the validated WOMBAT-method was utilized for data collection. Detailed descriptions of each discrete category were developed based on data from a pre-study period. The final discrete category-framework was tested in a pilot-period and work task categories was reviewed by a senior consultant and an experienced clinical pharmacist, which strengthens the internal validity of the recorded data. Two observers recorded data, and this also increase the validity, especially as the agreement between observers were substantial both before and during data collection. Majority of the outcomes were calculated from data directly harvested from the WOMBAT-software, hence measurable with high precision. The internal validity of the reported results per patient is more uncertain. Number of patients treated by the observed physicians was recorded by the observers consecutively after each session (outside the WOMBAT-software) and were not further verified. The number of treated patients was missing for one observation session, and classification information (new/follow-up patient)

was missing for 6 observation sessions. The per-patient calculation was conducted on the available data. These estimates were however presented together with the observed time spent on task and percentage of total task time which was reliable measures.

External validity

As discussed in the methodological considerations section, selection bias is an issue in all four studies included in this dissertation, which may reduce the external validity of our results.

In study I, we were able to compare the included patients with non-included patients regarding a selection of variables. It was found significant differences between groups regarding triage categorization and department allocation of tentative referral reason. These differences may reduce the generalizability of the results. We cannot claim that our results are representative for patients with triage 1 (red). There may also be uncertainty regarding the presented results of surgical referral reason as a risk factor for clinically relevant MDs. However, this finding is in line with other studies(76, 77).

Regarding study population in studies II (the RCT) and III, we were not permitted to record specific patient demographics for the non-included population due to patient data security guidelines. Summary statistics from the ED at Diakonhjemmet Hospital from 2017 to 2018 reveal that both the annual age distribution and distribution regarding allocation of referral reason were similar to the study population. However, the results may not be generalizable to patients with triage category 1 (red), as these patients were underrepresented in the study population.

Population in Norwegian EDs is found different from ED populations in other countries, this may reduce the generalizability of the results from studies I, II and III. Especially, the identified prevalence of clinically relevant MDs and drug-related ED visits in studies I and III is highly dependent on the investigated population. Age (studies I and III) and hospitalization rate (study III) were identified as risk factors and coincide with differences in ED populations comparing Norway to other countries. However, the prevalence reported in study I is in line with prior international studies, and the prevalence reported in study III is in line with international studies investigating populations with the same age diversity (79, 80), which support the external validity of our findings. The presented risk factors in studies I and III were identified by comparing patients with and without clinically relevant MDs/drug-related ED visits from the same population. Hence, the identified risk factors may be more

generalizable than the reported prevalence, which is supported by majority of the risk factors being in line with prior studies.

In study IV, it was necessary to conceptualize discrete categories tailored for the aim of the study. This may have reduced the external validity by making it more challenging to compare the results with other studies. It was, however, attempted to keep the main work task categories as similar as possible to prior studies (19, 166). In addition, detailed descriptions of all categories were provided to clarify interpretation. The results regarding physicians' time distribution from study IV depend on national specific organization of the ED and the patient flow to the investigated ED. As organization of EDs vary both between countries and even within countries, the results may not be directly generalizable to other EDs. However, as this is the first study to quantify physicians' distribution of time between drug-related and non-drug-related activities and our discreet categories are well described, this can be a useful framework for similar ED studies in other EDs both nationally and internationally.

8.2 Discussion of main findings

In this section, main findings of the studies included in the dissertation are discussed. Additional findings are discussed in each paper respectively. Some of the topics discussed in this section are scarcely investigated, these topics are therefore discussed in a broader context.

8.2.1 Medication reconciliation in emergency department - working model and prioritizing model

Study I propose a redesigned working model for MR adjusted to the ED setting. The redesigned working model was perceived more efficient compared to the original MR working model. However, results from study II suggest that additional redesign of the MR methodology is required to make the working model satisfactorily efficient in the ED setting. A proposal for further redesign of the methodology is to allow trained clinical pharmacists to obtain the drug history and document their findings directly in the medication chart (226). Such practice will reduce transfer errors as we observed in the RCT (study II). However, this practice is currently not systematically implemented in Norway. One recent study revealed that majority of the identified medication errors occurred on the first day of hospitalization (227), thus underlining the advantage of interventions conducted early during hospital admissions. However, even with an efficient working model, using pharmacist resources to perform ED MR solely, may not be cost-beneficial as other professions may do this task with equal quality at a lower price (107, 108). This was also confirmed in our study I, as there was no difference in frequency of identified clinically relevant MDs between the ED nurse and clinical pharmacists conducting MRs. Further, concentrating pharmacists in the ED may reduce in-hospital pharmacist resources at the expense of patients in need of in-hospital pharmacist interventions (45). Although, combining prioritized pharmacists-led ED MR with identification of suspected drug-related ED visits (study III) and a referring system of patients to in-hospital pharmacist interventions may lead more efficient use of pharmacist resources.

Study I also provided an implementable prioritizing model tailored for the ED setting aiming to identify patients at high risk of clinically relevant MDs occurring at ED admission. During data collection and after publication of our study (paper I), numerous risk assessment tools have been published. Majority of the developed risk assessment tools aim to predict whether a hospitalized patients will need intervention from a clinical pharmacist during hospital stay. Hence, this is the scope of several systematic reviews including and evaluating the developed

risk assessment tools (64, 225, 228-233). Only four risk assessment tools specifically aim to detect or has included assessments of MDs in the development of the tool (227, 234-236), and therefore are comparable to our prioritizing model. An external validation of one of these risk assessment tools (234) found that only four of the 38 included risk factors were significantly associated with at least one unintentional MD (237). A study using one of the other risk assessment tools (236) reported that the algorithm failed to identify unintended omission of drugs (238). As omission of drugs is found to be the most frequent MD type at hospital admission in several studies (227, 239-241) and also in our study I, this is a significant limitation of this risk assessment tool with regards to prioritizing patients for MR. With the exception of tentative referral reasons, the risk factors included in our prioritizing model (study I) are also included in the above mentioned risk assessment tools and one of the systematic reviews (64) (age (64, 227), female gender (64, 235), and prior hospital admissions (227, 234)). In addition, admission to a surgical department was found to have a non-significant association with medication errors in one of the risk assessment tool studies (227). The three other discussed risk assessment tool studies only included patients from medical department. The four discussed risk assessment tools all included number of drugs and other criteria not available at ED admission; *admitted to hospital following the ED-stay (yes/no)* (235), *use of specified drug groups* (227, 236, 237) (e.g., psycholeptics and anticoagulants) and *best possible drug history available (yes/no)* (227). This reflects that in contrast to our prioritizing model (study I), the discussed risk assessment tools are not solely developed to prioritize patients for MR in the ED. A unique feature and a strength with our prioritizing model, is that the model can be used to screen patients without having to check the patient record for all eligible patients. A disadvantage with all the discussed risk assessment tools, including our prioritizing model is that the assessment of patient must be performed manually by healthcare personnel. Recently, electronical risk assessment tools have been developed to prioritize patients for clinical pharmacists interventions in hospital setting (228), for instance systems which runs in the background of the electronic patient record to identify patients with preselected risk factor indicators (242).

An important perspective not addressed under external validity in this dissertation, is whether our results from study I are generalizable considering the rapid evolution of electronical databases (156, 157) and focus on MR (152, 153) in Norway in recent years. Introduction of the Prescription Intermediary and the Summary care record were believed to decrease MDs (152). These databases were fully implemented after completion of study I. However, in study

IV we revealed that ED physicians only used the Prescription Intermediary as a source for gathering drug-related information for every 4th patient. We proposed a hypothesis that physicians' limited use of the Prescription Intermediary could be related to reliability of this database. It has been reported that electronical drug/ medical records, such as the Prescription Intermediary and the Summary care record, may be incomplete and not accurately reflect what drugs patients are taking (243, 244). A recent Norwegian multicenter in-hospital study (currently unpublished, David Karimi, Helena Z. Mikaelsen, and Ingeborg H. Ulla, personal communication 22 April 2022) revealed that 42-60% of patients had one or more clinically relevant MDs. These results indicates that despite the comprehensive focus on MR through the Norwegian Patient program (153) the last decade and implementation of accessible electronical databases, MDs are still a significant concern in Norwegian hospitals.

8.2.2 Clinical impact of pharmacists-led interventions

In the study presented in paper II, we found no significant impact of the intervention tested in our RCT on clinical outcomes, and these results are similar to the three other ED-studies published after initiation of our RCT (196, 245, 246). Hohl et al. (245) conducted a quasi-randomized trial investigating clinical outcomes of pharmacists-led ED medication review and reported an 8% reduction in median LOS in hospital within 30 days from discharge compared with standard care. However, a follow-up study to the quasi-randomized study (197) found that there was no impact of the intervention on long-term changes to outpatient health services utilization. One arm in a RCT conducted by Graabæk et al. (246) investigated impact of a pharmacist-led medication review (including patient interview and MR) in the ED on drug-related readmissions. This study did not reveal any impact of the intervention on the selected outcomes. Further, Santolaya-Perrín et al. (196) conducted an RCT to assess the impact of a medication review program in the ED setting on the number of all-cause emergency visits and hospital admissions. In the study by Santolaya-Perrín et al. pharmacists assessed potentially inappropriate prescriptions (PIPs) based on the STOPP/START criteria, and also identifying DRPs spontaneously. If an ED specialist agreed on identified PIPs and DRPs (agreed in 87% of presented PIPs and DRPs), a recommendation was made to the patient's GP to alter the patient's drug list. No overall impact on emergency visits and hospital admissions was revealed. However, a significant effect of the intervention was observed in the two study-centers which achieved the highest acceptance rate from GPs on treatment recommendations (52-53%).

Most studies investigating medication review interventions, including our RCT, describe a intervention where issues and possible solutions are recommended to a prescribing physician (118). The impact of the interventions is thus more or less dependent of the acceptance rate of recommendations, which in previous and recent in-hospital studies varies between 18-82% (94, 111, 198-200, 219, 246, 247). In the ED setting, acceptance of recommendations are only investigated by Graabæk et al. (54%) (246), Santolaya-Perrín et al. (27-53% acceptance from GPs) (196) and our RCT (44.8%). Recent studies have raised concern regarding low acceptance of pharmacist recommendations being a threat to the success of medication review interventions(197, 200). Considering this, the RCT (study II) could have benefitted from being based on the knowledge from study IV. If we had known that physicians spend an average 8 minutes per hour on the patients' drug lists at admission when designing the RCT, we may have chosen a different strategy for our intervention. For instance, implementing direct documentation of the MR findings in the medication chart, and focused more on follow up of the identified DRPs and suspected drug-related ED visits (study III), could have been feasible intervention adjustments. As discussed broadly in paper II, the low implementation of the reconciled drug list (adjusted for in per-protocol analysis) and low acceptance rate of clinically relevant DRPs may have limited the impact of the intervention in our RCT. In addition, all studies conducted in the ED setting (196, 245, 246), including our RCT have a more pragmatic intervention design compared with in-hospital RCTs.

After conduction of our RCT (study II), several additional RCTs have been conducted to determine the impact of pharmacist-led in-hospital interventions on clinical outcomes. Studies from Scandinavian countries are heavily represented (94, 198, 200, 219, 246, 247), illustrating that clinical pharmacy is a growing profession in these countries. With regards to MR, additional systematic reviews (66, 69, 248), Cochrane reviews (249, 250), and overviews of systematic reviews (251, 252) have been published recent years. To summarize present literature, some recent primary studies (94, 198, 219) have revealed impact of in-hospital pharmacist-led interventions on clinical outcomes, whereas other recent studies reported no overall impact (94, 200, 246, 247). Thus, conclusions in recent systematic reviews are ambiguous regarding impact on clinical outcomes (119, 253). Complex interventions (195) are however highlighted as an important factor regarding impact on clinical outcomes of pharmacist-led interventions (119, 253). Hence, the investigated ED interventions (196, 245, 246), including our intervention, are as currently designed most likely too pragmatic to impact clinical outcomes. Most of the recent systematic reviews regarding MR (66, 69, 248, 250)

support the conclusions of prior systematic reviews (45, 103-106), reporting that MR efficiently reveals MDs and medication errors. The recent overviews of systematic reviews (251, 252) both focused on the impact of MR on clinical outcomes and concluded that MR alone has no measurable impact on clinical outcomes, underlining the need for complex interventions (119, 195, 253).

Even though complex interventions are found favourable (119, 253), it is important to keep in mind that hospital resources in the real-world setting are not unlimited. Pharmacist-led interventions therefore must be organized to be cost-beneficial. Heterogeneity in interventions and outcomes, and lack of full economic evaluations in previous studies have prevented systematic reviews to finally conclude regarding this aspect (254-256). Decreasing LOS worldwide (6) and majority of medication errors occurring on the first day of hospitalization (227) advocate that interventions conducted early during a hospital stay are necessary. However, the barrier regarding acceptance of pharmacists' recommendations must be managed with well-designed interventions. Further, chosen outcomes in previous studies, including our RCT, may not have been sufficiently related to the conducted interventions (204), this can have contributed to null results in several studies published up to now. As discussed in the Methodological considerations section in this dissertation, pharmacist-led interventions only affect a minor piece in a puzzle during a patients ED visit or hospital stay. Therefore, choosing more suitable outcomes in future RCTs are reasonable (204).

8.2.3 Drug related emergency department visits

Study III is currently the only Norwegian study investigating prevalence of drug-related ED visits. However, recently two Norwegian studies have investigated DRHAs (91, 92) among in-hospital multimorbid patients. Lea et al. (91) used a similar method as described in our study to reveal a DRHA prevalence of 38%. Wang-Hansen et al. (92) included patients aged over 75 years and used explicit criteria to identify adverse events and to assess the causality. This study reported a DRHA prevalence of 21%. According to the findings in these two studies conducted in Norwegian hospital departments (91, 92), our identified ED prevalence of 19.7% is thus realistic.

As discussed broadly in paper III, our prevalence of drug-related ED visits differs from some of the international studies, both previously and recently conducted in this field. A recent study revealed that prospective identification of DRHA provides a higher prevalence

compared with assessing coding in patient records retrospectively (90). This is in line with our findings, demonstrating a drug-related ED visits prevalence from the expert team assessment of 19.7% vs. prevalence when assessing documentation in discharge notes of 2.7%. Recent studies on drug-related ED visits assessing coding in patient records have reported prevalence between 2.3-3.4% (15, 16). Further, both previous and recent studies (15, 257) and systematic reviews (62, 258) has limited the investigation to adverse drug reaction-related hospital admissions/ED visits. This limitation of scope leads to an underestimation of the total burden of DRHAs and drug-related ED visits. Further, a recent study utilized the QUADRAT-tool (96) to assess DRHAs in the Netherlands between 2008-2013 (259). A mean prevalence of 2.7% was reported for patients aged 18-64 years and 10.2% for patients older than 65 years (259). As the QUADRAT-tool does not include non-adherence-related hospitalizations, the reported prevalence may be underestimated. A recent systematic review (260) found that the prevalence of hospital admissions associated with drug non-adherence ranged from 0.7% to 10.8%. This systematic review also reported that almost all of these admissions were considered preventable (260). The considerable variation in reported prevalence of DRHAs and drug-related ED visits in previous and recent studies underlines the impact of utilized identification methodology on revealed prevalence. It also calls for a universal definition of drug-related hospitalization, especially since DRHAs were proposed as a favorable outcome in RCTs investigating medication review interventions (204).

To simplify identification of patients with DRHAs for research purposes, two risk assessment tools have been developed recently (261, 262), in addition to the prior QUADRAT-tool (96). The two recent risk assessment tools (Assessment Tool for identifying Hospital Admissions Related to Medications (AT-HARM10) (261), and the assessment tool based on the OPtimising thERapy to prevent Avoidable hospital admissions in Multimorbid older people (OPERAM)-trial (97, 262)), are validated for older patients. Even though both studies have reported acceptable positive predictive values (PPV), both tools have their limitations. No information is available regarding the drug-related events not flagged (false negatives) by the OPERAM-tool (97). In the development and validation of the AT-HARM10-tool, an expert panel of only one physician and one clinical pharmacist was used as the gold standard when testing the AT-HARM10-tool (261). Due to possible bias in this gold standard, external validation of the AT-HARM10-tool is needed. Regarding both tools, further research is needed to determine whether the tools can be utilized in younger study populations (age under 65 years) as well.

8.2.4 Emergency department physicians' working patterns and time distribution

Currently, study IV is the only study to focusing on ED physicians' time spent on drug-related activities. The study revealed that ED physicians perform numerous essential tasks during patients' ED stay and obtaining and documenting patients' drug lists were only two of these tasks. Further, it was revealed that physicians used multiple sources to gather information, especially to obtain patients' drug lists. A recent report from the Office of the Audit General of Norway ("Riksrevisjonen") (263) revealed that 64% of hospital physicians *frequently find the referral letter from primary health care to lack information regarding complete drug list for the referred patient.* Prior and recent studies have revealed that in situations where physicians lack information, workarounds are frequently used (155, 264, 265). In the case of missing drug information at admission to the ED, a workaround can be to copy the drug list from the patient's last hospitalization instead of taking the drug history from scratch (155). Such workarounds can lead to unintended MDs, as patients' drug lists are frequently altered for different reasons after hospital discharges (266-268).

In study IV, it was revealed that physicians spent 7.8 minutes per hour (estimated to reflect time per patient), on obtaining and documenting patients' drug lists. A recent systematic review reported that pharmacists conducting MR in the ED setting spend 13.9-30 min per patient (66). Further, a recent Norwegian study found that by utilizing a more efficient MR methodology pharmacists conducting MR in the ED setting significantly reduced their time per patient from 56 minutes to 37 minutes (269). Hence, reported time spent on structured MR conducted in the ED setting is considerably higher than the time spent by ED physicians in our study. The recent systematic review (66) further reported that MDs were reduced with 88% when ED pharmacists performed the MR, indicating that the time spent was worthwhile. With this amount of time spent per patient on MR, it would require a massive pharmacist staff to cover all patients admitted to the ED. This may not be cost-beneficial as not all patients experience clinically relevant MDs as revealed by results in study I. Prioritizing patients for MR as proposed in results from study I and other studies previously discussed in this dissertation (227, 234-236) can thus be an important initiative.

Despite the limitations of the questionnaire from study I, results from ED physicians' self-reported time spent on drug history taking are remarkable similar to the results in study IV. Two prior studies conducted in hospital departments have investigated physicians' time spent on drug-related activities. Westbrook et al. (166) observed 19 physicians at different hospital

departments for 151 hours and found that 7% of their time was spent on drug-related activities. Furthermore, Richardson et al. (20) observed 16 physicians for 132.4 hours and reported that 7.6% of the physicians' time were spent on drug-related activities. Drug-related activities required on hospital departments compared with ED are different. It is therefore challenging to argue the plausibility of our results based on comparison with these in-hospital studies.

A recent time-motion study by Schneider et al. (270) investigated both ED physicians' and ED nurses' working patterns in one German ED and one ED in USA, with specific focus on interruptions. In total, 27 ED physicians and 31 ED nurses were observed for 85 hours, the study does not report separate observation time per profession group (270). Schneider et al. used a more manually data collection method compared with the WOMBAT-method (167, 178). Observers carried a clipboard, documentation sheets, and a digital wristwatch to record work activities and work interruptions. The discreet categories used in this study were thus broader, with less details compared with our study, which makes comparison of the reported results challenging. In addition, the favorable reporting checklist for time-motion studies by Zheng et al. (163, 223) or other study reporting guidelines was not applied in the publication (270), which limits the transparency and interpretation of the results. IRR testing was neither reported, which makes it challenging to evaluate observer bias in this study. Schneider et al. structured the used discreet categories regarding direct and indirect patient care instead of structured according to separate task-categories as in our study IV. For instance, in the study describe by Schneider et al. there was no separate category for gathering information, which was the most time-consuming task in our study IV. Gathering information was not described by Schneider et al. in other categories than communicating with patient/relatives, in which physicians spend 9.9% of their time. In our study IV, approximately 16% of physicians' time was spent communicating with patients or next of kins (counting both *drug-related* and *non-drug-related*; *gather information* and *professional communication*). National differences can be one explanation; however, it seems unlikely that the ED physicians investigated by Schneider et al. did not spend any time gathering information regarding patients' prior drug history from other sources that patients and relatives. The description of used discreet categories is deficient in the study published by Schneider et al., thus some of the time spent on gathering information may be hidden in the "documentation" category, in which physicians spent 29.4% of their time. This category is exampled as *maintenance of medical records (electronic and paper records); writing of medical reports* (270). What the authors

mean by maintenance of medical records remains unclear, underlining the importance of application of study reporting guideline in time-motion study to simplify interpretation.

The discussed study by Schneider et al. (270) and many of the other recent direct observation studies (169, 271-274) have focused on interruptions of ED physicians' activities. This is an important aspect as interruptions have been associated with negative impact on ED patients' satisfaction (275), and increased risk of prescribing errors when interruptions occur during drug prescription (169). In our study IV, physicians were interrupted less frequently compared with ED physicians in other studies (4.0 times/hour vs. 5.1-8.4/hour) (19, 168, 169, 270, 274, 276) and Schneider et al. (270) revealed differences in interruption patterns between their two investigated countries. This indicates that there may be cultural differences regarding interruptions. A recent commentary by Walter (277), however, argued that interruptions in the ED setting is not all negative. Walter states that "*even if the recipients are adversely affected by interruptions, the interrupter has received the information they required or has somehow been enabled to carry out his or her role".* Suggesting that frequent interactions between colleagues in the ED (including interruptions) are necessary to ensure the efficiency of the fast-paced workflow. This harmonizes with the results reported in paper IV regarding observed physicians spending more time interacting with other ED healthcare personnel than admitted patients. In addition, a systematic review (278) concluded that interventions to reduce interruptions have shown limited impact on clinical outcomes. Therefore, it may be reasonable to focus on interruptions which actually lead to errors and not interruptions in general.

As previously discussed, medication errors and MDs are found to be of significant concern in several countries. ED physicians are assigned the main responsibility with regards to drug history taking in many countries, including Norway. Results from a recent study indicate that obtaining drugs lists is down-prioritized by physicians when the ED is crowded (186). With increasing problems with ED crowding worldwide (9, 31, 32), and the result from study IV in mind, it is essential to develop reliable sources to patients' drug information which can be accessed easily in the fast-paced workflow of the ED. In Norway, two projects are initiated of which can provide such easily accessible drug information: "Pasientens legemiddelliste" (279) and "Helseplattformen" (280). "Pasientens legemiddelliste" is a shared drug list/ record between primary and secondary healthcare, pharmacies, and the patients. "Helseplattformen" is a shared patient record for primary and secondary healthcare, also accessible to patients and

municipal based healthcare (e.g., municipal emergency clinics, nursing homes, and home care service. However, complete national implementation of these projects is several years ahead (280, 281). It is important that these new electronical systems are perceived as reliable and efficient when implemented. A recent study investigating physicians' use of the Summary care record (282), revealed that the hospital-based physicians described the Summary care record as a source of additional workload. The explanation for this statement was that *documentation in hospital's patient records cannot directly be transferred to the Summary Care Record, and thus physicians ended up documenting the same information several times in different electronic systems.* A recent study from a Danish ED (283) revealed that even with an implemented shared drug list between primary and secondary healthcare 81% of patients had one or more MDs. As an explained to the findings the authors wrote: *All physicians are expected to update the shared medication record any time they change a patient's medication, but this does not always occur.* Hence, "Patients legemiddelliste" and "Helseplattformen" may not solve all problems related to drug-related patient safety in the ED. Therefore, it must be considered to engage personnel specifically focusing on drug history taking and assessment of the obtained drug lists at admission to Norwegian EDs, for instance clinical pharmacists as in several other countries (24, 25, 27, 28, 158).

9 Conclusion and clinical implications

This dissertation has summarized results from four studies with different perspective on factors of concern regarding drug-related patient safety in the emergency department setting. The conducted studies have generated new knowledge regarding drug information flow, drug-related emergency department admissions, and tailoring of pharmacists-led emergency department medication reconciliation and medication review. The results emphasizes that change is needed, both in mindset and workflow in Norwegian emergency departments to increase drug-related patient safety in transitions of care. Through the included papers and this dissertation strategies and actions which can contribute to provide safer transitions of care for emergency patients regarding their drug treatment are proposed.

Clinically relevant medication discrepancies were found to frequently occur among patients admitted to the emergency department. A prioritizing model and a tailored working model for medication reconciliation, to standardize drug history taking in the fast-paced workflow of the emergency department have been presented. Implementing systematic medication reconciliation for high-risk patients during the emergency department stay will increase the quality of the obtained drug lists.

Although not statistically significant, the pragmatic pharmacist-led intervention (medication reconciliation and medication review) tested in the randomized controlled trial prolonged the time to next unplanned contact with hospital with almost two months compared with standard care. These promising results have to be verified by future research. Based on experience from the randomized controlled trial, adjustments needed to tailor the intervention additionally to the emergency department setting were proposed; clinical pharmacists documenting their medication reconciliation findings directly in the drug chart, focusing on emergency drug-related problems in the emergency department, and referring patients in need of follow-up due to drug-related problems to an in-hospital clinical pharmacist. As one of the first randomized controlled trials investigating impact of a pharmacist-led emergency department intervention, this study generated valuable knowledge to facilitate future studies in this field.

Drug-related emergency department visits were found to be common, and the low documentation of drug-related emergency department visits/ hospital admissions by physicians in discharge notes is noteworthy. However, pharmacists were found to be a

valuable resource in flagging drug-related emergency department visits early during the admission. Based on the results from our studies, combining clinical pharmacist-led emergency department medication reconciliation with identification of suspected drug-related emergency department visits and clinically relevant drug-related problems are suggested as an initiative to increase drug-related patient safety. The identified risk factors (age, number of regular drugs, medical referral reason and risk drug-groups) can be used in the emergency department to flag drug-related visits, or in primary healthcare to indicate which patients are in need of a thorough evaluation of their drug list.

Our observations of emergency department physicians revealed that most time was spent on gathering information regarding admitted patients, which highlights the need for a more seamless information flow in general for patients admitted to hospital. The process of obtaining and documenting patients drug lists at emergency department admission was fragmented, due to interruptions, multitasking and the fact that physicians had to use multiple information sources. Clinical pharmacist-led medication reconciliation can thus both increase the quality of the drug list and decrease physicians' workload in the fast-paced workflow of the emergency department.

10 Future perspectives

In our paper II we have proposed how medication reconciliation and medication review methodology can be redesigned to fit the emergency department-setting in future studies. However, our randomized controlled trial did not reveal why implementation of pharmacists' recommendations was low. To answer this, future research in terms of focus group interviews with emergency department physicians could reveal important barriers which must be considered in the redesigning of the intervention in addition to the proposed actions from study II.

Before designing future randomized controlled trials investigating medication review interventions in the emergency department a consideration of the most fitting outcomes for such studies is necessary. As the recently published core outcome set (204) propose drug-related hospital admissions as a favorable outcome in such randomized controlled trials, reliable identification tools are needed. The two recently developed risk assessment tools to identify patients with drug-related hospital admissions (97, 261) need external validation. A future research project is therefore to classify the patients from study III according to AT-HARM10 (261) and the tool developed from the OPERAM trial (97, 262), and evaluate sensitivity, specificity, positive predictive value and negative predictive value of these tools.

Future research should investigate how limited clinical pharmacist resources in Norway is managed in the most beneficial way. In our studies, clinical pharmacists have been found valuable in identifying clinically relevant medication discrepancies, clinically relevant drug-related problems and to flag drug-related emergency department visits early during the emergency department visits. In many Norwegian hospitals clinical pharmacists are department based, meaning that they deliver their service to patients in a specific department. However, this may not be the best organization of pharmacists' resources, as not all patients in a hospital department necessarily need clinical pharmacist interventions. A future research project should investigate if clinical pharmacists conducting pharmacist services in the emergency department can refer patients in need of pharmacist in-hospital interventions through a referral system. Further, the impact of this targeted pharmacist-led intervention should be investigated.

11 References

1. Steptoe AP, Corel B, Sullivan AF, Camargo CA. Characterizing emergency departments to improve understanding of emergency care systems. Int J Emerg Med. 2011;4:42.
2. Oslo University Hospital, Retningslinje OUS-nivå 1 - Kjerneprosesser i Akuttmottaket, Available at: https://ehandboken.ous-hf.no/document/34208 [Norwegian procedure], [cited 30 March 2022].
3. Mackie D. Role of the emergency department. Emerg Med Australas. 2019;31(6):1109-10.
4. Graber TW. Structure and function of the emergency department: matching emergency department choices to the emergency department mission. Emerg Med Clin North Am. 2004;22(1):47-72.
5. Burgess L, Ray-Barruel G, Kynoch K. Association between emergency department length of stay and patient outcomes: A systematic review. Res Nurs Health. 2022;45(1):59-93.
6. OECD (2021), H*ealth at a Glance 2021: OECD Indicators* , OECD Publishing, Paris, [cited 06 January 2022].
7. Magnussen J VK, Saltman RB. (2009). Nordic Health Care Systems: Recent Reforms and Current Policy Challenges. Open University Press.
8. Bjørnsen LP, Uleberg O, Dale J. Patient visits to the emergency department at a Norwegian university hospital: variations in patient gender and age, timing of visits, and patient acuity. Emerg Med J. 2013;30(6):462-6.
9. Mentzoni I, Bogstrand ST, Faiz KW. Emergency department crowding and length of stay before and after an increased catchment area. BMC Health Serv Res. 2019;19(1):506.
10. Blinkenberg J, Pahlavanyali S, Hetlevik Ø, Sandvik H, Hunskaar S. General practitioners' and out-of-hours doctors' role as gatekeeper in emergency admissions to somatic hospitals in Norway: registry-based observational study. BMC Health Serv Res. 2019;19(1):568.
11. Blinkenberg J, Pahlavanyali S, Hetlevik Ø, Sandvik H, Hunskaar S. Correction to: General practitioners' and out-of-hours doctors' role as gatekeeper in emergency admissions to somatic hospitals in Norway: registry-based observational study. BMC Health Serv Res. 2020;20(1):876.
12. The Norwegian Directorate of Health, Norwegian national guidelines for the organization and operation of somatic emergency departments, 2014, Available at: https://www.helsedirektoratet.no/retningslinjer/kvalitetskrav-for-somatiske-akuttmottak/Faglige%20og%20organisatoriske%20kvalitetskrav%20for%20somatiske%20akuttmottak%20%E2%80%93%20Nasjonal%20faglig%20retningslinje.pdf/_/attachment/inline/aea8baff-94d2-44f5-b525-f6c1f518aed5:029310dc7ad46980ba0fe85bdd9887148d4206b1/Faglige%20og%20organisatoriske%20kvalitetskrav%20for%20somatiske%20akuttmottak%20%E2%80%93%20Nasjonal%20faglig%20retningslinje.pdf. [cited 25 September 2021]
13. Wen LS, Anderson PD, Stagelund S, Sullivan AF, Camargo CA. National survey of emergency departments in Denmark. Eur J Emerg Med. 2013;20(3):205-9.
14. Hohl CM, Zed PJ, Brubacher JR, Abu-Laban RB, Loewen PS, Purssell RA. Do emergency physicians attribute drug-related emergency department visits to medication-related problems? Ann Emerg Med. 2010;55(6):493-502.e4.
15. de Almeida SM, Romualdo A, de Abreu Ferraresi A, Zelezoglo GR, Marra AR, Edmond MB. Use of a trigger tool to detect adverse drug reactions in an emergency department. BMC Pharmacol Toxicol. 2017;18(1):71.
16. Lo Giudice I, Mocciaro E, Giardina C, Barbieri MA, Cicala G, Gioffrè-Florio M, et al. Characterization and preventability of adverse drug events as cause of emergency department visits: a prospective 1-year observational study. BMC Pharmacol Toxicol. 2019;20(1):21.
17. World Health Organization, Regional office for Europe, Acute care hospital discharges per 100, Available at https://gateway.euro.who.int/en/indicators/hfa_536-6020-acute-care-hospital-discharges-per-100/, [cited 25 November 2021].
18. Statistics Norway, Patients, discharges and bed-days at general hospitals, by sex, age and diagnosis 2018, Available at: https://www.ssb.no/en/statbank/table/10261/, [cited 25 November 2021].
19. Füchtbauer LM, Nørgaard B, Mogensen CB. Emergency department physicians spend only 25% of their working time on direct patient care. Dan Med J. 2013;60(1):A4558.
20. Richardson LC, Lehnbom EC, Baysari MT, Walter SR, Day RO, Westbrook JI. A time and motion study of junior doctor work patterns on the weekend: a potential contributor to the weekend effect? Intern Med J. 2016;46(7):819-25.
21. Galletta G, Løvstakken K. Emergency medicine in Norway: The road to specialty recognition. J Am Coll Emerg Physicians Open. 2020;1(5):790-4.

22. Fitzgerald RJ. Medication errors: the importance of an accurate drug history. Br J Clin Pharmacol. 2009;67(6):671-5.
23. Institute of healthcare improvement, Reconcile Medications at all transition points, Available at: http://www.ihi.org/knowledge/Pages/Changes/ReconcileMedicationsatAllTransitionPoints.aspx [cited 16 February 2022].
24. Collignon U, Oborne CA, Kostrzewski A. Pharmacy services to UK emergency departments: a descriptive study. Pharm World Sci. 2010;32(1):90-6.
25. Thomas MC, Acquisto NM, Shirk MB, Patanwala AE. A national survey of emergency pharmacy practice in the United States. Am J Health Syst Pharm. 2016;73(6):386-94.
26. Wanbon R, Lyder C, Villeneuve E, Shalansky S, Manuel L, Harding M. Clinical Pharmacy Services in Canadian Emergency Departments: A National Survey. Can J Hosp Pharm. 2015;68(3):191-201.
27. Welch SA, Graudins LV. (2007) Scope of Pharmacy Services to the Emergency Department, Journal of Pharmacy Practice and Research, 37: 27-29.
28. Vand S, Kjeldsen LJ, Kart T. Clinical pharmacy services are performed at several emergency wards in Denmark. *Scand J Trauma Resusc Emerg Med* 20, P9 (2012).
29. American College of Emergency Physicians. Policy Statement, approved April 2019. Crowding. Available at: https://www.acep.org/globalassets/new-pdfs/policystatements/ crowding.pdf. [cited 25 November 2021].
30. Christ M, Grossmann F, Winter D, Bingisser R, Platz E. Modern triage in the emergency department. Dtsch Arztebl Int. 2010;107(50):892-8.
31. Di Somma S, Paladino L, Vaughan L, Lalle I, Magrini L, Magnanti M. Overcrowding in emergency department: an international issue. Intern Emerg Med. 2015;10(2):171-5.
32. Schuur JD, Venkatesh AK. The growing role of emergency departments in hospital admissions. N Engl J Med. 2012;367(5):391-3.
33. Morley C, Unwin M, Peterson GM, Stankovich J, Kinsman L. Emergency department crowding: A systematic review of causes, consequences and solutions. PLoS One. 2018;13(8):e0203316.
34. Carter EJ, Pouch SM, Larson EL. The relationship between emergency department crowding and patient outcomes: a systematic review. J Nurs Scholarsh. 2014;46(2):106-15.
35. Asplin BR, Magid DJ, Rhodes KV, Solberg LI, Lurie N, Camargo CA. A conceptual model of emergency department crowding. Ann Emerg Med. 2003;42(2):173-80.
36. Mackway-Jones K MJ, Windle J. Emergency Triage Manchester Triage Group, 3rd Edition, John Wiley & Sons Inc, 2013, ISBN: 9781118299067.
37. Azeredo TR, Guedes HM, Rebelo de Almeida RA, Chianca TC, Martins JC. Efficacy of the Manchester Triage System: a systematic review. Int Emerg Nurs. 2015;23(2):47-52.
38. Hoot NR, Aronsky D. Systematic review of emergency department crowding: causes, effects, and solutions. Ann Emerg Med. 2008;52(2):126-36.
39. Mason S, Weber EJ, Coster J, Freeman J, Locker T. Time patients spend in the emergency department: England's 4-hour rule-a case of hitting the target but missing the point? Ann Emerg Med. 2012;59(5):341-9.
40. The Norwegian Directorate of Health. Pasientskader i Norge 2020. Målt med Global Trigger Tool [Patient injuries in Norway. Measured with Global Trigger Tool]. Norwegian report. Available at: https://www.helsedirektoratet.no/rapporter/pasientskader-i-norge-2020-malt-med-global-trigger-tool/Pasientskader%20i%20Norge%202020%20-%20m%C3%A5lt%20med%20Global%20Trigger%20Tool.pdf/_/attachment/inline/776effa4-08ec-4d17-89d1-495214e9762f:f36bcf550e31c0a87501e952ee5d805a7e5bb1f9/Pasientskader%20i%20Norge%202020%20-%20m%C3%A5lt%20med%20Global%20Trigger%20Tool.pdf [cited 20 February 2022].
41. Elliott RA, Camacho E, Jankovic D, Sculpher MJ, Faria R. Economic analysis of the prevalence and clinical and economic burden of medication error in England. BMJ Qual Saf. 2021;30(2):96-105.
42. Wester K, Jönsson AK, Spigset O, Druid H, Hägg S. Incidence of fatal adverse drug reactions: a population based study. Br J Clin Pharmacol. 2008;65(4):573-9.
43. World Health Organization, Transitions of Care: Technical Series on Safer Primary Care. Geneva; 2016. Licence: CC BY-NC-SA 3.0 IGO. Available at: https://apps.who.int/iris/bitstream/handle/10665/252272/9789241511599-eng.pdf [cited 16 February 2022].
44. World health Organization, Medication Safety in Transitions of Care. Geneva; 2019 (WHO/UHC/SDS/2019.9). Licence: CC BY-NC-SA 3.0 IGO. Available at: https://www.who.int/publications/i/item/WHO-UHC-SDS-2019.9 [cited 17 February 2022].

45. Kwan JL, Lo L, Sampson M, Shojania KG. Medication reconciliation during transitions of care as a patient safety strategy: a systematic review. Ann Intern Med. 2013;158(5 Pt 2):397-403.
46. do Nascimento Rocha HM, da Costa Farre AGM, de Santana Filho VJ. Adverse Events in Emergency Department Boarding: A Systematic Review. J Nurs Scholarsh. 2021;53(4):458-67.
47. Cornish PL, Knowles SR, Marchesano R, Tam V, Shadowitz S, Juurlink DN, et al. Unintended medication discrepancies at the time of hospital admission. Arch Intern Med. 2005;165(4):424-9.
48. Nebeker JR, Barach P, Samore MH. Clarifying adverse drug events: a clinician's guide to terminology, documentation, and reporting. Ann Intern Med. 2004;140(10):795-801.
49. Falconer N, Barras M, Martin J, Cottrell N. Defining and classifying terminology for medication harm: a call for consensus. Eur J Clin Pharmacol. 2019;75(2):137-45.
50. Ferner RE, Aronson JK. Clarification of terminology in medication errors: definitions and classification. Drug Saf. 2006;29(11):1011-22.
51. Aronson JK. Medication errors: definitions and classification. Br J Clin Pharmacol. 2009;67(6):599-604.
52. Bates DW, Boyle DL, Vander Vliet MB, Schneider J, Leape L. Relationship between medication errors and adverse drug events. J Gen Intern Med. 1995;10(4):199-205.
53. Ferner RE, Aronson JK. Preventability of drug-related harms - part I: a systematic review. Drug Saf. 2010;33(11):985-94.
54. Aronson JK, Ferner RE. Clarification of terminology in drug safety. Drug Saf. 2005;28(10):851-70.
55. Uppsala Monitoring Centre, Glossary of Pharmacovigilance team, Available at: https://www.who-umc.org/global-pharmacovigilance/publications/glossary/.[cited 5 July 2021]
56. Hepler CD, Strand LM. Opportunities and responsibilities in pharmaceutical care. Am J Hosp Pharm. 1990;47(3):533-43.
57. Pharmaceutical Care Network Europe Association, 2003-2020, The PCNE Classification V 9.1, Available at: https://www.pcne.org/upload/files/417_PCNE_classification_V9-1_final.pdf, [cited 10 February 2022].
58. Ruths S, Viktil KK, Blix HS. [Classification of drug-related problems]. Tidsskr Nor Laegeforen. 2007;127(23):3073-6.
59. Classen DC, Pestotnik SL, Evans RS, Lloyd JF, Burke JP. Adverse drug events in hospitalized patients. Excess length of stay, extra costs, and attributable mortality. JAMA. 1997;277(4):301-6.
60. Krähenbühl-Melcher A, Schlienger R, Lampert M, Haschke M, Drewe J, Krähenbühl S. Drug-related problems in hospitals: a review of the recent literature. Drug Saf. 2007;30(5):379-407.
61. Laatikainen O, Sneck S, Turpeinen M. Medication-related adverse events in health care-what have we learned? A narrative overview of the current knowledge. Eur J Clin Pharmacol. 2022;78(2):159-70.
62. Alhawassi TM, Krass I, Bajorek BV, Pont LG. A systematic review of the prevalence and risk factors for adverse drug reactions in the elderly in the acute care setting. Clin Interv Aging. 2014;9:2079-86.
63. Ayalew MB, Tegegn HG, Abdela OA. Drug Related Hospital Admissions; A Systematic Review of the Recent Literatures. Bull Emerg Trauma. 2019;7(4):339-46.
64. Suggett E, Marriott J. Risk Factors Associated with the Requirement for Pharmaceutical Intervention in the Hospital Setting: A Systematic Review of the Literature. Drugs Real World Outcomes. 2016;3(3):241-63.
65. Mihajlovic S, Gauthier J, MacDonald E. Patient Characteristics Associated with Adverse Drug Events in Hospital: An Overview of Reviews. Can J Hosp Pharm. 2016;69(4):294-300.
66. Choi YJ, Kim H. Effect of pharmacy-led medication reconciliation in emergency departments: A systematic review and meta-analysis. J Clin Pharm Ther. 2019;44(6):932-45.
67. Caglar S, Henneman PL, Blank FS, Smithline HA, Henneman EA. Emergency department medication lists are not accurate. J Emerg Med. 2011;40(6):613-6.
68. Tong EY, Roman CP, Mitra B, Yip GS, Gibbs H, Newnham HH, et al. Reducing medication errors in hospital discharge summaries: a randomised controlled trial. Med J Aust. 2017;206(1):36-9.
69. De Oliveira GS, Castro-Alves LJ, Kendall MC, McCarthy R. Effectiveness of Pharmacist Intervention to Reduce Medication Errors and Health-Care Resources Utilization After Transitions of Care: A Meta-analysis of Randomized Controlled Trials. J Patient Saf. 2021;17(5):375-80.
70. Forster AJ, Murff HJ, Peterson JF, Gandhi TK, Bates DW. The incidence and severity of adverse events affecting patients after discharge from the hospital. Ann Intern Med. 2003;138(3):161-7.
71. Kahn JM, Angus DC. Going home on the right medications: prescription errors and transitions of care. JAMA. 2011;306(8):878-9.
72. Nilsson N LM, Lao Y , Wendelbo K , Gløersen G , Mowé M , Blix HS , Viktil KK. Medication discrepancies revealed by medication reconciliation and their potential short-term and long-term effects: a Norwegian multicentre study carried out on internal medicine wards European Journal of Hospital Pharmacy 2015; 22: 298-303.

73. Belda-Rustarazo S, Cantero-Hinojosa J, Salmeron-García A, González-García L, Cabeza-Barrera J, Galvez J. Medication reconciliation at admission and discharge: an analysis of prevalence and associated risk factors. Int J Clin Pract. 2015;69(11):1268-74.
74. Santell JP. Reconciliation failures lead to medication errors. Jt Comm J Qual Patient Saf. 2006;32(4):225-9.
75. Quélennec B, Beretz L, Paya D, Blicklé JF, Gourieux B, Andrès E, et al. Potential clinical impact of medication discrepancies at hospital admission. Eur J Intern Med. 2013;24(6):530-5.
76. Unroe KT, Pfeiffenberger T, Riegelhaupt S, Jastrzembski J, Lokhnygina Y, Colón-Emeric C. Inpatient medication reconciliation at admission and discharge: A retrospective cohort study of age and other risk factors for medication discrepancies. Am J Geriatr Pharmacother. 2010;8(2):115-26.
77. Crook M, Ajdukovic M, Angley C, Soulsby N, Doecke C, Stupans I, et al. Eliciting comprehensive medication histories in the emergency department: the role of the pharmacist. Pharm Pract (Granada). 2007;5(2):78-84.
78. Zed PJ, Abu-Laban RB, Balen RM, Loewen PS, Hohl CM, Brubacher JR, et al. Incidence, severity and preventability of medication-related visits to the emergency department: a prospective study. CMAJ. 2008;178(12):1563-9.
79. McLachlan CY, Yi M, Ling A, Jardine DL. Adverse drug events are a major cause of acute medical admission. Intern Med J. 2014;44(7):633-8.
80. Roulet L, Ballereau F, Hardouin JB, Chiffoleau A, Moret L, Potel G, et al. Assessment of adverse drug event recognition by emergency physicians in a French teaching hospital. Emerg Med J. 2013;30(1):63-7.
81. Wu C, Bell CM, Wodchis WP. Incidence and economic burden of adverse drug reactions among elderly patients in Ontario emergency departments: a retrospective study. Drug Saf. 2012;35(9):769-81.
82. Convertino I, Salvadori S, Pecori A, Galiulo MT, Ferraro S, Parrilli M, et al. Potential Direct Costs of Adverse Drug Events and Possible Cost Savings Achievable by their Prevention in Tuscany, Italy: A Model-Based Analysis. Drug Saf. 2019;42(3):427-44.
83. Perrone V, Conti V, Venegoni M, Scotto S, Degli Esposti L, Sangiorgi D, et al. Seriousness, preventability, and burden impact of reported adverse drug reactions in Lombardy emergency departments: a retrospective 2-year characterization. Clinicoecon Outcomes Res. 2014;6:505-14.
84. Ahern F, Sahm LJ, Lynch D, McCarthy S. Determining the frequency and preventability of adverse drug reaction-related admissions to an Irish University Hospital: a cross-sectional study. Emerg Med J. 2014;31(1):24-9.
85. Nickel CH, Ruedinger JM, Messmer AS, Maile S, Peng A, Bodmer M, et al. Drug-related emergency department visits by elderly patients presenting with non-specific complaints. Scand J Trauma Resusc Emerg Med. 2013;21:15.
86. Gustafsson M, Sjölander M, Pfister B, Jonsson J, Schneede J, Lövheim H. Drug-related hospital admissions among old people with dementia. Eur J Clin Pharmacol. 2016;72(9):1143-53.
87. Alghamdy MS, Randhawa MA, Al-Wahhas MH, Al-Jumaan MA. Admissions for drug-related problems at the Emergency Department of a University Hospital in the Kingdom of Saudi Arabia. J Family Community Med. 2015;22(1):44-8.
88. Jatau AI, Aung MM, Kamauzaman TH, Rahman AF. Prevalence of Drug-Related Emergency Department Visits at a Teaching Hospital in Malaysia. Drugs Real World Outcomes. 2015;2(4):387-95.
89. Al-Arifi M, Abu-Hashem H, Al-Meziny M, Said R, Aljadhey H. Emergency department visits and admissions due to drug related problems at Riyadh military hospital (RMH), Saudi Arabia. Saudi Pharm J. 2014;22(1):17-25.
90. Parameswaran Nair N, Chalmers L, Peterson GM, Bereznicki BJ, Curtain CM, Bereznicki LR. Prospective identification versus administrative coding of adverse drug reaction-related hospitalizations in the elderly: A comparative analysis. Pharmacoepidemiol Drug Saf. 2018;27(11):1281-5.
91. Lea M, Mowe M, Mathiesen L, Kvernrød K, Skovlund E, Molden E. Prevalence and risk factors of drug-related hospitalizations in multimorbid patients admitted to an internal medicine ward. PLoS One. 2019;14(7):e0220071.
92. Wang-Hansen MS, Wyller TB, Hvidsten LT, Kersten H. Can screening tools for potentially inappropriate prescriptions in older adults prevent serious adverse drug events? Eur J Clin Pharmacol. 2019;75(5):627-37.
93. Hellström LM, Bondesson A, Höglund P, Midlöv P, Holmdahl L, Rickhag E, et al. Impact of the Lund Integrated Medicines Management (LIMM) model on medication appropriateness and drug-related hospital revisits. Eur J Clin Pharmacol. 2011;67(7):741-52.

94. Gustafsson M, Sjölander M, Pfister B, Jonsson J, Schneede J, Lövheim H. Pharmacist participation in hospital ward teams and hospital readmission rates among people with dementia: a randomized controlled trial. Eur J Clin Pharmacol. 2017;73(7):827-35.
95. Warlé-van Herwaarden MF, Kramers C, Sturkenboom MC, van den Bemt PM, De Smet PA, Force DH-WT. Targeting outpatient drug safety: recommendations of the Dutch HARM-Wrestling Task Force. Drug Saf. 2012;35(3):245-59.
96. Warlé-van Herwaarden MF, Valkhoff VE, Herings RM, Engelkes M, van Blijderveen JC, Rodenburg EM, et al. Quick assessment of drug-related admissions over time (QUADRAT study). Pharmacoepidemiol Drug Saf. 2015;24(5):495-503.
97. Zerah L, Henrard S, Thevelin S, Feller M, Meyer-Masseti C, Knol W, et al. Performance of a trigger tool for detecting drug-related hospital admissions in older people: analysis from the OPERAM trial. Age Ageing. 2022;51(1).
98. Roulet L BF, Hardouin JB, Chiffoleau A, Potel G, Asseray N. Adverse drug event nonrecognition in emergency departments: an exploratory study on factors related to patients and drugs. *J Emerg Med* . ; 2014.
99. Bénard-Laribière A, Miremont-Salamé G, Pérault-Pochat MC, Noize P, Haramburu F, centres ESGobotFnop. Incidence of hospital admissions due to adverse drug reactions in France: the EMIR study. Fundam Clin Pharmacol. 2015;29(1):106-11.
100. Institute for Healthcare Improvements, Medication Reconciliation to Prevent Adverse Drug Events (2018) Available at: http://www.ihi.org/Topics/ADEsMedicationReconciliation/Pages/default.aspx [cited 10 February 2022].
101. World Health Organization, High 5's: Standard Operating Procedures (2014), Available at: https://cdn.who.int/media/docs/default-source/integrated-health-services-(ihs)/psf/high5s/h5s-sop.pdf?sfvrsn=e3e53c9_4&ua=1 [cited 10 February 2022].
102. Penm J, Vaillancourt R, Pouliot A. Defining and identifying concepts of medication reconciliation: An international pharmacy perspective. Res Social Adm Pharm. 2019;15(6):632-40.
103. Mekonnen AB, McLachlan AJ, Brien JA. Effectiveness of pharmacist-led medication reconciliation programmes on clinical outcomes at hospital transitions: a systematic review and meta-analysis. BMJ Open. 2016;6(2):e010003.
104. Mueller SK, Sponsler KC, Kripalani S, Schnipper JL. Hospital-based medication reconciliation practices: a systematic review. Arch Intern Med. 2012;172(14):1057-69.
105. Greenwald JL, Halasyamani LK, Greene J, LaCivita C, Stucky E, Benjamin B, et al. Making inpatient medication reconciliation patient centered, clinically relevant, and implementable: a consensus statement on key principles and necessary first steps. Jt Comm J Qual Patient Saf. 2010;36(11):504-13, 481.
106. Mekonnen AB, McLachlan AJ, Brien JA. Pharmacy-led medication reconciliation programmes at hospital transitions: a systematic review and meta-analysis. J Clin Pharm Ther. 2016;41(2):128-44.
107. Henriksen JP, Noerregaard S, Buck TC, Aagaard L. Medication histories by pharmacy technicians and physicians in an emergency department. Int J Clin Pharm. 2015;37(6):1121-7.
108. Aag T, Garcia BH, Viktil KK. Should nurses or clinical pharmacists perform medication reconciliation? A randomized controlled trial. Eur J Clin Pharmacol. 2014;70(11):1325-32.
109. Griese-Mammen N, Hersberger KE, Messerli M, Leikola S, Horvat N, van Mil JWF, et al. PCNE definition of medication review: reaching agreement. Int J Clin Pharm. 2018;40(5):1199-208.
110. Holte HH, Hafstad E, Vist GE. Overview of Reviews on Effect of Medical Reconciliation. 2015.
111. 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.
112. Phatak A, Prusi R, Ward B, Hansen LO, Williams MV, Vetter E, et al. Impact of pharmacist involvement in the transitional care of high-risk patients through medication reconciliation, medication education, and postdischarge call-backs (IPITCH Study). J Hosp Med. 2016;11(1):39-44.
113. Hawes EM, Maxwell WD, White SF, Mangun J, Lin FC. Impact of an outpatient pharmacist intervention on medication discrepancies and health care resource utilization in posthospitalization care transitions. J Prim Care Community Health. 2014;5(1):14-8.
114. Scullin C, Scott MG, Hogg A, McElnay JC. An innovative approach to integrated medicines management. J Eval Clin Pract. 2007;13(5):781-8.
115. Farris KB, Carter BL, Xu Y, Dawson JD, Shelsky C, Weetman DB, et al. Effect of a care transition intervention by pharmacists: an RCT. BMC Health Serv Res. 2014;14:406.

116. Lisby M, Thomsen A, Nielsen LP, Lyhne NM, Breum-Leer C, Fredberg U, et al. The effect of systematic medication review in elderly patients admitted to an acute ward of internal medicine. Basic Clin Pharmacol Toxicol. 2010;106(5):422-7.
117. Bladh L, Ottosson E, Karlsson J, Klintberg L, Wallerstedt SM. Effects of a clinical pharmacist service on health-related quality of life and prescribing of drugs: a randomised controlled trial. BMJ Qual Saf. 2011;20(9):738-46.
118. Christensen M, Lundh A. Medication review in hospitalised patients to reduce morbidity and mortality. Cochrane Database Syst Rev. 2016;2:CD008986.
119. Huiskes VJ, Burger DM, van den Ende CH, van den Bemt BJ. Effectiveness of medication review: a systematic review and meta-analysis of randomized controlled trials. BMC Fam Pract. 2017;18(1):5.
120. Meid AD, Lampert A, Burnett A, Seidling HM, Haefeli WE. The impact of pharmaceutical care interventions for medication underuse in older people: a systematic review and meta-analysis. Br J Clin Pharmacol. 2015;80(4):768-76.
121. Patterson SM, Cadogan CA, Kerse N, Cardwell CR, Bradley MC, Ryan C, et al. Interventions to improve the appropriate use of polypharmacy for older people. Cochrane Database Syst Rev. 2014(10):CD008165.
122. Graabaek T, Kjeldsen LJ. Medication reviews by clinical pharmacists at hospitals lead to improved patient outcomes: a systematic review. Basic Clin Pharmacol Toxicol. 2013;112(6):359-73.
123. Renaudin P, Boyer L, Esteve MA, Bertault-Peres P, Auquier P, Honore S. Do pharmacist-led medication reviews in hospitals help reduce hospital readmissions? A systematic review and meta-analysis. Br J Clin Pharmacol. 2016;82(6):1660-73.
124. Hohl CM, Wickham ME, Sobolev B, Perry JJ, Sivilotti ML, Garrison S, et al. The effect of early in-hospital medication review on health outcomes: a systematic review. Br J Clin Pharmacol. 2015;80(1):51-61.
125. Verdoorn S, Kwint HF, Faber A, Gussekloo J, Bouvy ML. Majority of drug-related problems identified during medication review are not associated with STOPP/START criteria. Eur J Clin Pharmacol. 2015;71(10):1255-62.
126. Beers MH. Explicit criteria for determining potentially inappropriate medication use by the elderly. An update. Arch Intern Med. 1997;157(14):1531-6.
127. Panel BtAGSBCUE. American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc. 2019;67(4):674-94.
128. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age Ageing. 2015;44(2):213-8.
129. Gallagher P, Ryan C, Byrne S, Kennedy J, O'Mahony D. STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. Int J Clin Pharmacol Ther. 2008;46(2):72-83.
130. Delgado-Silveira E, Albiñana-Pérez MS, Muñoz-García M, García-Mina Freire M, Fernandez-Villalba EM, Group C. Pharmacist comprehensive review of treatment compared with STOPP-START criteria to detect potentially inappropriate prescription in older complex patients. Eur J Hosp Pharm. 2018;25(1):16-20.
131. Gallagher PF, O'Connor MN, O'Mahony D. Prevention of potentially inappropriate prescribing for elderly patients: a randomized controlled trial using STOPP/START criteria. Clin Pharmacol Ther. 2011;89(6):845-54.
132. Scott M, Scullin C, Hogg A, Fleming G, McElnay J. Integrated medicines management to medicines optimisation in Northern Ireland (2000–2014): a review European Journal of Hospital Pharmacy 2015; 22: 222-228.
133. Roman C, Edwards G, Dooley M, Mitra B. Roles of the emergency medicine pharmacist: A systematic review. Am J Health Syst Pharm. 2018;75(11):796-806.
134. Roman CP, Dooley MJ, Mitra B. (2019), Emergency medicine pharmacy practice in Australia: a national survey. J Pharm Pract Res, 49: 439-446.
135. Morgan SR, Acquisto NM, Coralic Z, Basalyga V, Campbell M, Kelly JJ, et al. Clinical pharmacy services in the emergency department. Am J Emerg Med. 2018;36(10):1727-32.
136. K R. Midtnorsk storsatsing på klinisk farmasi, 2021. Norsk Farmaceutisk Tidsskrift. Available at: Midtnorsk storsatsing på klinisk farmasi | Farmatid [cited 21 February 2022].

137. Garcia B, Halvorsen K. Klinisk praksis – en veletablert undervisningsform I tromsø, 2020. Norsk Farmaceutisk Tidsskrift. Available at: Klinisk praksis – en veletablert undervisningsform i Tromsø | Farmatid [cited 21 February 2022].
138. Major A. IMM-modellen til Norge [Norwegian article], Norsk Farmaceutisk Tidsskrift. 2012;1:12-4, Available at: https://www.farmatid.no/vitenskap-og-fag/faglige-artikler/article-973 [cited 21 April 2022].

139. Vesela R, Elenjord R, Lehnbom EC, Ofstad EH, Johnsgård T, Zahl-Holmstad B, et al. Integrating the clinical pharmacist into the emergency department interdisciplinary team: a study protocol for a multicentre trial applying a non-randomised stepped-wedge study design. BMJ Open. 2021;11(11):e049645.
140. Stasiak P, Afilalo M, Castelino T, Xue X, Colacone A, Soucy N, et al. Detection and correction of prescription errors by an emergency department pharmacy service. CJEM. 2014;16(3):193-206.
141. Brown JN, Barnes CL, Beasley B, Cisneros R, Pound M, Herring C. Effect of pharmacists on medication errors in an emergency department. Am J Health Syst Pharm. 2008;65(4):330-3.
142. Rothschild JM, Churchill W, Erickson A, Munz K, Schuur JD, Salzberg CA, et al. Medication errors recovered by emergency department pharmacists. Ann Emerg Med. 2010;55(6):513-21.
143. Patanwala AE, Sanders AB, Thomas MC, Acquisto NM, Weant KA, Baker SN, et al. A prospective, multicenter study of pharmacist activities resulting in medication error interception in the emergency department. Ann Emerg Med. 2012;59(5):369-73.
144. Marconi GP, Claudius I. Impact of an emergency department pharmacy on medication omission and delay. Pediatr Emerg Care. 2012;28(1):30-3.
145. Hatch J, Becker, T., Fish, J. T. Difference between Pharmacist-Obtained and Physician-Obtained Medication Histories in the Intensive Care Unit. *Hospital Pharmacy*. 2011;*46* (4):262–8.
146. Reeder TA, Mutnick A. Pharmacist- versus physician-obtained medication histories. Am J Health Syst Pharm. 2008;65(9):857-60.
147. Hayes BD, Donovan JL, Smith BS, Hartman CA. Pharmacist-conducted medication reconciliation in an emergency department. Am J Health Syst Pharm. 2007;64(16):1720-3.
148. Carter MK, Allin DM, Scott LA, Grauer D. Pharmacist-acquired medication histories in a university hospital emergency department. Am J Health Syst Pharm. 2006;63(24):2500-3.
149. Mogensen CB, Thisted AR, Olsen I. Medication problems are frequent and often serious in a Danish emergency department and may be discovered by clinical pharmacists. Dan Med J. 2012;59(11):A4532.
150. Shaw PB, Delate T, Lyman A, Adams J, Kreutz H, Sanchez JK, et al. Impact of a Clinical Pharmacy Specialist in an Emergency Department for Seniors. Ann Emerg Med. 2016;67(2):177-88.
151. Awad N, Cocchio C, Bridgeman P. Clinical Pharmacists Are Essential to the Care of Patients in the Emergency Department. Ann Emerg Med. 2016;68(3):392-3.
152. The Norwegian Directorate of Health, Final report The Norwegian Patient Safety Campaigne, In safe hands 2011-2013 [Norwegian report], Available at: https://omsorgsforskning.brage.unit.no/omsorgsforskning-xmlui/bitstream/handle/11250/2445319/Sluttrapport%20for%20pasientsikkerhetskampanjen%202011-2013.pdf?sequence=1&isAllowed=y , [cited 6 April 2022].
153. Deloitte, Final evaluation report of The Norwegian patient safety program "In safe hands 24-7", 2019, Available at: https://www.itryggehender24-7.no/om-i-trygge-hender-24-7/_/attachment/download/3303e001-4efe-47be-85bc-505b1d47789c:380d3bdfbcfed7887b853cf160d755c78856c6b9/Sluttrapport_Pasientsikkerhetsprogrammet.pdf, [cited 6 April 2022].
154. The Norwegian Directorate of Health, 2019, National action plan for patient safety and quality improvement (2019-2023), Available at: https://www.helsedirektoratet.no/veiledere/ledelse-og-kvalitetsforbedring-i-helse-og-omsorgstjenesten/Nasjonal%20handlingsplan%20for%20pasientsikkerhet%20og%20kvalitetsforbedring%202019-2023.pdf/_/attachment/inline/79c83e08-c6ef-4adc-a29a-4de1fc1fc0ef:94a7c49bf505dd36d59d9bf3de16769bad6c32d5/Nasjonal%20handlingsplan%20for%20pasientsikkerhet%20og%20kvalitetsforbedring%202019-2023.pdf [Norwegian action plan], [cited 6 April 2022].
155. Remen VM, Grimsmo A. Closing information gaps with shared electronic patient summaries: how much will it matter? Int J Med Inform. 2011;80(11):775-81.
156. The Norwegian health network. What is e-prescription? 2019, Available at: https://helsenorge.no/other-languages/english/what-is-e-prescription?redirect=false. [cited 6 April 2022]
157. Warth LL. (2016) Innføring av kjernejournal i de fire helseregionene: Faktorer som fremmer og hemmer innføring av kjernejournal i spesialisthelsetjenesten fra et prosjektlederperspektiv, Nasjonalt senter for e-helseforskning, [Norwegian report], Available at: Innføring og bruk av kjernejournal - Ehealthresearch.no (NO), [cited 6 April 2022].
158. Wanbon R, Lyder C, Villeneuve E, Shalansky S, Manuel L, Harding M. Medication Reconciliation Practices in Canadian Emergency Departments: A National Survey. Can J Hosp Pharm. 2015;68(3):202-9.
159. Walker PC, Bernstein SJ, Jones JN, Piersma J, Kim HW, Regal RE, et al. Impact of a pharmacist-facilitated hospital discharge program: a quasi-experimental study. Arch Intern Med. 2009;169(21):2003-10.

160. Field TS, Gurwitz JH, Harrold LR, Rothschild J, DeBellis KR, Seger AC, et al. Risk factors for adverse drug events among older adults in the ambulatory setting. J Am Geriatr Soc. 2004;52(8):1349-54.
161. Kripalani S, Roumie CL, Dalal AK, Cawthon C, Businger A, Eden SK, et al. Effect of a pharmacist intervention on clinically important medication errors after hospital discharge: a randomized trial. Ann Intern Med. 2012;157(1):1-10.
162. Shah M, Norwood CA, Farias S, Ibrahim S, Chong PH, Fogelfeld L. Diabetes transitional care from inpatient to outpatient setting: pharmacist discharge counseling. J Pharm Pract. 2013;26(2):120-4.
163. Lopetegui M, Yen PY, Lai A, Jeffries J, Embi P, Payne P. Time motion studies in healthcare: what are we talking about? J Biomed Inform. 2014;49:292-9.
164. Westbrook JI, Woods A, Rob MI, Dunsmuir WT, Day RO. Association of interruptions with an increased risk and severity of medication administration errors. Arch Intern Med. 2010;170(8):683-90.
165. Hefter Y, Madahar P, Eisen LA, Gong MN. A Time-Motion Study of ICU Workflow and the Impact of Strain. Crit Care Med. 2016;44(8):1482-9.
166. Westbrook JI, Ampt A, Kearney L, Rob MI. All in a day's work: an observational study to quantify how and with whom doctors on hospital wards spend their time. Med J Aust. 2008;188(9):506-9.
167. Westbrook JI, Ampt A. Design, application and testing of the Work Observation Method by Activity Timing (WOMBAT) to measure clinicians' patterns of work and communication. Int J Med Inform. 2009;78 Suppl 1:S25-33.
168. Weigl M, Müller A, Zupanc A, Glaser J, Angerer P. Hospital doctors' workflow interruptions and activities: an observation study. BMJ Qual Saf. 2011;20(6):491-7.
169. Westbrook JI, Raban MZ, Walter SR, Douglas H. Task errors by emergency physicians are associated with interruptions, multitasking, fatigue and working memory capacity: a prospective, direct observation study. BMJ Qual Saf. 2018;27(8):655-63.
170. Berg LM, Ehrenberg A, Florin J, Ostergren J, Göransson KE. An observational study of activities and multitasking performed by clinicians in two Swedish emergency departments. Eur J Emerg Med. 2012;19(4):246-51.
171. Mache S, Vitzthum K, Klapp BF, Groneberg DA. Doctors' working conditions in emergency care units in Germany: a real-time assessment. Emerg Med J. 2012;29(12):e1.
172. Diakonhjemmet Hospital, The Emergency Department (Akuttmottaket) Available at: https://diakonhjemmetsykehus.no/avdelinger/klinikk-for-medisin/akuttmottaket#les-mer-om-akuttmottaket (in Norwegian), [cited 10 February 2022].
173. The Norwegian Patient Registry (NPR), [Norwegian webpage] Available at: https://www.helsedirektoratet.no/tema/statistikk-registre-og-rapporter/helsedata-og-helseregistre/norsk-pasientregister-npr [cited 24 February 2022].
174. WHO. causality assessment.pdf [Internet].. Available at: https://www.who.int/medicines/areas/quality_safety/safety_efficacy/WHOcausality_assessment.pdf. [cited 20 January 2021]
175. Hallas J, Harvald B, Gram LF, Grodum E, Brøsen K, Haghfelt T, et al. Drug related hospital admissions: the role of definitions and intensity of data collection, and the possibility of prevention. J Intern Med. 1990;228(2):83-90.
176. Lehnbom EC, Li L, Prgomet M, Lam WY, Westbrook JI. Little Things Matter: A Time and Motion Study of Pharmacists' Activities in a Paediatric Hospital. Stud Health Technol Inform. 2016;227:80-6.
177. Schofield B, Cresswel K, Westbrook J, Slee A, Girling A, Shah S, et al. The impact of electronic prescribing systems on pharmacists' time and workflow: protocol for a time-and-motion study in English NHS hospitals. BMJ Open. 2015;5(10):e008785.
178. Ballermann MA, Shaw NT, Mayes DC, Gibney RT, Westbrook JI. Validation of the Work Observation Method By Activity Timing (WOMBAT) method of conducting time-motion observations in critical care settings: an observational study. BMC Med Inform Decis Mak. 2011;11:32.
179. Walter SR, Dunsmuir WTM, Westbrook JI. Inter-observer agreement and reliability assessment for observational studies of clinical work. J Biomed Inform. 2019;100:103317.
180. Janson H, Olsson, U. A Measure of Agreement for Interval or Nominal Multivariate Observations. *Educational and Psychological Measurement*. 2001;*61* (2):277–89.
181. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977;33(1):159-74.
182. World Health Organization . (2015). International statistical classification of diseases and related health problems, 10th revision, Fifth edition, 2016. World Health Organization.

183. The Directorate of e-health, FinnKode, Last revision 01.01.2021, Available at: https://finnkode.ehelse.no/2021/#icd10/0/0/0/-1 [cited 24 February 2022].
184. World Health Organization, Anatomical Therapeutic Chemical (ATC) Classification, Available at: https://www.who.int/tools/atc-ddd-toolkit/atc-classification, [cited 26 February 2021].
185. WHO. Collaborating Centre for Drug Statistics Methodology, ATC/DDD Index 2021, [cited 1 September 2021], Available at: https://www.whocc.no/atc_ddd_index/.
186. Welch S, Finckh A. Prescribing errors in emergency department medication history taking: will electronic medication management systems help?. J Pharm Pract Res, (2019) 49: 400-402.
187. OECD. (2019), "Average length of stay in hospitals", in Health at a Glance 2019: OECD Indicators, OECD Publishing, Paris. Available at: https://www.oecd-ilibrary.org/docserver/0d8bb30a-en.pdf?expires=1651141741&id=id&accname=guest&checksum=20731B1BD832B37DB1156C9F0C107CB4 [cited 28 April 2022].
188. Mann CJ. Observational research methods. Research design II: cohort, cross sectional, and case-control studies. Emerg Med J. 2003;20(1):54-60.
189. Aalen O, Frigessi A, Moger T, Scheel I, Skovlund E, Veierød M. Statistiske metoder i medisin og helsefag. [Statistical methods in medicine and health.] Norwegian. Chapter 9-10. 1 ed: Gyldendal Norsk Forlag AS; 2006.
190. Agbabiaka TB, Savović J, Ernst E. Methods for causality assessment of adverse drug reactions: a systematic review. Drug Saf. 2008;31(1):21-37.
191. Behera SK, Das S, Xavier AS, Velupula S, Sandhiya S. Comparison of different methods for causality assessment of adverse drug reactions. Int J Clin Pharm. 2018;40(4):903-10.
192. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30(2):239-45.
193. Théophile H, Arimone Y, Miremont-Salamé G, Moore N, Fourrier-Réglat A, Haramburu F, et al. Comparison of three methods (consensual expert judgement, algorithmic and probabilistic approaches) of causality assessment of adverse drug reactions: an assessment using reports made to a French pharmacovigilance centre. Drug Saf. 2010;33(11):1045-54.
194. Mannion R, Thompson C. Systematic biases in group decision-making: implications for patient safety. Int J Qual Health Care. 2014;26(6):606-12.
195. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M, et al. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ. 2008;337:a1655.
196. Santolaya-Perrín R, Calderón-Hernanz B, Jiménez-Díaz G, Galán-Ramos N, Moreno-Carvajal MT, Rodríguez-Camacho JM, et al. The efficacy of a medication review programme conducted in an emergency department. Int J Clin Pharm. 2019;41(3):757-66.
197. Kitchen SA, McGrail K, Wickham ME, Law MR, Hohl CM. Emergency department-based medication review on outpatient health services utilization: interrupted time series. BMC Health Serv Res. 2020;20(1):254.
198. Lea M, Mowé M, Molden E, Kvernrød K, Skovlund E, Mathiesen L. Effect of medicines management versus standard care on readmissions in multimorbid patients: a randomised controlled trial. BMJ Open. 2020;10(12):e041558.
199. Buck TC, Brandstrup L, Brandslund I, Kampmann JP. The effects of introducing a clinical pharmacist on orthopaedic wards in Denmark. Pharm World Sci. 2007;29(1):12-8.
200. Lisby M, Bonnerup DK, Brock B, Gregersen PA, Jensen J, Larsen ML, et al. Medication Review and Patient Outcomes in an Orthopedic Department: A Randomized Controlled Study. J Patient Saf. 2018;14(2):74-81.
201. Skivington K, Matthews L, Simpson SA, Craig P, Baird J, Blazeby JM, et al. A new framework for developing and evaluating complex interventions: update of Medical Research Council guidance. BMJ. 2021;374:n2061.
202. Holland R, Desborough J, Goodyer L, Hall S, Wright D, Loke YK. Does pharmacist-led medication review help to reduce hospital admissions and deaths in older people? A systematic review and meta-analysis. Br J Clin Pharmacol. 2008;65(3):303-16.
203. Beuscart JB, Pont LG, Thevelin S, Boland B, Dalleur O, Rutjes AWS, et al. A systematic review of the outcomes reported in trials of medication review in older patients: the need for a core outcome set. Br J Clin Pharmacol. 2017;83(5):942-52.
204. Beuscart JB, Knol W, Cullinan S, Schneider C, Dalleur O, Boland B, et al. International core outcome set for clinical trials of medication review in multi-morbid older patients with polypharmacy. BMC Med. 2018;16(1):21.

205. Asmar R, Hosseini H. Endpoints in clinical trials: does evidence only originate from 'hard' or mortality endpoints? J Hypertens Suppl. 2009;27(2):S45-50.
206. Baker DW, Chassin MR. Holding Providers Accountable for Health Care Outcomes. Ann Intern Med. 2018;168(7):527.
207. The Norwegian Directorate of Health, National quality indicator set, Propability for readmission of elderly patients within 30 days of discharge. Published 07.03.19. Available at: https://www.helsedirektoratet.no/statistikk/kvalitetsindikatorer/kommunale-helse-og-omsorgstjenester/reinnleggelse-blant-eldre-30-dager-etter-utskrivning-per-kommune/13-10391-12%20Re-innleggelse%20av%20eldre%20per%20kommune.pdf/_/attachment/inline/617f1211-5314-4fbc-b6b2-0105502e7518:22f7695ec706c8fd10799ca73047af98965c25f5/13-10391-12%20Re-innleggelse%20av%20eldre%20per%20kommune.pdf [cited 5 March 2022].
208. Sundhedsstyrelsen. Genindlæggelser af ældre i Danmark 2008. København: Sundhedsstyrelsen. Available at: https://www.sst.dk/~/media/B26892B0EF824EDF9C1EA42E29CEF072.ashx [cited 5 March 2022].

209. Fischer C, Anema HA, Klazinga NS. The validity of indicators for assessing quality of care: a review of the European literature on hospital readmission rate. Eur J Public Health. 2012;22(4):484-91.
210. Kristoffersen DT, Hansen TM, Tomic O, Helgeland J. Kvalitetsindikatoren 30 dagers reinnleggelse etter sykehusopphold. Resultater for helseforetak og kommuner 2016. The quality indicator 30-day readmission after hospitalisation – results for Norwegian hospital trusts and municipalities 2016. Oslo: Folkehelseinstituttet, 2017. Available at: https://www.fhi.no/globalassets/dokumenterfiler/rapporter/2017/30-dagers-reinnleggelse-etter-sykehusopphold-resultater-2016.pdf [cited 5 March 2022].
211. Norwegian Board of Health Supervision. Informasjonen var mangelfull og kom ofte for sent. Oppsummering av landsomfattende tilsyn i 2015 med samhandling om utskrivning av pasienter fra spesialisthelsetjenesten til kommunen. 2016. 1/2016. [Norwegian report] Available at: https://www.helsetilsynet.no/publikasjoner/rapport-fra-helsetilsynet/2016/informasjonen-var-mangelfull-og-kom-ofte-for-sent-oppsummering-av-landsomfattande-tilsyn-i-2015/ [cited 5 March 2022].
212. Clarke A. Readmission to hospital: a measure of quality or outcome? Qual Saf Health Care. 2004 Feb;13(1):10-1.
213. Clarke A, Rosen R. Length of stay. How short should hospital care be? Eur J Public Health. 2001 Jun;11(2):166-70.
214. Stenson BA, Antkowiak PS, Balaji L, Grossestreuer AV, Joseph JW, Chiu DT, et al. Analysis of time-to-disposition intervals during early and late parts of an emergency department shift. Am J Emerg Med. 2021;50:477-80.
215. Baek H, Cho M, Kim S, Hwang H, Song M, Yoo S. Analysis of length of hospital stay using electronic health records: A statistical and data mining approach. PLoS One. 2018;13(4):e0195901.
216. Khosravizadeh O, Vatankhah S, Bastani P, Kalhor R, Alirezaei S, Doosty F. Factors affecting length of stay in teaching hospitals of a middle-income country. Electron Physician. 2016;8(10):3042-7.
217. Myrli TR, Mortensen SM, Aufles B. Utvikling og variasjon i opphold, liggetid og andel reinnleggelser for utskrivningsklare pasienter 2011-2018 (2019) Published by The Norwegian Directorate of Health [Norwegian report]. Available at: https://www.helsedirektoratet.no/rapporter/utvikling-og-variasjon-i-opphold-liggetid-og-andel-reinnleggelser-for-utskrivningsklare-pasienter/IS_2813_Liggetid%20og%20reinnleggelser%20for%20utskrivningsklare%20pasienter%202011-18.pdf/_/attachment/inline/87530703-2216-46eb-83a6-624683c546c7:794262362a9ae906f49c7b0c53dd73efe8dec0e8/IS_2813_Liggetid%20og%20reinnleggelser%20for%20utskrivningsklare%20pasienter%202011-18.pdf [cited 7 March 2022].
218. El Morabet N, Uitvlugt EB, van den Bemt BJF, van den Bemt PMLA, Janssen MJA, Karapinar-Çarkit F. Prevalence and Preventability of Drug-Related Hospital Readmissions: A Systematic Review. J Am Geriatr Soc. 2018;66(3):602-8.
219. Ravn-Nielsen LV, Duckert ML, Lund ML, Henriksen JP, Nielsen ML, Eriksen CS, et al. Effect of an In-Hospital Multifaceted Clinical Pharmacist Intervention on the Risk of Readmission: A Randomized Clinical Trial. JAMA Intern Med. 2018;178(3):375-82.
220. Mc Cord KA, Ewald H, Agarwal A, Glinz D, Aghlmandi S, Ioannidis JPA, et al. Treatment effects in randomised trials using routinely collected data for outcome assessment versus traditional trials: meta-research study. BMJ. 2021;372:n450.
221. Burke TA, McKee JR, Wilson HC, Donahue RM, Batenhorst AS, Pathak DS. A comparison of time-and-motion and self-reporting methods of work measurement. J Nurs Adm. 2000;30(3):118-25.

222. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ. 2007;335(7624):806-8.
223. Zheng K, Guo MH, Hanauer DA. Using the time and motion method to study clinical work processes and workflow: methodological inconsistencies and a call for standardized research. J Am Med Inform Assoc. 2011;18(5):704-10.
224. Franke R, Kaul J. The Hawthorne experiments: first statistical interpretation. Am Sociol Rev 1978;43:623–43.
225. Brady A, Curtis CE, Jalal Z. Screening Tools Used by Clinical Pharmacists to Identify Elderly Patients at Risk of Drug-Related Problems on Hospital Admission: A Systematic Review. Pharmacy (Basel). 2020;8(2).
226. Mansell HH, Y.M. Should hospital pharmacists prescribe?contre. Can J Hosp Pharm. 2014;67(5):390-3.
227. Nguyen TL, Leguelinel-Blache G, Kinowski JM, Roux-Marson C, Rougier M, Spence J, et al. Improving medication safety: Development and impact of a multivariate model-based strategy to target high-risk patients. PLoS One. 2017;12(2):e0171995.
228. Alshakrah MA, Steinke DT, Lewis PJ. Patient prioritization for pharmaceutical care in hospital: A systematic review of assessment tools. Res Social Adm Pharm. 2019;15(6):767-79.
229. Alshakrah MA, Steinke DT, Lewis PJ. Corrigendum to "Patient prioritization for pharmaceutical care in hospital: A systematic review of assessment tools" [Res Soc Adm Pharm, 15 6 (2019) 767-779]. Res Social Adm Pharm. 2020;16(7):993.
230. Botelho SF, Neiva Pantuzza LL, Marinho CP, Moreira Reis AM. Prognostic prediction models and clinical tools based on consensus to support patient prioritization for clinical pharmacy services in hospitals: A scoping review. Res Social Adm Pharm. 2021;17(4):653-63.
231. Falconer N, Barras M, Cottrell N. Systematic review of predictive risk models for adverse drug events in hospitalized patients. Br J Clin Pharmacol. 2018;84(5):846-64.
232. Deawjaroen K, Sillabutra J, Poolsup N, Stewart D, Suksomboon N. Clinical usefulness of prediction tools to identify adult hospitalized patients at risk of drug-related problems: A systematic review of clinical prediction models and risk assessment tools. Br J Clin Pharmacol. 2021.
233. Puumalainen E, Airaksinen M, Jalava SE, Chen TF, Dimitrow M. Comparison of drug-related problem risk assessment tools for older adults: a systematic review. Eur J Clin Pharmacol. 2020;76(3):337-48.
234. Falconer N, Nand S, Liow D, Jackson A, Seddon M. Development of an electronic patient prioritization tool for clinical pharmacist interventions. Am J Health Syst Pharm. 2014;71(4):311-20.
235. Audurier Y, Roubille C, Manna F, Zerkowski L, Faucanie M, Macioce V, et al. Development and validation of a score to assess risk of medication errors detected during medication reconciliation process at admission in internal medicine unit: SCOREM study. Int J Clin Pract. 2021;75(2):e13663.
236. Saedder EA, Lisby M, Nielsen LP, Rungby J, Andersen LV, Bonnerup DK, et al. Detection of Patients at High Risk of Medication Errors: Development and Validation of an Algorithm. Basic Clin Pharmacol Toxicol. 2016;118(2):143-9.
237. Falconer N, Liow D, Zeng I, Parsotam N, Seddon M, Nand S. Validation of the assessment of risk tool: patient prioritisation technology for clinical pharmacist interventions. Eur J Hosp Pharm. 2017;24(6):320-6.
238. Bonnerup DK, Lisby M, Sædder EA, Sørensen CA, Brock B, Andersen L, et al. Risk of prescribing errors in acutely admitted patients: a pilot study. Int J Clin Pharm. 2016;38(5):1157-63.
239. Sund JK, Sletvold O, Mellingsæter TC, Hukari R, Hole T, Uggen PE, et al. Discrepancies in drug histories at admission to gastrointestinal surgery, internal medicine and geriatric hospital wards in Central Norway: a cross-sectional study. BMJ Open. 2017;7(9):e013427.
240. Mills PR, McGuffie AC. Formal medicine reconciliation within the emergency department reduces the medication error rates for emergency admissions. Emerg Med J. 2010;27(12):911-5.
241. de Andrés-Lázaro AM, Sevilla-Sánchez D, Ortega-Romero MeM, Codina-Jané C, Calderón-Hernanz B, Sánchez-Sánchez M. [Accuracy in the medication history and reconciliation errors in the emergency department]. Med Clin (Barc). 2015;145(7):288-93.
242. Abuzour AS, Hoad-Reddick G, Shahid M, Steinke DT, Tully MP, Williams SD, et al. Patient prioritisation for hospital pharmacy services: current approaches in the UK. Eur J Hosp Pharm. 2021;28(Suppl 2):e102-e8.
243. Sutherland JJ, Morrison RD, McNaughton CD, Daly TM, Milne SB, Daniels JS, et al. Assessment of Patient Medication Adherence, Medical Record Accuracy, and Medication Blood Concentrations for Prescription and Over-the-Counter Medications. JAMA Netw Open. 2018;1(7):e184196.
244. Monte AA, Anderson P, Hoppe JA, Weinshilboum RM, Vasiliou V, Heard KJ. Accuracy of Electronic Medical Record Medication Reconciliation in Emergency Department Patients. J Emerg Med. 2015;49(1):78-84.

245. Hohl CM, Partovi N, Ghement I, Wickham ME, McGrail K, Reddekopp LN, et al. Impact of early in-hospital medication review by clinical pharmacists on health services utilization. PLoS One. 2017;12(2):e0170495.
246. Graabaek T, Hedegaard U, Christensen MB, Clemmensen MH, Knudsen T, Aagaard L. Effect of a medicines management model on medication-related readmissions in older patients admitted to a medical acute admission unit-A randomized controlled trial. J Eval Clin Pract. 2019;25(1):88-96.
247. Bonnerup DK, Lisby M, Sædder EA, Brock B, Truelshøj T, Sørensen CA, et al. Effects of stratified medication review in high-risk patients at admission to hospital: a randomised controlled trial. Ther Adv Drug Saf. 2020;11:2042098620957142.
248. Manias E, Kusljic S, Wu A. Interventions to reduce medication errors in adult medical and surgical settings: a systematic review. Ther Adv Drug Saf. 2020;11:2042098620968309.
249. Redmond P, Grimes TC, McDonnell R, Boland F, Hughes C, Fahey T. Impact of medication reconciliation for improving transitions of care. Cochrane Database Syst Rev. 2018;8:CD010791.
250. Ciapponi A, Fernandez Nievas SE, Seijo M, Rodríguez MB, Vietto V, García-Perdomo HA, et al. Reducing medication errors for adults in hospital settings. Cochrane Database Syst Rev. 2021;11:CD009985.
251. Anderson LJ, Schnipper JL, Nuckols TK, Shane R, Le MM, Robbins K, et al. Effect of medication reconciliation interventions on outcomes: A systematic overview of systematic reviews. Am J Health Syst Pharm. 2019;76(24):2028-40.
252. Guisado-Gil AB, Mejías-Trueba M, Alfaro-Lara ER, Sánchez-Hidalgo M, Ramírez-Duque N, Santos-Rubio MD. Impact of medication reconciliation on health outcomes: An overview of systematic reviews. Res Social Adm Pharm. 2020;16(8):995-1002.
253. Dautzenberg L, Bretagne L, Koek HL, Tsokani S, Zevgiti S, Rodondi N, et al. Medication review interventions to reduce hospital readmissions in older people. J Am Geriatr Soc. 2021;69(6):1646-58.
254. Gallagher J, McCarthy S, Byrne S. Economic evaluations of clinical pharmacist interventions on hospital inpatients: a systematic review of recent literature. Int J Clin Pharm. 2014;36(6):1101-14.
255. Dawoud DM, Smyth M, Ashe J, Strong T, Wonderling D, Hill J, et al. Effectiveness and cost effectiveness of pharmacist input at the ward level: a systematic review and meta-analysis. Res Social Adm Pharm. 2019;15(10):1212-22.
256. Bullock B, Coombes I, Mitchell C, Donovan P, Whitty JA. A systematic review of the costs and cost-effectiveness of clinical pharmacists on hospital ward rounds. Expert Rev Pharmacoecon Outcomes Res. 2019;19(5):551-9.
257. Schmiedl S, Rottenkolber M, Szymanski J, Drewelow B, Siegmund W, Hippius M, et al. Preventable ADRs leading to hospitalization - results of a long-term prospective safety study with 6,427 ADR cases focusing on elderly patients. Expert Opin Drug Saf. 2018;17(2):125-37.
258. Oscanoa TJ, Lizaraso F, Carvajal A. Hospital admissions due to adverse drug reactions in the elderly. A meta-analysis. Eur J Clin Pharmacol. 2017;73(6):759-70.
259. Lghoul-Oulad Saïd F, Hek K, Flinterman LE, Herings RM, Warlé-van Herwaarden MF, de Bie S, et al. Prevalence and incidence rate of hospital admissions related to medication between 2008 and 2013 in The Netherlands. Pharmacoepidemiol Drug Saf. 2020;29(12):1659-68.
260. Mongkhon P, Ashcroft DM, Scholfield CN, Kongkaew C. Hospital admissions associated with medication non-adherence: a systematic review of prospective observational studies. BMJ Qual Saf. 2018;27(11):902-14.
261. Kempen TGH, Hedström M, Olsson H, Johansson A, Ottosson S, Al-Sammak Y, et al. Assessment tool for hospital admissions related to medications: development and validation in older patients. Int J Clin Pharm. 2019;41(1):198-206.
262. Thevelin S, Spinewine A, Beuscart JB, Boland B, Marien S, Vaillant F, et al. Development of a standardized chart review method to identify drug-related hospital admissions in older people. Br J Clin Pharmacol. 2018;84(11):2600-14.
263. Office of the Audit General of Norway [Norwegian report] Riksrevisjonens undersøkelse av myndighetenes arbeid med å sikre god henvisningspraksis fra fastlegene til spesialisthelsetjenesten, Dokument 3:4 (2017–2018) Available at: https://www.riksrevisjonen.no/globalassets/rapporter/no-2017-2018/henvisningspraksis.pdf [cited 15 March 2022].
264. Greenhalgh T, Stramer K, Bratan T, Byrne E, Russell J, Potts HW. Adoption and non-adoption of a shared electronic summary record in England: a mixed-method case study. BMJ. 2010;340:c3111.
265. Boonstra A, Jonker TL, van Offenbeek MAG, Vos JFJ. Persisting workarounds in Electronic Health Record System use: types, risks and benefits. BMC Med Inform Decis Mak. 2021;21(1):183.

266. Burns JM, Sneddon I, Lovell M, McLean A, Martin BJ. Elderly patients and their medication: a post-discharge follow-up study. Age Ageing. 1992;21(3):178-81.
267. Viktil KK, Blix HS, Eek AK, Davies MN, Moger TA, Reikvam A. How are drug regimen changes during hospitalisation handled after discharge: a cohort study. BMJ Open. 2012;2(6).
268. Mortelmans L, De Baetselier E, Goossens E, Dilles T. What Happens after Hospital Discharge? Deficiencies in Medication Management Encountered by Geriatric Patients with Polypharmacy. Int J Environ Res Public Health. 2021;18(13).
269. Hermann M, Holt MD, Kjome RLS, Teigen A. Medication reconciliation -is it possible to speed up without compromising quality? A before–after study in the emergency department. Eur J Hosp Pharm. 2022.
270. Schneider A, Williams DJ, Kalynych C, Wehler M, Weigl M. Physicians' and nurses' work time allocation and workflow interruptions in emergency departments: a comparative time-motion study across two countries. Emerg Med J. 2021;38(4):263-8.
271. Fong A, Ratwani RM. Understanding Emergency Medicine Physicians Multitasking Behaviors Around Interruptions. Acad Emerg Med. 2018;25(10):1164-8.
272. Weigl M, Catchpole K, Wehler M, Schneider A. Workflow disruptions and provider situation awareness in acute care: An observational study with emergency department physicians and nurses. Appl Ergon. 2020;88:103155.
273. Schneider A, Wehler M, Weigl M. Provider interruptions and patient perceptions of care: an observational study in the emergency department. BMJ Qual Saf. 2019;28(4):296-304.
274. Weigl M, Beck J, Wehler M, Schneider A. Workflow interruptions and stress atwork: a mixed-methods study among physicians and nurses of a multidisciplinary emergency department. BMJ Open. 2017;7(12):e019074.
275. Jeanmonod R, Boyd M, Loewenthal M, Triner W. The nature of emergency department interruptions and their impact on patient satisfaction. Emerg Med J. 2010;27(5):376-9.
276. Berg LM, Källberg AS, Göransson KE, Östergren J, Florin J, Ehrenberg A. Interruptions in emergency department work: an observational and interview study. BMJ Qual Saf. 2013;22(8):656-63.
277. Walter SR. Interruptions in Emergency Medicine: Things Are Not Always What They Seem. Acad Emerg Med. 2018;25(10):1178-80.
278. Raban MZ, Westbrook JI. Are interventions to reduce interruptions and errors during medication administration effective?: a systematic review. BMJ Qual Saf. 2014;23(5):414-21.
279. The Directorate of e-health, 2019, revised 2021, Pasientens legemiddelliste, Available at: https://www.ehelse.no/prosjekt/pasientens-legemiddelliste-pll/_/attachment/download/3086c338-34d9-431e-ae57-a472b19571ee:c4add0686d1099c1dd76769204adc657241145d0/Pasientens%20legemiddelliste%20brosjyre%20v2.0.pdf [Norwegian leflet], [cited 26 March 2022].
280. Helseplattformen AS, 2019, revised 2022, Available at: https://helseplattformen.no/om-oss/prosjektet [Norwegian web-page], [cited 26 March 2022].
281. The Directorate for e-health, 2022, Available at: https://www.ehelse.no/prosjekt/pasientens-legemiddelliste-pll [Norwegian web-page], [cited 26 March 2022].
282. Dyb K, Warth LL. The Norwegian National Summary Care Record: a qualitative analysis of doctors' use of and trust in shared patient information. BMC Health Serv Res. 2018;18(1):252.
283. Andersen TS, Gemmer MN, Sejberg HRC, Jørgensen LM, Kallemose T, Andersen O, et al. Medicines Reconciliation in the Emergency Department: Important Prescribing Discrepancies between the Shared Medication Record and Patients' Actual Use of Medication. Pharmaceuticals (Basel). 2022;15(2).

Paper I

Paper II

Impact of systematic medication review in emergency department on patients' post-discharge outcomes -a randomized controlled clinical trial

Lisbeth D. Nymoen [1, 2], Trude E. Flatebø[1], Tron A. Moger[3], Erik Øie[4], Espen Molden[2, 5], Kirsten K. Viktil[1, 2]

[1] Diakonhjemmet Hospital Pharmacy AS, Oslo, Norway
[2] Department of Pharmacy, University of Oslo, Oslo, Norway
[3] Department of Health Management and Health Economics, University of Oslo, Oslo, Norway
[4] Department of Internal Medicine, Diakonhjemmet Hospital, Oslo, Norway
[5] Department of Psychopharmacology, Diakonhjemmet Hospital, Oslo, Norway

Corresponding author:
Lisbeth D. Nymoen
e-mail: lisbetd@student.matnat.uio.no

Abstract

The main objective of this study was to investigate whether systematic medication review conducted by clinical pharmacists can impact clinical outcomes and post-discharge outcomes for patients admitted to the emergency department. *Method:* This parallel group, non-blinded, randomized controlled trial was conducted in the emergency department, Diakonhjemmet Hospital, Oslo, Norway. The study was registered in ClinicalTrials.gov, Identifier: NCT03123640 in April 2017. From April 2017 to May 2018, patients ≥18 years were included and randomized (1:1) to intervention- or control group. The control group received standard care from emergency department physicians and nurses. In addition to standard care, the intervention group received systematic medication review including medication reconciliation conducted by pharmacists, during the emergency department stay. The primary outcome was proportion of patients with an unplanned contact with hospital within 12 months from inclusion stay discharge. *Results:* In total, 807 patients were randomized, 1:1, to intervention or control group. After excluding 8 patients dying during hospital stay and 10 patients lacking Norwegian personal identification number, the primary analysis comprised 789 patients: 394 intervention group patients and 395 control group patients. Regarding the primary outcome, there was no significant difference in proportion of patients with an unplanned contact with hospital within 12 months after inclusion stay discharge between groups (51.0% of intervention group patients vs. 53.2% of control group patients, p=0.546). *Conclusion:* As currently designed, emergency department pharmacist-led medication review did not significantly influence clinical- or post-discharge outcomes. A combination of a heterogenous study population and low implementation of pharmacists' recommendations, may explain the lack of impact of the intervention which had a pragmatic design. This study did, however pinpoint important practical implementations, which can be

used to design improved workflow regarding drug-related issues in the emergency department setting.

Introduction

Overcrowding in the emergency department (ED) is an increasing worldwide challenge[1-3]. Faced with this challenge ED physicians are forced to prioritize their time to ensure that all admitted patients receive appropriate emergency care. The time-pressured environment in the ED have been identified as a barrier to obtaining an accurate and complete drug list[4]. Prior studies have reported that more than 60% of patients referred to EDs are registered with incorrect or incomplete drug lists at admission[5-8]. Incomplete information about patients' drug lists during transition of care have negative effects on patient safety and quality of care[9-11], as this can affect the clinical assessments of patients' presented symptoms and further drug treatment[12]. It has been reported that prescribing errors are70 % more likely to occur at the time of hospital admission than during the hospital stay[13]. In addition, drug-related problems are common in the ED. One prior study found that 85% of patients admitted to the ED had at least one drug-related problem[14]. And further, several prior studies have raised concerns regarding physicians not recognizing that drug-related problems could be the cause of the ED visit[15-17].

Pharmacists-led medication reconciliation increase the quality of the ED drug lists by decreasing medication discrepancies between the registered drug list and the drugs actually used by patients before ED admission[6,18,19]. Furthermore, systematic medication review is a validated method to identify and resolve drug-related problems[20], and also a useful method to identify drug-related ED visits[15, 17].

Majority of the previous randomized controlled trials (RCT) investigating pharmacist-led interventions have included in-hospital patients[21-27]. According to two systematic reviews meta-analyzing results from these RCTs, pharmacists-led interventions reduce

medication errors and reduce subsequent ED visits after hospital discharge[9]. Further, results also indicate that a pharmacist-led medication reconciliation at hospital transitions decreases drug-related hospital revisits, all-cause readmissions, and ED visits[18]. The interventions in some of these prior in-hospital RCTs have demanded massive resources due to follow up, for instance following the patient with several medication reconciliations and medication reviews during the entire hospital stay and further contacting the patients, by phone after discharge[21-25]. As hospital resources in the real-world setting is not unlimited, studies investigating more pragmatic and more implementable interventions are necessary. In addition, length of hospital stay has decreased worldwide the last decades[28]. Therefore, investigating interventions conducted during the ED stay i.e., early during the hospital admission is important.

When initiating the present study, the clinical impact of pharmacists-led interventions in the ED-setting was only investigated in one small prior RCT[29] including patients >70 years. Therefore, the aim of the present study was to perform the first large scale RCT to investigate whether implementing pharmacist-led systematic medication reviews in the ED can impact clinical and post-discharge outcomes for a general ED population.

Methods

Study design

This parallel group, non-blinded RCT was conducted at the ED, Diakonhjemmet Hospital, a local, urban hospital in Oslo, Norway. Patients were included consecutively in periods from 24 April 2017 until the predetermined target number of 800 patients was enrolled on 16 May 2018. Fig 1 presents the patient flow of the study

The study was approved by the institutional review board at Diakonhjemmet Hospital and the Regional Committee for Medical and Health Research Ethics (2015/1356/ REK south-eastern A). Written informed consent was obtained from all patients before inclusion. The study was designed and reported according to the CONSORT 2010 Statement[30] (S1 Appendix CONSORT checklist). The study was registered in ClinicalTrials.gov, Identifier: NCT03123640 in April 2017, and closed for new participants May 2018. Fig 2 gives a graphical depiction of the study design. S2 Appendix shows the original study protocol, protocol amendments, and the timeline of the study with milestones.

Data for 12 months follow-up was harvested from the Norwegian Patient Registry (18/12607-10). Each patient was followed for 12 months from their inclusion stay discharge and follow-up was stopped for the last patient on 30 May 2019.

Study setting

In Norway general practitioners (GPs) and the municipal emergency clinics have a gatekeeper function and handle less severe conditions. More severe conditions are referred from GPs or municipal emergency clinics or other healthcare personnel of the primary healthcare e.g., nursing home physicians, or paramedics, to the hospitals' EDs. The referring healthcare personnel set a tentative referral reason after assessing the patient's symptoms and conducting an initial examination (before the ED admission). Based on the tentative referral reason patients are allocated to see a physician from the Department of Internal Medicine (Medical referral reasons), or a physician from the Department of Surgery (Surgical referral reasons) at admission to the investigated ED.

In Norwegian EDs physicians are responsible for obtaining and documenting patients' drug lists at admission. In some Norwegian EDs clinical pharmacists are conducting

medication reconciliation and communicate their findings to ED physicians. However, this is not established as standard care.

Participants

Annually, 13500 patients 18 years or older with both medical and gastrointestinal or orthopedic surgical symptoms are referred to the ED at Diakonhjemmet Hospital. The average length of stay in the investigated ED was 3.2 hours in 2018. All patients arriving at the investigated ED, willing to/capable of providing written, informed consent were eligible for inclusion. Unconscious patients were not included e.g., severe intoxications. Patients aged ≥65 with hip-fracture were admitted to a specialized ED at another location, hence these patients were not included. The patient inclusion was performed by study pharmacists working shifts according to a pre-set study schedule, either between 9:00 am and 4:00 pm or between 4:00 pm and 10:00 pm, on both weekdays and weekends.

Originally an exclusion criterion regarding terminal ill patients with short life expectancy was stated. This criterion was not feasible to meet in the fast-paced workflow of the ED. Hence, patients were included regardless of this issue. Patients readmitted during the study period were not invited for 'a second' inclusion.

Randomization

After inclusion, patients were randomized to intervention- or control-group (1:1). Department of Biostatistics and Epidemiology at Oslo University Hospital organized the randomization procedure. This department had no contact with patients, study pharmacists or ED personnel. A random number generator program was used for randomization sequencing with a permuted block design. The study pharmacists were blinded to block size, which was randomly varied. Allocation information was packed in sequentially numbered, opaque,

sealed envelopes and delivered to study pharmacists. At randomization the study pharmacists assigned the envelope with the lowest number to the individual participant.

It was neither feasible to blind patients nor study pharmacists to the allocation. It was also impossible to blind the hospital staff regarding which of the patients belonged to the intervention group. Affiliates at the ED and hospital were, however, unable to distinguish between patients randomized to the control group and patients not participating in the study.

The Norwegian Patient Registry providing outcome data were blinded to group allocation.

Intervention

The control group received standard care during the ED stay, consisting of triage-nurse consultation (often included physical measurements), consultation by physician (including physical examination, medical and medication history taking) and nurse consultation. In addition, laboratory tests were taken, analyzed, and assessed by physicians during the ED stay. Regarding ethical concerns, patients from the control group were excluded after randomization if; 1) Physicians at the ED requested an assessment from a pharmacist regarding the control group patient, 2) Study pharmacist revealed obvious drug-related problems of major clinical relevance during inclusion of the control group patient and had to intervene.

The intervention group received, in addition to standard care, a systematic medication review including medication reconciliation conducted by a study pharmacist early during the ED stay. The intervention was based on the integrated medicine management (IMM)-model[31], adjusted to the fast-paced workflow of the ED-setting[5], and conducted by experienced clinical pharmacists (study pharmacists).

The medication reconciliation consisted of a standardized patient interview, including use of a checklist with specific questions about drugs often omitted, e.g., eyedrops, inhalation drugs, contraceptives, drugs not taken daily etc. If the patient received assistance with taking drugs, the supporting person/personnel was contacted to be interviewed. In addition, sources providing information on drug prescribing, e.g., electronical prescription database, drug-list of a multi-dose patients, GPs, and other hospitals, were used to verify drugs in use and the respective dosages and brand names. The medication reconciliation was preferably conducted before the ED physician consultation[5], thus the ED physicians could utilize the results from the medication reconciliation during their consultation. Due to the critically illness of some patients and occasional ED crowding the medication reconciliation was not completed before ED physicians' consultations for all included patients. The ED physician in charge of the patient was, however always alerted orally when the medication reconciliation was conducted. In addition, the complete drug list was documented in the hospital's electronic patient record by the study pharmacists.

Following the reconciliation, a systematic medication review was performed. All drugs in the reconciled list were assessed according to predefined drug-related problems categories; drug monitoring, adherence issues, adverse effects, drug-interactions, non-optimal drug therapy, unnecessary drug (detailed description of the drug-related problems categories are presented in Table A in S3 Appendix), based on a validated medication review-tool[32]. The systematic medication review was conducted by interviewing patients and assessing initial examinations performed by ED nurses as well as laboratory tests results. In addition, computer resources were utilized (e.g., interaction databases, summary of product characteristics for drugs, and medical databases), and referral letters from GPs and municipal emergency were reviewed. After identifying drug-related problems in the medication review, possible actions to manage or solve the problems were suggested by the study pharmacists

and documented in the electronic patient record, as well as orally communicated to the ED physician in charge of the patient.

After discharge an interdisciplinary team consisting of two chief physicians and three experienced clinical pharmacists classified all identified drug-related problems according to clinical relevance (issues of importance for the patient treatment). The interdisciplinary team had access to the following information for all intervention group patients; demographic data, results from laboratory tests during hospital stay, tentative referral reasons, final diagnoses (documented in the discharge note by the physician discharging the patient), the patient's reconciled drug list, and identified drug-related problems. The interdisciplinary team classified the drug-related problems as clinically relevant to identify in the ED, clinically relevant to identify during the hospital stay, or not clinically relevant during the ED/hospital stay.

To investigate the efficiency of the intervention, implementation of study pharmacists' recommendations regarding the documented reconciled drug list and drug-related problems was assessed. A study pharmacist retrospectively reviewed admission notes and discharge notes written by physicians, in addition to assessing laboratory tests from the ED visit ordered according to the medication review findings. The drug lists for intervention group patients documented by physicians at admission were considered complete if there were no medication discrepancies regarding regular drugs compared with the reconciled drug list documented by study pharmacists. Physicians' acceptance of the study pharmacists' recommendations regarding drug-related problems was determined by reviewing if changes related to the recommendations were made in the drug list.

Outcome measures

The primary outcome measure was proportion of patients with an unplanned contact with hospital within 12 months after inclusion stay discharge (both ED visits and hospital readmissions). This was chosen as primary outcome as only 12 months data were available for sample size calculation.

Secondary follow-up outcomes were:

- Proportion of patients with an unplanned contact with hospital within 180 days after inclusion stay discharge
- Number of unplanned contacts with hospital per patient within 12 months after inclusion stay discharge
- Time to next unplanned contact with a hospital within 12 months after inclusion stay discharge

Secondary inclusion stay outcomes were:

- Proportion of patients not hospitalized following admission to the ED (patients with conditions resolved in the ED)
- Length of stay at the ED
- Overall length of hospital stay
- Efficiency of the intervention (working model for conducting medication reconciliation and medication review in the ED-setting)

Amendment to study outcomes after the study commenced, although before any outcome data files were available:

- Proportion of patients with an unplanned contact with hospital:
    - within 90 days after inclusion stay discharge
    - within 30 days after inclusion stay discharge

It was decided to add these amendments due to the relatively short intervention compared with the long follow-up time.

Sample size calculation

The sample size calculation was based on an expected readmission frequency of 50% during 12 months following inclusion[31], which is also in line with Norwegian readmission frequency. A 10% reduction in hospital readmissions was defined as a clinically relevant effect of the intervention, which was considered realistic according to earlier studies and accounting for our general population[22]. Accordingly, it was calculated that 385 patients would have to be included into each group, with significance level of 5% and study power of 80%. To compensate for dropouts, it was decided to include 400 patients in each project group, i.e., a total of 800 patients.

Statistics

Data handling were conducted in EPIDATA manager and EPIDATA entry client 4.4.3.1 r691. Statistical analyses were carried out in Stata SE version 16. Demographic statistics are given as median and interquartile ranges (IQRs) for continuous variables and as percentage for categorical variables. Mann-Whitney test was utilized to compare demographics of groups regarding continuous variables (due to skewed data). For categorical variables Pearson-Chi^2 were applied. Patients who died during hospital stay were excluded from both *inclusion stay analysis* and *follow-up analysis.* Sensitivity analysis on inclusion stay data was conducted with these patients and showed that results did not change (Table A in S4 Appendix).

Pearson chi^2 was applied to determine proportion of patients with unplanned contact with hospital during follow-up time, and logistic regression were applied to determine odds ratio with 95% confidence interval (CI). Kaplan-Meier plots and log-rank test were applied to compare groups regarding time to next unplanned contact with hospital (event) and Cox-regression was utilized to determine hazard ratios and 95% CI. Death within 12 months from

inclusion stay discharge was censored during survival analysis as there was no statistically significant difference in death rate between the groups (Fig B in S4 Appendix). Sensitivity analysis with death as competing risk was conducted and did not change the results (Fig A in S4 Appendix). Negative binomial regression was utilized to compare mean length of stay and number of unplanned hospital events within 12 months after inclusion stay discharge, in the latter individual patient-time in study was applied as exposure-variable. Mann-Whitney test was applied to compare median length of stay. For all comparative statistics, significance level was set to 0.05.

Intention-to-treat analysis was conducted on all patients with follow-up data allocated to each group. Per-protocol analysis was conducted on intervention group patients where the intervention medication reconciliation was completed, excluding patients where 1) no drugs were recorded by physicians in the electronical patient record (based on retrospective assessment of admission-note, medication chart and discharge note) and 2) information about regular drugs was omitted by physicians from the electronical patient record for unknown reason (based on retrospective assessment of admission-note and medication chart). All control group patients with follow-up data were included in per-protocol analysis.

Results

During the data-collection shifts between 24 April 2017 to 16 May 2018, approximately 1900 patients were admitted to the ED at Diakonhjemmet Hospital. Of these, 831 (43.7%) patients were considered for inclusion (Fig 1), whereas the remaining patients were not assessed due to ED crowding which exceeded study pharmacists' capacity. Eighteen patients were excluded before randomization as they were not capable of providing written, informed consent or declined to participate. A total of 813 patients were included and

randomized. After randomization, 6 patients were excluded, leaving 807 patients eligible for inclusion stay analysis, 405 in the intervention group and 402 in the control group.

Mean age for included patients (n=807) was 65.4 years (±18.5), median age was 69.2 years (IQR 26.6, range 18.7-99.4). A total of 56.8% of the patients were aged over 65 years and 51.7% were men. According to the hospital medication chart, physicians had documented 3.6 (±3.8) regular drugs on average per included patient, whereas the median number of documented regular drugs were 3 (IQR 6, range 0-19). Table 1 shows demographics for included patients in their allocated group.

Table 1. Demographics of included patients.

Variable	Categories	Intervention group *n= 405*	Control group *n= 402*	P-value
Age	*Median, years (IQR, range)*	67.2 (27.3, 18.7-96.4)	70.2 (25.1, 19.1-99.4)	0.132
	Patients ≥65 years number (%)	218 (53.8)	240 (59.7)	0.092
Sex (men) *number (%)*		212 (52.4)	205 (51.0)	0.701
Distribution of referral reasons *number (%)*	*Medical*	281 (69.4)	282 (70.2)	0.972
	Surgical	123 (30.4)	119 (29.6)	
	Rheumatological [c]	1 (0.3)	1 (0,3)	
Triage category(33) *number (%)*	*Triage 1*	0	1 (0,3)	0.621
	Triage 2	127 (31.9)	136 (34.4)	
	Triage 3	157 (39.5)	147 (37.2)	
	Triage 4	111 (27.9)	110 (27.9)	
	Triage 5	3 (0,8)	1 (0,3)	
Admitted from *number (%)*	*General practitioner*	105 (25.9)	123 (30.6)	0.678
	Nursing home	10 (2.5)	12 (3.0)	
	Other hospital	40 (9.9)	38 (9.5)	
	Municipal emergency room	134 (33.1)	112 (27.9)	
	Emergency medical communication centre	47 (11.6)	43 (10.7)	
	Directly to emergency department [d]	6 (1.5)	7 (1.7)	
	Various [e]	63 (15.6)	67 (16.7)	
Living situation before admission *number (%)*	*Home without help*	354 (87.4)	330 (82.1)	0.106
	Home with assistant living (home care and/or multidose packed drugs)	40 (9.9)	55 (13.7)	
	Nursing home/ Rehabilitation	11 (2.7)	17 (4.2)	
Admissions to DH[a] 12 months before inclusion stay admission	*Median number of admissions (IQR, range)*	0 (1, 0-26)	0 (1, 0-28)	0.223
	Number of patients with at least one admission (%)	128 (31.6)	148 (36.8)	0.119
Tentative referral reasons[34] (communicated by referring healthcare personnel) [b] *number (%)*	*Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified*	149 (36.8)	144 (35.8)	0.775
	Diseases of the circulatory system	88 (21.7)	93 (23.1)	0.632
	Diseases of the digestive system	37 (9.1)	40 (10.0)	0.694
	Injury, poisoning and certain other consequences of external causes	31 (7.7)	31 (7.7)	0.976
	Diseases of the respiratory system	25 (6.2)	32 (8.0)	0.322
Discharge diagnoses[34] (set by the hospital physician discharging the patient) [b] *number (%)*	*Diseases of the circulatory system*	115 (28.4)	120 (29.9)	0.649
	Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified	84 (20.7)	70 (17.4)	0.229
	Diseases of the respiratory system	65 (16.0)	68 (16.9)	0.740
	Diseases of the digestive system	57 (14.1)	56 (13.9)	0.953
	Factors influencing health status and contact with health services	48 (11.9)	56 (13.9)	0.378
	Endocrine, nutritional, and metabolic diseases	48 (11.9)	43 (10.7)	0.604

All patients receiving allocated intervention or care are included in the table.

[a] DH: Diakonhjemmet Hospital

[b] The table presents only the most frequent tentative referral reasons and discharge diagnoses, each patient had 1-3 tentative referral reasons and 1-7 discharge diagnoses

[c] Patients with rheumatological referral reasons are seldom admitted to the investigated ED, majority of these patients are admitted elective

[d] Patients arrived directly to the emergency department without referral

[e] Various includes free referral (patients with frequent hospitalization/ or patients with unresolved conditions can be offered this solution, and can contact the hospital directly), patients with complications after recent surgical or medical hospital treatment (within 3 months), elective admissions, transfer from other unit at Diakonhjemmet Hospital, e.g., out-patient clinic, psychiatry unit.

During the inclusion stay 6 (1.5%) intervention group patients and 2 (0.5%) control group patients died (p=0.158). Further, during 12 months from inclusion stay discharge 33

(8.4%) intervention group patients and 37 (9.4%) control group patients died (p=0.640) (Fig B in S4 Appendix present survival curve with death as event).

Primary outcome:

Intention-to-treat analysis showed that there was no significant difference in proportion of patients with an unplanned contact with hospital (ED-visit or hospital admission) within 12 months after inclusion stay discharge, i.e., a total of 201 patients (51.0%) in the intervention group (n= 394) and 210 patients (53.2%) in the control group (n=395) (p=0.546, OR 0.92, 95%CI 0.69, 1.21).

According to *per-protocol* analysis 130 (48.7%) intervention group patients (n=267) compared with 210 (53.2%) control group patients (n=395) had an unplanned contact with hospital (ED-visit or hospital admission) within 12 months after inclusion stay discharge. However, the difference was not statistically significant, p=0.258, OR 0.84, 95%CI 0.61, 1.14.

Secondary outcomes

In the *intention-to-treat* analysis, 12 months follow-up revealed that median time to next unplanned contact with hospital (ED-visit or hospital admission) (Fig 3A) was 330 days for the intervention group and 308 days for the control group. However, this difference was not statistically significant (p=0.755, HR 0.97, 95%CI 0.80, 1.18). In the *per-protocol analysis*, the median time to next unplanned contact with hospital (ED-visit or hospital admission) (Fig 3B) exceeded follow-up time for the intervention group and was 308 days for the control group. The difference was not statistically significant (p=0.378, HR 0.91, 95%CI 0.73, 1.13).

Median number of regular orders (both drugs and supplements) documented by physicians in medication chart/ electronic patient record at admission was 3 (IQR 6, 0-16) for the intervention group and 3 (IQR 6, 0-19) for the control group (p=0.796). For 64 (15.8%) patients in the intervention group and 61 (15.2%) patients in the control group no drugs were recorded by physicians at admission. However, medication reconciliation revealed that the 64 intervention group patients in fact used median 2 (IQR 5, 0-15) regular drugs and median 1 (IQR 2, 0-5) regular supplements. In addition, for 66 (16.3%) of the intervention group patients the drug list was not complete, information about one or more of their regular drugs was omitted by physicians for unknown reason. According to reconciled drug lists documented by study pharmacists the median number of regular drugs used by the intervention group patients in total (n=405) was 4 (IQR 6, 0-19), and median number of regular supplements 0 (IQR 2, 0-11). Hence, study pharmacists documented a higher number of regular drugs compared with physicians for the intervention group patients at admission (p<0.001).

A total of 646 drug-related problems were identified and documented by study pharmacists through medication review. The interdisciplinary team assessed 23.1% of the drug-related problems to be clinically relevant to identify during the ED stay. Among these the most frequent drug-related problems were adverse effects (25.5%), drug monitoring (10.1%), adherence issues (9.4%) and drug-interactions (9.4%). Further, 50.9% of the drug-related problems were found to be clinically relevant during the hospital stay, whereas 26.0% were not clinically relevant to the patients' treatment during hospital stay. According to the discharge note review, physicians implemented the study pharmacists' recommendations for 44.8% of the drug-related problems where the interdisciplinary team concluded clinically relevant to identify during the ED or hospital stay.

There were no statistically significant differences between groups regarding secondary outcomes, presented in Table 2. However, length of stay in ED and mean length of hospital stay tended to be higher for the intervention group compared with the control group (Table 2).

Table 2. Secondary outcomes (*Intention-to-treat* analysis) comparing intervention- and control group patients.

Inclusion stay endpoints		**Intervention group *n=399***	**Control group *n=400***	**P-value**
Patients not hospitalized	*Number (%)*	129 (32.3%)	130 (32.5%)	0.959 [a]
Length of emergency department stay,	*Median, hours (IQR, range)*	3.1 (2.1, 0.6-10.6)	3.0 (1.9, 0.6-8.9)	0.079 [b]
	Mean, hours (±SD)	3.5 (±1.5)	3.3 (±1.4)	0.119 [c]
Length of hospital stay	*Median, days (IQR, range)*	1.0 (2.0, 0.0-37.8)	1.0 (2.7, 0.0-34.1)	0.730 [b]
	Mean, days (±SD)	2.1 (±4.1)	1.7 (±2.9)	0.073 [c]
Follow-up endpoints		***n= 394***	***n= 395***	
Patients in contact with hospital within 180 days from inclusion stay discharge	*Number (%)*	163 (41.4%)	163 (41.3%)	0.976 [a]
Patients in contact with hospital within 90 days from inclusion stay discharge	*Number (%)*	141 (35.8%)	125 (31.7%)	0.219 [a]
Patients in contact with hospital within 30 days from inclusion stay discharge	*Number (%)*	89 (22.6%)	87 (22.0%)	0.849 [a]
Number of contacts with hospital within 12 months from inclusion stay discharge	*Median, IQR, range*	1 (2, 0-34)	1 (2, 0-28)	0.523 [c]

Inclusion stay endpoints are presented for all patients who survived the inclusion stay. Follow-up endpoints are presented for all patients with available follow-up data.

[a] P-values generated with Pearson chi^2

[b] P-values generated with Mann-Whitney test

[c] P-values generated with negative binomial regression

Clinical pharmacists part-time affiliated at hospital wards are included in standard care during the hospital stay. They conducted medication reconciliation for 3.0% of the control group patients and 0.7% of the intervention group patients during inclusion hospital stay. Further, medication review was conducted by clinical pharmacists at the wards for 11.9% of the control group patients and 15.6% of the intervention group patients during inclusion hospital stay.

Discussion

Pharmacists-led ED medication review did not significantly reduce the proportion of patients with an unplanned contact with hospital compared with standard care in the present study. The intervention did neither have a significant effect on secondary clinical or post-discharge outcomes. These results are in line with a previous small RCT with a similar intervention[29]. Further, a recent RCT investigated the efficacy of a medication review program conducted in the ED[35]. No overall impact of the program on the number of ED visits and hospital admissions compared to standard care was reported, no other clinical and post-discharge outcomes was investigated[35]. A recent quasi-randomized trial investigating clinical outcomes of pharmacists-led ED medication reviews[36] did however, report an 8% reduction in median length of stay in hospital over 30 days from discharge compared with standard care. Meanwhile, a follow-up study to the quasi-randomized study found that pharmacist-led ED medication review did not result in long-term changes to outpatient health services utilization[37]. The results from our study and the other studies conducted in the ED are however in contrast with previous RCTs investigating pharmacists-led interventions on in-hospital patients which have reported reduction in ED visits, hospital admissions [9, 22, 23, 26] and overall survival[24] as effects of their interventions. The difference in impact between in-hospital RCTs and studies performed in the ED may be explained by the study setting, the patient population, the degree of acceptance of pharmacists' recommendations and also the pragmatic nature of the ED interventions compared with the in-hospital interventions.

The RCTs reporting effects on clinical outcomes after in-hospital pharmacist-led intervention investigated specific risk patient groups[22-24, 26], such as patients older than 80 years[22], patients using specific risk-drugs[23], multimorbid patients[24] or having specific prior diagnoses[26]. The three previous ED studies also included specific patient groups; patients aged over 65[35] and 70 years[29], and patients at high risk of adverse drug events[36]. In our study, we included a heterogeneous group of patients, including all ages ≥

18 years, regardless of triage-category and referral reason. We revealed that the number of unplanned contacts with hospital within 12 months after inclusion stay discharge varied between 0 to 34 contacts. Further, 32% of patients in each group were discharged directly from ED, indicating that the study population in our study also varied regarding the severity of their acute problem and general needs for healthcare utilization. The lack of effect on clinical outcomes in our study may be explained by a too heterogeneous patient population. Hence, the diversity in patient population may have obscured the effect of the intervention.

The ED setting is a challenging study setting compared to the in-hospital setting. Average length of stay in the investigated ED was 3.2 hours in 2018, and the limited timeframe may have affected the communication between physicians and study pharmacists necessary for implementation of the intervention. The acceptance of the study pharmacists' recommendations in our study was higher than reported in the previous ED RCTs[29, 35]. However, the most recent of these RCTs reported various acceptance of recommendations between study sites (27-53%)[35]. The recent quasi-randomized trial[36] and the follow-up study[37] did not investigate this concern, however reported that low acceptance of pharmacists' recommendations could be a study limitation. Earlier RCTs on in-hospital patients[22, 24, 29] has reported higher acceptance of pharmacists' recommendations compared to the present study. Studies identifying non-adherence to pharmacist recommendations as a threat to the success of medication review interventions have been published after data collection of the present study was finalized[37, 38]. And the most recent ED RCT reported significant effect of the medication review program in the two study sites with the highest acceptance[35]. Hence, the low acceptance of recommendations may partly explain the lack of significant effects on outcome measures in our study, as this resulted in not reaching the calculated sample size on per protocol patients.

In the real-world work-chain healthcare professionals have to rely on the next link of the chain for follow-up[39]. And as hospital resources in the real-world setting are not unlimited, the present study aimed to investigate a pragmatic less resource-demanding intervention than utilized in some of the prior in-hospital RCTs[21-25]. Hence, the study pharmacists did no further follow-up after communicating findings from the intervention to the ED physicians responsible for treating the patient and documenting the findings in the electronic patient record. According to a recent study at Diakonhjemmet hospital, physicians spend on average 4 minutes obtaining a patient's drug list at admission[40]. It was therefore not surprising that the study pharmacists documented a higher number of the patients' drugs at admission compared with physicians. However, the documented reconciled drug lists were only implemented for 66% of the intervention group patients (per-protocol patients). This indicates that the working model for medication reconciliation utilized in the present study, may not represent the most efficient working model in the time-pressured ED setting. A proposal for working model redesign to prevent future transfer errors regarding drug information is to allow trained clinical pharmacists to obtain the medication history and document their findings directly in the medication chart[41]. This practice is currently not systematically implemented in Norway.

Regarding drug-related problems identified during ED medication review, it must be considered whether the ED is the suitable setting for identification. In the ED setting, the focus is on the acute problem bringing the patient to hospital. Hence, preventative longer-term drug management decisions may not be prioritized[37]. However, according to the interdisciplinary team's retrospectively assessment in our study, 23.1% of the drug-related problems identified by study pharmacists were found clinically relevant to identify during ED visit. If conducting medication review in the ED, the working model for medication review must be redesigned to fit the ED setting. Whilst conducting medication reconciliation

efficiently in the ED may reduce the physicians' workload[40], identification of drug-related problems requires dialogue and may be comprehensive. This can contribute to explain the results regarding length of ED stay in our study, which tended to be longer in the intervention group compared with the control group. Even though the acceptance of the study pharmacists' recommendations regarding drug-related problems were low, some of the drug-related problems demanded the ED physicians' attention. Hence it must be considered that the intervention may have prolonged the ED stay. Medication review fitted to the ED setting should focus on acute drug-related problems. According to the interdisciplinary team adverse effects, adherences issues, drug monitoring and interactions are clinically relevant to identify during the ED visit. Long-term drug management alterations must be followed-up during hospital stay or by healthcare personnel in the primary healthcare. However, our results indicates that this follow-up cannot solely rely on the next link of the chain. A proposal can be referral of the patient to follow-up by a clinical pharmacist during the hospital stay. And for patients directly discharged from ED, the ED pharmacist can write a follow-up assessment addressed to relevant health care personnel in the primary healthcare[35, 42].

Mean length of hospital stay tended to be longer in the intervention group compared with control group, though there were no difference in median length of hospital stay. This indicates that for most patients the intervention did not prolong hospital stay. It can, however, not be ruled out that the intervention prolonged hospital stay for a minor part of the patients. Taking into consideration the pragmatic intervention and the low acceptance of recommendations, it was more likely patient-specific factors which influenced the length of stay.

Strengths and limitations

This study was an RCT, and there were no significant differences between demographics in groups at ED admission. However, given the single study location, in one specific healthcare system (where patients are referred to the ED by healthcare personnel of the primary healthcare system), the results are not necessarily generalizable to EDs in other countries. Three study pharmacists were involved in conducting the intervention, and strict guidelines for the conduction of the intervention were made, which limits the inter-individual variability of the performed intervention.

Blinding to group allocation was not possible due to the nature of the intervention. Hence, a spillover effect of the intervention to control group patients cannot be ruled out. In addition, registration of clinical pharmacists' ward activities revealed that 14.9% of the control groups patients and 16.3% of the intervention group patients received medication reconciliation and/or medication review during their hospital stay, as part of standard care. This may have affected the results and making it more difficult to reveal differences between groups.

Only 41.6% of patients admitted to the ED were assessed regarding eligibility for inclusion. Study pharmacists had no specific criteria for which patients to include in case of ED crowding. Summary statistics from Diakonhjemmet Hospital for the period from 2017 to 2018 reveal that 57.2% of patients admitted to the ED were aged over 65 years, further 73% of patients were referred with a medical referral reason, 27% with a surgical referral reason. Hence, both the annual age-distribution and distribution regarding referral reason were similar to the study population in the present study. However, selection bias regarding other variables cannot be rejected.

An interdisciplinary team was utilized to assess the clinical relevance of the identified drug-related problems in this study, verifying the importance of the intervention findings.

Further, adherence to the intervention findings was registered. Despite designing the study to be sufficiently powered, calculated sample size regarding per-protocol patients in the intervention group was not reached. The results should therefore be interpreted with some caution.

Conclusion

This RCT revealed that ED pharmacist-led medication review as currently designed, did not influence clinical outcomes or post-discharge outcomes. A combination of a heterogenous study population and the pragmatic nature of the intervention which in the real-world ED setting may have led to a low implementation of pharmacists' recommendations, can contribute to explain the lack of impact. This study did, however pinpoint important practical implementations, which can be used to design improved workflow regarding drug-related issues in the emergency department setting.

Acknowledgements

The authors thank Ann-Christin Riddarsporre who contributed as study pharmacist, Therese Tran and Ingrid Kinne Tunestveit who summarized patient information presented to the interdisciplinary team, Merethe Nilsen and Aasmund Godø who contributed as members of the interdisciplinary team, employees at the emergency department and physicians affiliated to the emergency department during the data collection for the positive attitude to the study, and finally, Andrew H. Reiner at Oslo Center for Biostatistics and Epidemiology for valuable support during the preparation of outcome data files.

References

1. Mentzoni I, Bogstrand ST, Faiz KW. Emergency department crowding and length of stay before and after an increased catchment area. BMC Health Serv Res. 2019;19(1):506.
2. Di Somma S, Paladino L, Vaughan L, Lalle I, Magrini L, Magnanti M. Overcrowding in emergency department: an international issue. Intern Emerg Med. 2015;10(2):171-5.
3. Schuur JD, Venkatesh AK. The growing role of emergency departments in hospital admissions. N Engl J Med. 2012;367(5):391-3.
4. Welch S, Finckh A (2019). Prescribing errors in emergency department medication history taking: will electronic medication management systems help?. *Journal of Pharmacy Practice and Research* , *49* , 400-402. https://doi.org/10.1002/jppr.1599.
5. Damlien L, Davidsen N, Nilsen M, Godø A, Moger TA, Viktil KK. Drug safety at admission to emergency department: an innovative model for PRIOritizing patients for MEdication Reconciliation (PRIOMER). Eur J Emerg Med. 2017;24(5):333-9.
6. Choi YJ, Kim H. Effect of pharmacy-led medication reconciliation in emergency departments: A systematic review and meta-analysis. J Clin Pharm Ther. 2019;44(6):932-45.
7. Caglar S, Henneman PL, Blank FS, Smithline HA, Henneman EA. Emergency department medication lists are not accurate. J Emerg Med. 2011;40(6):613-6.
8. Tong EY, Roman CP, Mitra B, Yip GS, Gibbs H, Newnham HH, et al. Reducing medication errors in hospital discharge summaries: a randomised controlled trial. Med J Aust. 2017;206(1):36-9.
9. De Oliveira GS, Castro-Alves LJ, Kendall MC, McCarthy R. Effectiveness of Pharmacist Intervention to Reduce Medication Errors and Health-Care Resources Utilization After Transitions of Care: A Meta-analysis of Randomized Controlled Trials. J Patient Saf. 2021;17(5):375-80.
10. Forster AJ, Murff HJ, Peterson JF, Gandhi TK, Bates DW. The incidence and severity of adverse events affecting patients after discharge from the hospital. Ann Intern Med. 2003;138(3):161-7.
11. Kahn JM, Angus DC. Going home on the right medications: prescription errors and transitions of care. JAMA. 2011;306(8):878-9.
12. Santell JP. Reconciliation failures lead to medication errors. Jt Comm J Qual Patient Saf. 2006;32(4):225-9.
13. Ashcroft DM, Lewis PJ, Tully MP, Farragher TM, Taylor D, Wass V, et al. Prevalence, Nature, Severity and Risk Factors for Prescribing Errors in Hospital Inpatients: Prospective Study in 20 UK Hospitals. Drug Saf. 2015;38(9):833-43.
14. Nielsen TR, Andersen SE, Rasmussen M, Honoré PH. Clinical pharmacist service in the acute ward. Int J Clin Pharm. 2013;35(6):1137-51.
15. Hohl CM, Zed PJ, Brubacher JR, Abu-Laban RB, Loewen PS, Purssell RA. Do emergency physicians attribute drug-related emergency department visits to medication-related problems? Ann Emerg Med. 2010;55(6):493-502.e4.
16. Roulet L BF, Hardouin JB, Chiffoleau A, Potel G, Asseray N. Adverse drug event nonrecognition in emergency departments: an exploratory study on factors related to patients and drugs. *J Emerg Med* . ; 2014.
17. Roulet L, Ballereau F, Hardouin JB, Chiffoleau A, Moret L, Potel G, et al. Assessment of adverse drug event recognition by emergency physicians in a French teaching hospital. Emerg Med J. 2013;30(1):63-7.
18. Mekonnen AB, McLachlan AJ, Brien JA. Effectiveness of pharmacist-led medication reconciliation programmes on clinical outcomes at hospital transitions: a systematic review and meta-analysis. BMJ Open. 2016;6(2):e010003.
19. Hatch J, Becker, T., Fish, J. T. Difference between Pharmacist-Obtained and Physician-Obtained Medication Histories in the Intensive Care Unit. *Hospital Pharmacy*. 2011;*46* (4):262–8.
20. Blenkinsopp A, Bond C, Raynor DK. Medication reviews. Br J Clin Pharmacol. 2012;74(4):573-80.

21. Farris KB, Carter BL, Xu Y, Dawson JD, Shelsky C, Weetman DB, et al. Effect of a care t ransition intervention by pharmacists: an RCT. BMC Health Serv Res. 2014;14:406.
22. 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.
23. Phatak A, Prusi R, Ward B, Hansen LO, Williams MV, Vetter E, et al. Impact of pharmacist involvement in the transitional care of high-risk patients through medication reconciliation, medication education, and postdischarge call-backs (IPITCH Study). J Hosp Med. 2016;11(1):39-44.
24. Lea M, Mowé M, Molden E, Kvernrød K, Skovlund E, Mathiesen L. Effect of medicines management versus standard care on readmissions in multimorbid patients: a randomised controlled trial. BMJ Open. 2020;10(12):e041558.
25. Kripalani S, Roumie CL, Dalal AK, Cawthon C, Businger A, Eden SK, et al. Effect of a pharmacist intervention on clinically important medication errors after hospital discharge: a randomized trial. Ann Intern Med. 2012;157(1):1-10.
26. Hawes EM, Maxwell WD, White SF, Mangun J, Lin FC. Impact of an outpatient pharmacist intervention on medication discrepancies and health care resource utilization in posthospitalization care transitions. J Prim Care Community Health. 2014;5(1):14-8.
27. Shah M, Norwood CA, Farias S, Ibrahim S, Chong PH, Fogelfeld L. Diabetes transitional care from inpatient to outpatient setting: pharmacist discharge counseling. J Pharm Pract. 2013;26(2):120-4.
28. OECD (2021), H*ealth at a Glance 2021: OECD Indicators* , OECD Publishing, Paris, https://doi.org/10.1787/ae3016b9-en . Accessed: 06.01.22.
29. Lisby M, Thomsen A, Nielsen LP, Lyhne NM, Breum-Leer C, Fredberg U, et al. The effect of systematic medication review in elderly patients admitted to an acute ward of internal medicine. Basic Clin Pharmacol Toxicol. 2010;106(5):422-7.
30. Schulz KF, Altman DG, Moher D, Group C. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. PLoS Med. 2010;7(3):e1000251.
31. Scullin C, Scott MG, Hogg A, McElnay JC. An innovative approach to integrated medicines management. J Eval Clin Pract. 2007;13(5):781-8.
32. Ruths S, Viktil KK, Blix HS. [Classification of drug-related problems]. Tidsskr Nor Laegeforen. 2007;127(23):3073-6.
33. Mackway-Jones K MJ, Windle J. Emergency Triage Manchester Triage Group, 3rd Edition, John Wiley & Sons Inc, 2013, ISBN: 9781118299067.
34. World Health Organization . (2015). International statistical classification of diseases and related health problems, 10th revision, Fifth edition, 2016. World Health Organization.
35. Santolaya-Perrín R, Calderón-Hernanz B, Jiménez-Díaz G, Galán-Ramos N, Moreno-Carvajal MT, Rodríguez-Camacho JM, et al. The efficacy of a medication review programme conducted in an emergency department. Int J Clin Pharm. 2019;41(3):757-66.
36. Hohl CM, Partovi N, Ghement I, Wickham ME, McGrail K, Reddekopp LN, et al. Impact of early in-hospital medication review by clinical pharmacists on health services utilization. PLoS One. 2017;12(2):e0170495.
37. Kitchen SA, McGrail K, Wickham ME, Law MR, Hohl CM. Emergency department-based medication review on outpatient health services utilization: interrupted time series. BMC Health Serv Res. 2020;20(1):254.
38. Lisby M, Bonnerup DK, Brock B, Gregersen PA, Jensen J, Larsen ML, et al. Medication Review and Patient Outcomes in an Orthopedic Department: A Randomized Controlled Study. J Patient Saf. 2018;14(2):74-81.
39. Frankel RM, Tilden VP, Suchman A. Physicians' Trust in One Another. JAMA. 2019;321(14):1345-6.
40. Nymoen LD, Tran T, Walter SR, Lehnbom EC, Tunestveit IK, Øie E, et al. Emergency department physicians' distribution of time in the fast paced-workflow-a novel time-motion study of drug-related activities. Int J Clin Pharm. 2021.
41. Should hospital pharmacists prescribe?contre. Can J Hosp Pharm. 2014;67(5):390-3.

42. Cavanaugh J, Pinelli N, Eckel S, Gwynne M, Daniels R, Hawes EM. Advancing Pharmacy Practice through an Innovative Ambulatory Care Transitions Program at an Academic Medical Center. Pharmacy (Basel). 2020;8(1).

Supporting information

S1 Appendix CONSORT checklist

S2 Appendix original study protocol, protocol amendments, and the timeline of the study with milestones

S3 Appendix Detailed description of the drug-related problems categories

S4 Appendix Sensitivity analyses and survival curves

Figures

Fig 1. Flow chart of patients assessed for eligibility for inclusion in the Emergency Department (ED).

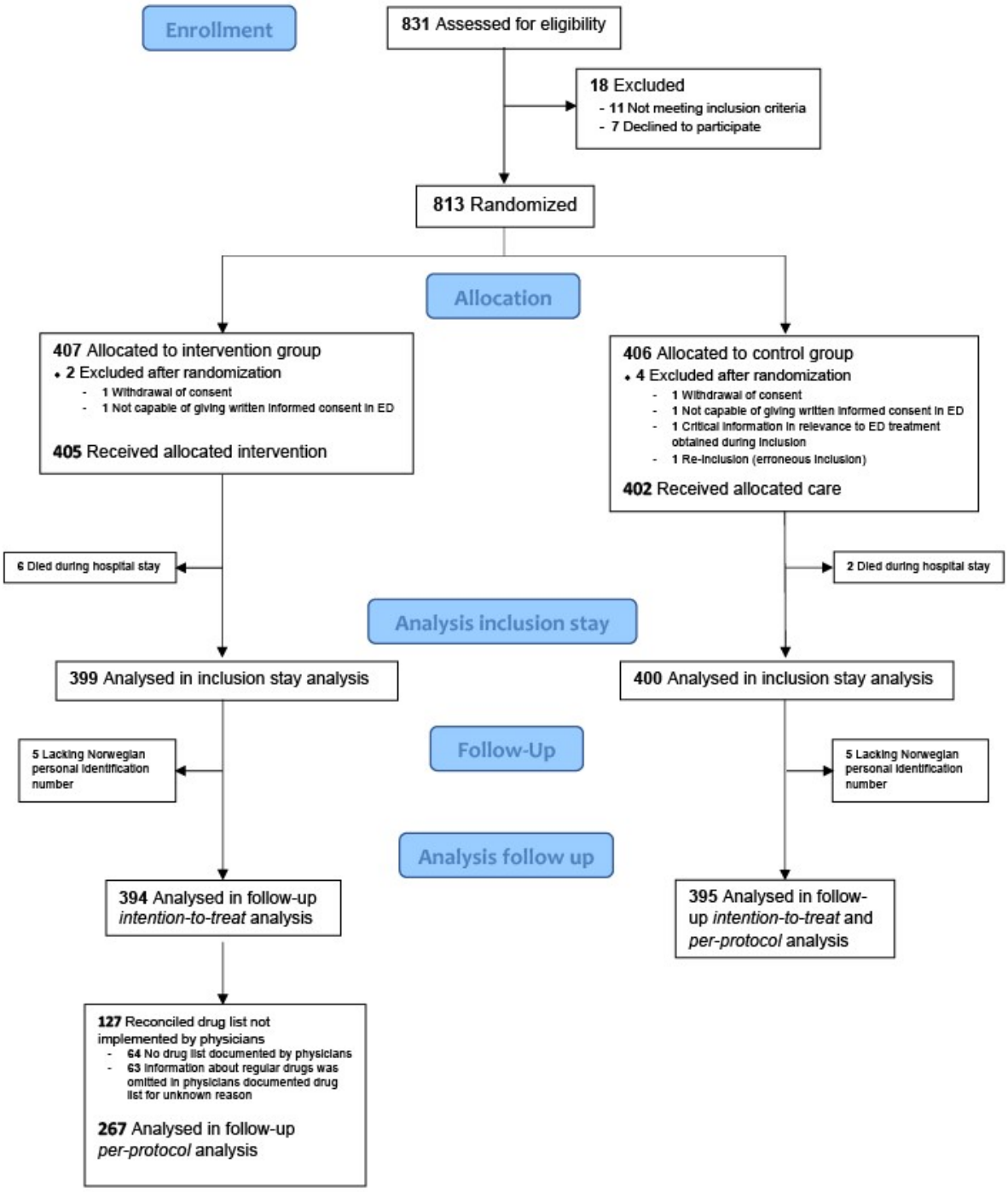


Fig 2. Study design. During emergency department (ED) stay the Intervention group (a) received standard care and pharmacist conducted systematic medication review (identifying drug-related problem), including medication reconciliation (obtaining patients' actual drug lists). Findings from medication reconciliation and medication review were discussed with ED physician and documented in the electronical patient record. The control group (b) received standard care (by physicians and nurses).

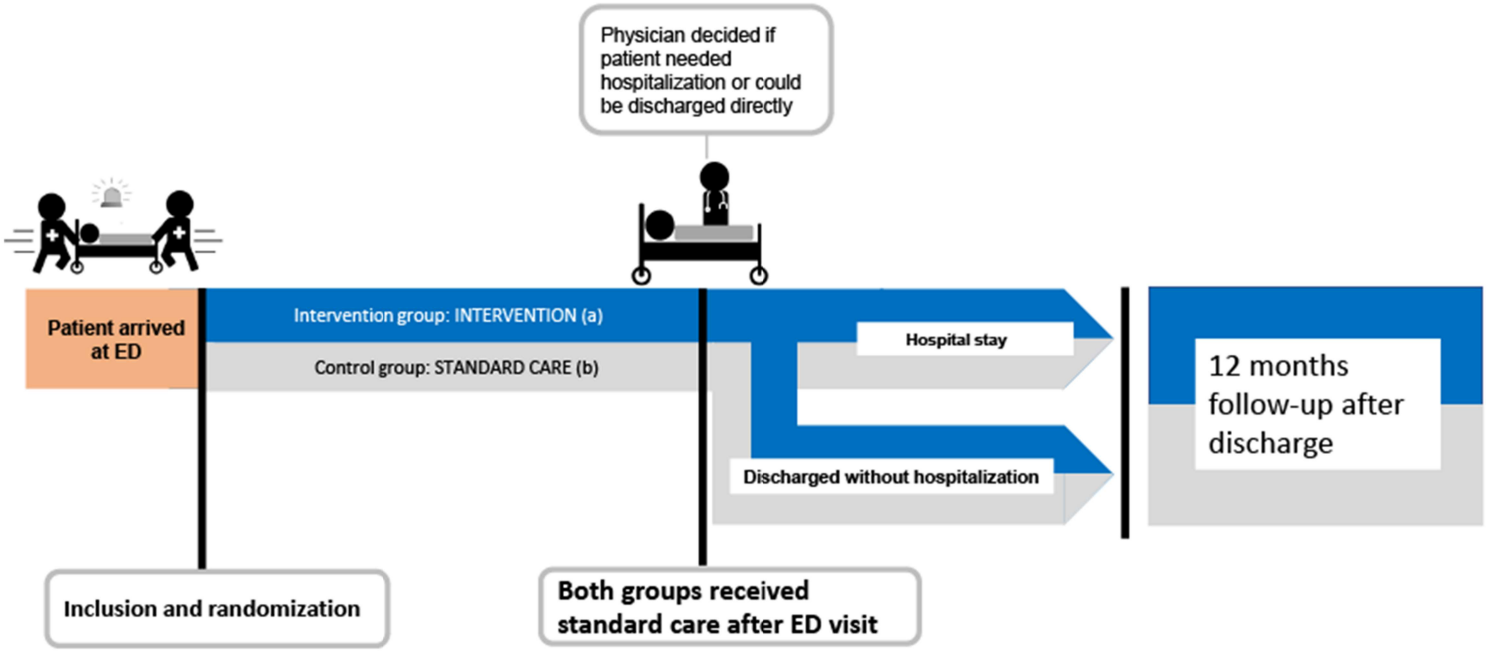
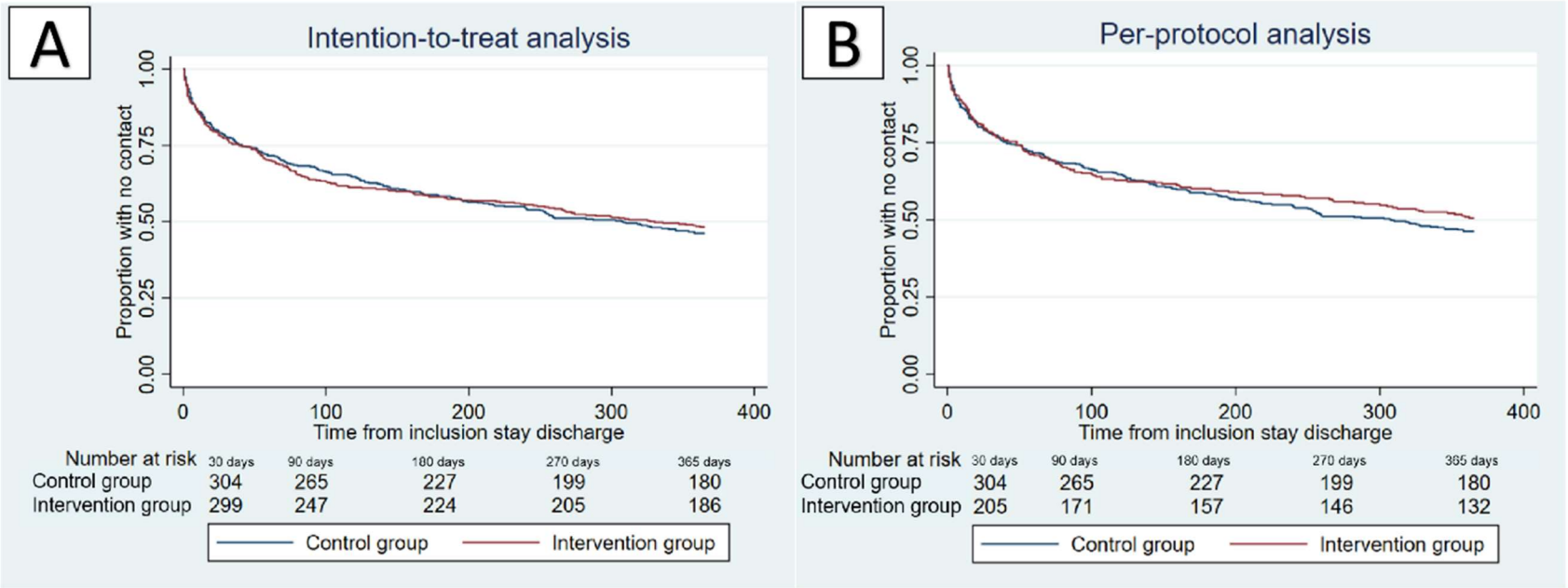


Fig 3. Time to next unplanned contact with hospital (ED-visit or hospital admission).

(A) Intention-to-treat analysis of patients with follow-up data, intervention group (n=394) vs. control group (n=395)

(B) Per-protocol analysis of patients with follow-up data, intervention group (n=267) vs. control group (n=395)



CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2-3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3-4
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4-5, 7
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	6
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	5-6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7-9
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	10-11
	6b	Any changes to trial outcomes after the trial commenced, with reasons	11
Sample size	7a	How sample size was determined	11
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	7
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	7
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	7
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6-7

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	7
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	11-12
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	12
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	5, 15
	13b	For each group, losses and exclusions after randomisation, together with reasons	5
Recruitment	14a	Dates defining the periods of recruitment and follow-up	4-5
	14b	Why the trial ended or was stopped	4
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	14
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	4, 15-17
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	15-17
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	15, 17
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	15-16
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	17
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	22-23
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	22
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	18-21
Other information			
Registration	23	Registration number and name of trial registry	2, 5
Protocol	24	Where the full trial protocol can be accessed, if available	5
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	Entered in submission system

Appendix S1 CONSORT checklist

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

S2 Appendix

Contents

Original trial protocol, June 08, 2015

Improving drug safety in emergency patients –a randomised controlled trial to investigate the effect of medication reconciliation and review on readmission rate

Study group:

Study leader: Erik H. Øie, dr.med, Chief physician medical department, Diakonhjemmet Hospital

Ph.D. –student and study manager: Lisbeth Damlien, MSc Pharmacy

Main supervisor: Kirsten K. Viktil, Associate professor II, University of Oslo, Head of Research and Pharmaceutical service. Diakonhjemmet Hospital Pharmacy

Co-supervisor: Espen Molden, Professor II, University of Oslo and Research leader, Center for Psychopharmacology, Diakonhjemmet Hosipital

Study collaborators: Ole K. Roald, dr.med., Head of the Anaesthesia and Intensive care department at Diakonhjemmet Hospital

Lasse Andreassen, MSc Health Management, unit manager at the emergency department, Diakonhjemmet Hospital

Statistician: Tron Anders Moger, PhD, MSc in Statistics, Department of Health Management and Health Economics, University of Oslo

Patient representative: Liv Hopen, member of the Norwegian Heart- and Lung Association

Reference group:

Liv Mathisen, Ph.D., Head of Research and development at Hospital Pharmacies Enterprise, South Eastern Norway

Marianne Lea, MSc Clinical Pharmacy, Ph.D.-student at Hospital Pharmacies Enterprise, South Eastern Norway

Ulrika Gillespie, PhD, Researcher at Uppsala University Hospital, Uppsala, Sweden

Summary

Background: An accurate medication history is a vital part of any hospital admission. However, studies have shown that 60-70% of hospitalised patients have at least one unintended medication discrepancy between their actual ('home') drug treatment and medication list registered at hospital admission. Medication discrepancies and drug-related problems (e.g. adverse drug reactions) is a recognised health care challenge. Currently there is lack of studies investigating the effect of interventions and actions to improve the quality of medication history recording and assessments in the emergency setting where critical decisions are made regarding further 'patient processing'. **Objective:** To test if a new working model combining medication reconciliation and medication review in emergency patients can decrease the readmission rate. **Study design:** Randomised, controlled trial at the Emergency Department, Diakonhjemmet Hospital. The control group receives standard care, while in the intervention group a clinical pharmacist is integrated in the interdisciplinary team and conducts medication reconciliation and review.

1. Background

An accurate medication history is a vital part of any hospital admission. As different sources present different information about the patient's medication history, it can be challenging identifying which medications the patients actually have been using (1-3). Studies have shown that 60-70% of hospitalised patients have at least one unintended medication discrepancy regarding their home medication regimen and the admission orders (4-8). Further, studies have estimated that 15% of hospital admissions in elderly patients are cause by adverse drug events (drug-related problems) (9, 10), studies indicates that majority of these admissions could have been prevented (10-12). Admission to an emergency department is a key vulnerable moment when patients are at increased risk of medication discrepancies, and also identification of relevant adverse drug events, such as drug-related cause of admission, is crucial. If medication discrepancies and drug-related causes of admission are not revealed in the emergency department, physicians at hospital wards potentially can inflict the patients with side-effects, interactions or therapeutic failure.

High risk patients

Through a pilot study conducted in 2014 in the emergency department, Diakonhjemmet Hospital, we found that approximately 40% of patients were admitted to the emergency department regarding their heart or lung disease. About 60% of these patients had 3 or more registered diseases and thereby had a higher risk of having a clinical relevant medication discrepancy, according to our results. Co-morbidity and extensive use of medication have also been proven as risk factors for medication discrepancies and drug-related problems by other researchers (13-19). Data from Diakonhjemmet Hospital estimates that 29.2% of patients admitted to Diakonhjemmet Hospital with asthma/COPD related cause of admission were readmitted within 30 days. Also patients with heart failure are at high risk for readmissions; 24.3% of patients admitted to Diakonhjemmet Hospital with heart failure were readmitted within 30 days. In the impending study we will get an overview of what patients are at increased risk of drug-related admissions and drug-related problems at admission, but patients with heart or lung-diseases is two of our focus groups, due to the high proportion of co-morbidity and high risk of readmissions in these patients.

Medication reconciliation and medication review

Medication reconciliation is the systematic process of obtaining a complete overview of the patients medications, including name, strength, dosage and route of administration. Preferably this is obtained by interviewing the patient and using a checklist, when needed, complimentary information is obtained from relevant level of care. If the patient is not in charge of their medication an updated medication list is obtained from the relevant level of care. Medication review is the systematic process of evaluating the patient's medication regimen individually to optimise the effect of and reduce the risk of medication use.

Medication reconciliation performed at hospital wards within 48 hours after the patient is admitted, is proved through both national and international studies to be an effective way of reducing the number of medication discrepancies (20-22). However a recently report from the Norwegian knowledge centre for the health service states that there is lack of studies investigating the clinically relevant outcome of performing medication reconciliation, e.g. effect on readmissions and length of stay (22). To identify, prevent, and solve clinical relevant drug-related problems such as interaction, adverse drug reactions, too high dosages etc. a systematic medication review is shown to be an effective method (23, 24), traditionally this is conducted during the hospital stay. It is a fact that the length of stay in Norwegian hospitals is becoming shorter, and therefore, in a perspective of patient safety and also to secure an

effectively hospital stay, medication reconciliation and medication review could advantageously be conducted during the stay at the emergency department. This to ensure that the physician at the emergency department has all the information he need to make an informed decision about the patient being hospitalised or not, and about the further treatment of the patient.

In the earlier mentioned pilot study we developed a working model for conducting medication reconciliation at the point of admission, and further, we evolved a prioritising model for identifying patients with increased risk of medication discrepancies at admission to the emergency department (paper submitted). We found that 62% of the patients admitted to the emergency department had one or more clinical relevant medication discrepancy when we compared the medication list obtained by physicians in the emergency department and the list obtained through medication reconciliation. We also found that the working model we developed was perceived efficient by physicians at the emergency department. In Norway it is currently no established procedure for systematically conducting medication reconciliation and medication review at the point of admission to the emergency department. The clinically relevant outcome of conducting these interventions at the point of admission to the emergency department is scarcely investigated.

2. Hypothesis and objectives

2.1 Research hypothesis

Implementation of a working model for combined medication reconciliation and medication review at point of admission to the emergency department will improve drug safety and reduce the proportion of patients who are readmitted after 12 months (included visits to the emergency department).

2.2 Objective

The overall primary objective of this study is to test if a working model for performing medication reconciliation and medication review at the emergency department can decrease proportion of patients who is readmitted (included visits to emergency department).

Secondary objectives is to test if the working model for performing combined medication reconciliation and medication review at the emergency department can decrease the average length of stay in the emergency department and for the total hospital stay.

And also investigate if the working model can increases the proportion of patients who are sent home or is referred to the out-patient-clinic opposed to being hospitalised.

Further, it will be investigated if a prioritising model can be used to predict what patients have the highest risk of drug-related admissions and drug-related problems at admission to the emergency department.

We will be investigating if the new working model is perceived as effective by the health personnel and patients at the emergency department through a semi structural questionnaire.

To obtain the patients perspective of the challenges outlined in this study, we will invite a random sample of included patients to a group interview.

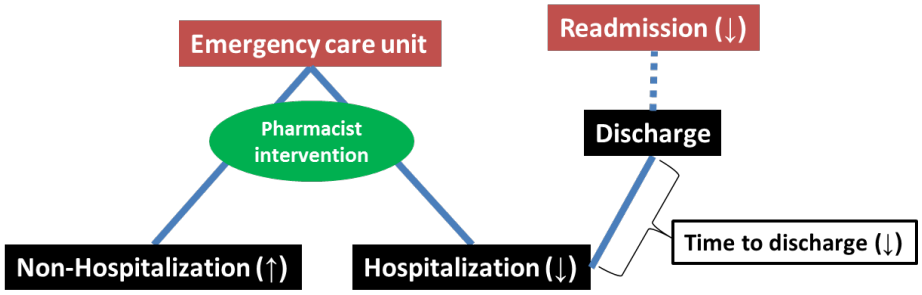


Figure 1: Illustration of the hypothesis of this study, i.e. that the intervention increases the proportion of non-hospitalised patients (indicated by upward arrow) while decreasing hospitalisation degree, readmission rate (primary endpoint) and time to discharge (indicated by downward arrows)

3. Methods

3.1 Study design

This is a randomised, controlled trial, non-blinded. Patients admitted to the emergency department will be included. Patients will be randomised into two groups; one control group, who will receive standard care and one intervention group, who will receive medication reconciliation and medication review at the emergency department. These interventions will be conducted by a clinical pharmacist in the interdisciplinary team. The study design is illustrated in figure 2.

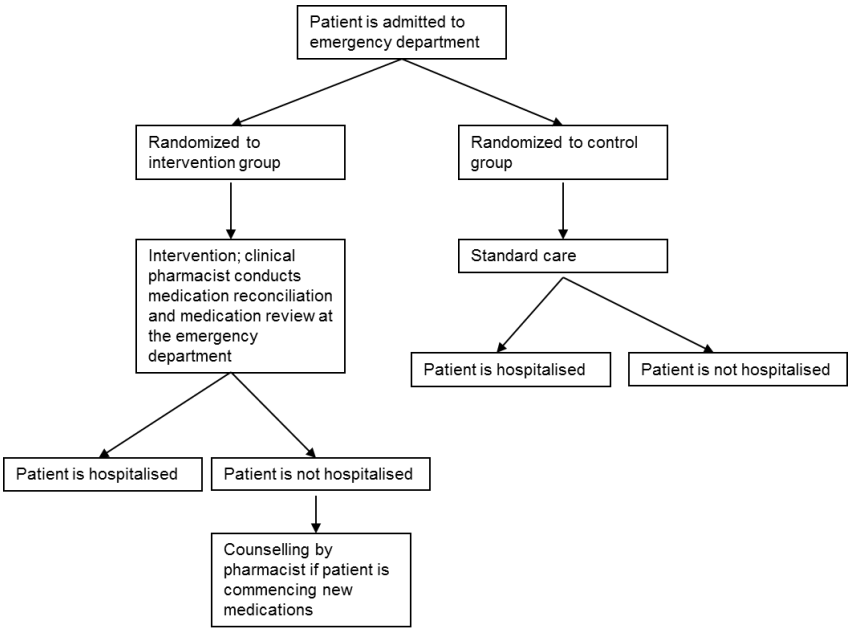


Figure 2: Illustration of the study design

3.2 Patients and study settings

Patients admitted to the emergency department at Diakonhjemmet Hospital will be included consecutively. Yearly about 13.000 patients are presented to this emergency department and the number has increased rapidly over the past years. In 2015, 40-45 patients are daily presented to the emergency department. Patients with medical and surgical issues are admitted to the same emergency department and therefore both groups of patients will be included in the study. However, elderly patients with hip fractures are because of high risk of post-operative infections fast-tracked directly to a surgical ward and are not triaged or examined in the emergency department, hence these patients will not be included in this study. The mean length of stay at the emergency department at Diakonhjemmet Hospital is 2.8 hours (2014). The study will be carried out as collaboration between the emergency department at the hospital and the hospital pharmacy.

3.3 Inclusion and exclusion criteria

Patients will be included if they meet the following criteria:

- Patients ≥ 18 years admitted to the emergency department
- Able and willing to provide written consent (*see 3.4 Inclusion procedure and 3.13 Ethics*)

Patients will be excluded if they meet one of the following criteria:

- Patient are already included
- Terminal ill patients with short life expectancy
- Control group patients where physician at the emergency department request an assessment from a pharmacist
- Control group patients where the study pharmacist reveal drug-related problems of major clinical relevance and has to intervene

3.4 Inclusion procedure

Staff at the emergency department, including physicians and nurses will be informed about the study. At admission, if the patient is eligible, the study pharmacist will describe the study to each potential participant and/or their next of kin, then provide written information about the study and answer potential questions. If patients temporary are unable to consent when asked to participate (e.g. delirium) their next of kin will be asked to supply a preliminary consent in the patients place. If the patient later refuses to participate he/she will be excluded from the trial, and any registered data on the patient will be deleted.

3.5 Randomisation

Patients will be randomised to control- or intervention group at admission to the emergency department. We will randomise the days and not patients, this to reduce the spill over of methodology because the same nurses and physicians are involved in both study groups (*see 8. Risk management)*. Per week we therefore will randomise what days will be intervention days and what days will be control days. The randomisation process will be conducted by department of Biostatistics and epidemiology at Oslo University Hospital. They will deliver randomisation envelopes, and the study manager will follow randomisation procedure for all included patients.

3.6 Standard care

A physician and a nurse will perform relevant examinations when a patient is admitted to the emergency department, and further, it will be decided if the patient will be hospitalised or not. Pharmacist will not intervene on these patients. Before the patients are transferred to a specialised ward, the physician will acquire the patient's medication history, either by asking the patient and/or using available information from relevant sources for instance from the referral papers. This is the standard routine care as it is performed today. The medication list is documented in the electronic patient record and also handwritten by the physician in the medication chart.

3.7 The intervention

3.7.1 Admission

In addition to physicians, nurses and others, pharmacist will be a part of the interdisciplinary team at the emergency department. Medication reconciliation will be conducted by a clinical pharmacist before the patient's medication history is registered by the physician at the emergency department. Information obtained will be communicated to the physician in charge of the patient. Medication review will be conducted on the basis of data from the medication reconciliation and available clinical information; clinical chemical information is available in most patients within short time of admission. Revealed drug-related problems relevant to the admission will be discussed with physician at the emergency department. Other drug-related problems considered clinical relevant by the study pharmacist will either be discussed with physician at the emergency department or be documented in the electronically patient journal for follow up at the hospital ward or general practitioner/nursing home etc. if the patient is not hospitalised.

3.7.2 Discharge from the emergency department:

When an intervention group patient is discharged directly from the emergency department, with new medications prescribed, an education session with the pharmacist will be arranged. The goal is that patients get all the information they need to use their medicines correctly after discharge. The patients are encouraged to ask questions about their medicines during this session. If any additional drug-related problems are identified during the education session, these will be discussed with the physician at the emergency department immediately, i.e. before the patient leaves the hospital.

3.8 Data collection and follow up

The data collection for the study will start 01.05.2016. A total of 800 study participants will be included (*see 3 .11 Sample size calculation*).

Baseline data will be collected at inclusion for both study arms. Data will be collected from hospital and pharmacy records, general practitioners, primary care (e.g. nursing home, community health service), patients and/or relatives. General demographics to be collected include age, gender, cause of admission to the emergency department, help from community health services with medications and delivery of multi-dosage packed medications, earlier registered medication history. For the control group medical and medication history will be obtained from the electronically patient journal and medication charts. For the intervention group, information will be collected as described in the medication reconciliation procedure above. If other clinical pharmacists at the different hospital wards intervene on the patients during hospital stay, this will be registered. Follow-up regarding registration of readmissions will be recorded at 6 and 12 months after inclusion for both study arms. To be able to register readmissions access to the Norwegian Patient Registry must be granted.

Clinical relevance of the drug-related admissions and other drug-related problems revealed will be evaluated retrospectively by an interdisciplinary team, using a published scale (25).

3.9 Data management

Each study participant will be given a unique study number. The code list will be kept electronically in the hospitals password-secured research server. Patient data will be collected on a customised data collection form; this form will be piloted during the study preparation phase (*see 4. Progress plan*). Patient-identifiable data registered on paper forms will be stored at the hospital in accordance with hospital journal information routines (*see 3.13 Ethics*).

3.10 Outcome measures

Primary endpoint:

- Difference between control and intervention groups in proportion of patients readmitted to any hospital within 12 months (endpoint including revisits to the emergency department)

Secondary endpoints:

- Difference between control and intervention groups in proportion of patients not hospitalised following admission to in the emergency department
- Difference between control and intervention groups in the length of stay at the emergency department.
- Difference between control group and groups in the overall length of hospital stay
- Describe the frequency of drug-related admissions in the intervention group, describe consequences, out-come and follow up for these patients.
- Difference between control group and intervention group, in regards to average time to next contact with hospital and average number of readmissions.

Other outcomes:

- Describe workflow, information flow and multidisciplinary collaboration using results from survey amongst the involved physicians and other healthcare personnel at the emergency department and relevant hospital wards
- Describe patients view on medication regimen, believes and concerns about medication (26, 27), medication lists and drug-related admissions using results from group interview and survey amongst a randomised sample of patients. Every 10^{th} included patient (10%) will retrospectively be invited to participate in the group interview. And every 4^{th} included patient (25%) will retrospectively be invited to fill out a survey.

3.11 Sample size calculation

Available information about readmission frequency at Diakonhjemmet Hospital is based on 30 days follow up, and therefore cannot be used to calculate proportion of patients readmitted after 12 months. However, numbers from Oslo University Hospital estimate a readmission proportion of 50% after 12 months in a comparable patient population. We therefore use this estimate as the expected readmission rate in the control group.

In a previous Swedish study conducted by Ulrika Gillespie (12) who is member of our reference group, a 16% reduction in hospital revisits within 12 months was found amongst older patients (>80 years) following a comparable intervention as described in our protocol.

On this basis, it will be necessary to include at least 146 patients in each group to show a significant effect on the primary endpoint (significance level of 5%, study power of 80%). However, the elderly patients included in the Swedish study have more comorbidity and therefore more use of health care resources. The patients in our study will be 18 years and older and thereby the difference between our control group and intervention group probably will be smaller. A more realistic difference between our groups is 10%, thereby 385 patients would have to be included in each group to show a significant effect on the primary endpoint. To compensate for dropout we aim to include 400 patients in each study group, thus a total of 800 patients. Based on statistics from Diakonhjemmet Hospital, inclusion of this amount of patients from the Emergency Department would require an inclusion period of 12 months.

3.12 Statistics and analysis

Statistical analyses will be conducted in IBM SPSS Statistics. Data will be assessed for normality and analysed according to appropriate statistical tests. The baseline demographic and clinical characteristics will be summarised using proportions, means and standard deviations, or median and interquartile range, as appropriate. Baseline comparisons: characteristics of study participants in the two study groups will be compared using the chi-square test for categorical variables and the Student's *t*-test or non-parametric equivalent (e.g. the Mann-Whitney *U* test) for continuous variables. Multivariable analysis (logistic regression) will be used to compare endpoints between study groups while adjusting for prognostic variables and potential confounders. All statistical tests will be interpreted with a significance level of 5% (two-tailed). For building the model for prioritising patients at increased risk of drug-related admissions and drug-related problems at admission to the emergency department binary regression analysis will be used. Data will be analysed according to intention-to-treat (ITT) principles. In addition to ITT analysis, per protocol analysis will also be performed.

3.13 Ethics

Implementing a working model for medication reconciliation and medication review in the emergency department will not have any other disadvantages for the patients than they may, in the study setting, have to answer the same questions several times and this may be an additional burden. Overall the patient will probably benefit from participating in the study, as their medication list will be quality assured, and assessed for drug-related problems at admission to the emergency department. The study will however strive for establishing a working model causing the patient least possible burden. The procedures implemented in this study will not delay the acute treatment of the patient.

Preferably patients will be asked for written consent before they are included in the study. Although in the acute situation many patient will temporarily not be able to give written consent for participating. However it is not ethical just to exclude these patients since our hypothesis is that medication reconciliation and medication review are beneficial for the patients. In such cases the patient will be asked for written consent as soon as he or she is able to do so or their next of kin will be asked to supply consent in the patients place. If the patient later refuses to participate he/she will be excluded from the trial and all registered patient data will be deleted. Patients who are mentally unable to consent to participate, their next of kin will be asked to supply consent in the patients place.

Patient data will be registered on paper forms, which will be de-identified after the patient data is transferred de-identified to the study database on the hospital research server; password protected. Only a code list will connect the patient to his or her data. Paper forms will at all times be kept locked in a fire safe cabinet and be accessible only to authorised study personnel, and eventually the forms will be maculated. De-identified patient information will not be brought out of the hospital. The code

list connecting the patients to their data will at the latest be deleted 3 years after start of data collection.

When results are published it will not be possible to identify individual patients.

An application for ethical approval will be submitted to the Regional committee for medical and health research ethics (REC). The study protocol also has to be approved by the research committee at Diakonhjemmet Hospital.

4. Progress plan

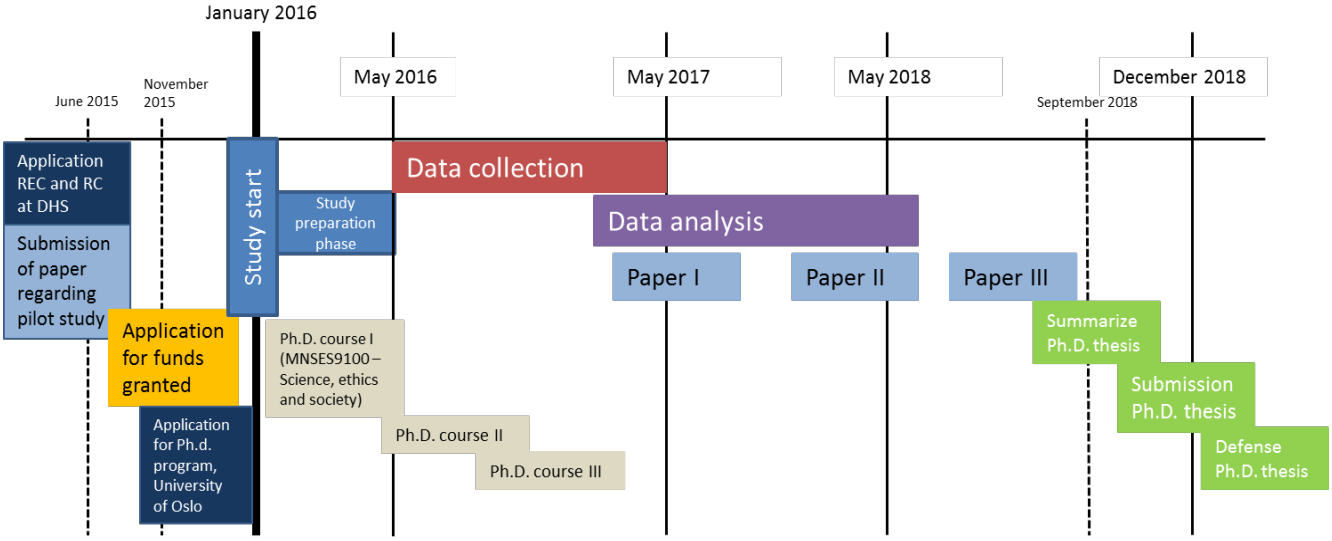


Illustration of progress plan, REC: Regional committee for medical and health research ethics, RC at DHS: the Research Committee at Diakonhjemmet Hospital.

- Before study start at 1. January 2016, an application for ethical approval will be submitted to the Regional Committee for Medical and Health Research Ethics (REC). The study protocol will also be sent to the Research Committee at Diakonhjemmet Hospital (RC at DHS) for approval.
- The Ph.D.-Candidate will apply for admission to the Ph.D.-program at the University of Oslo before study start. The Ph.D.-program require that the Ph.D. –candidate complete Ph.D.-courses rewarded with at least 30 credits, the course MNSES9100 –Science, ethics and society is mandatory.
- In the study preparation phase from 01.01.16-01.05.16 preparations for the data collection is done (pilot-test the data collection forms, inform the staff at the emergency department, prepare the study-database etc.)
- Data collection starts 01.05.16 and will continue for approximately one year or until 800 patients is included.
- 2017-18: analysing data and preparing/organising data for publication of papers
- 2017: Publication first paper
- 2018: Publication second paper
- 2018: Publication third paper
- 2018: Summarize Ph.D.-thesis
- December 2018: Submission Ph.D.-thesis
- January 2019: Defence of the Ph.D.-thesis

5. Patient involvement

A patient-representative has been involved in the evolvement of the study design. The patient-representative will be involved in evaluation of the working model for medication reconciliation and medication review in the emergency department. When the results of the study are disseminated the patient-representative will be important for distributing the results to patient organisations. The patient perspective is important in the clinical practice, therefore a survey regarding the effectiveness of the new working model in the emergency department will be conducted amongst a randomised sample of the included patients. The results of this survey will be part of the evaluation of the working model.

To get more insight in the patient's perspective of the challenges outlined in this study we will invite a random sample of included patients to a group interview. The results of the interviews will provide the basis for customising the working model to the patients' beliefs and needs.

6. Publication and dissemination of results

The already performed pilot study and planned RCT will provide data for at least four scientific papers (see specifications below), which will have the potential for publications in international peer-reviewed medical, pharmaceutical and nursing journals. We will aim for publications in recognized journals, and pay for "open access".

1. Drug Safety at admission to Emergency Department - an innovative model for prioritising patients for Medication Reconciliation (PRIOMER) (Submitted)
2. Drug safety at admission to emergency department -an innovative model for prioritising patients for medication review
3. A novel interdisciplinary model at an emergency department –how does it influence readmission rate and how does it influence work flow and effectiveness?
4. Incidence of drug-related admissions to a Norwegian emergency department –could some of the admission have been prevented?

During the study period, the Ph.D.-student will attend and present research results for instance at the following meetings:

- The European Society for Emergency Medicine
- International Conference of Emergency Medicine
- The International Society for Pharmacoepidemiology Congress (ISPE)
- European Society of Clinical Pharmacy (ESCP)
- Nordic Social Pharmacy and Health Services Research Conference
- Norwegian yearly conference on patient safety

A key component in this study is also to disseminate the results to the relevant patients groups. We will take advantage of the hospitals own Department of Communication, which helps researchers with dissemination of results. Additionally dissemination channels of the Norwegian Heart- and Lung Association, our collaborator will be utilized to disclose the results from the study. And also the patient representative will be involved in the dissemination process.

7. Foundation of the study

The study is a collaboration between the emergency department, Diakonhjemmet Hospital and Diakonhjemmet Hospital Pharmacy, head of both divisions supports the study.

Since 2011 the Norwegian patient safety program, initiated by the Norwegian Ministry of Health and Care Service, has been focusing on medication reconciliation conducted in hospitals as one of several initiatives to reduce patient harm. According to this Diakonhjemmet Hospital has implemented some of the initiatives presented by the patient safety program to reduce medication discrepancies in hospital. Our study does not inflict with the initiative in the Norwegian patient safety program, on the contrary our study will give additional information about how to perform medication reconciliation in the most efficient manner in the hospital setting and also information about clinically relevant outcomes of medication reconciliation. The common focus on medication reconciliation indicates that the challenges outlined in our study are challenges that also are identified by the Norwegian authorities.

8. ***Risk management***

The most important risk of the study is not to reach the needed number of patients to get enough power to receive statistical significant results. If we after 6 months have not recruited 50 % of the patients we will recruit more clinical pharmacists to include patients. Another present risk is the risk of spill over of methodology because the same nurses and physicians are involved in treating patients in both study groups. However, we believe that the intervention, the methodology of medication reconciliation and medication review, is so comprehensive that it is not easily transferred without being thoroughly taught and trained. We also will randomise the days for intervention and control to try to control the spill over effect.

As part of the hospital's aim of improving medication safety, some of the elements of the medication reconciliation might be implemented as part of standard care during the study period (*see 7. Foundation of the study)*. This might reduce the differences between the groups. We can only handle this by keeping track of patients and take this into concern in analysis.

At Diakonhjemmet Hospital clinical pharmacists is member of the interdisciplinary team at the hospital wards. Therefore patients in both study arms can be seen by a pharmacist during the hospital stay. This can affect the outcome in reducing the differences between the groups. We can only handle this by keeping track of patients and take this into concern in analysis.

References

1. Midlov P, Bergkvist A, Bondesson A, Eriksson T, Hoglund P. Medication errors when transferring elderly patients between primary health care and hospital care. Pharm World Sci. 2005;27(2):116-20.
2. Bakken K, Larsen E, Lindberg PC, Rygh E, Hjortdahl P. [Insufficient communication and information regarding patient medication in the primary healthcare]. Tidsskr Nor Laegeforen. 2007;127(13):1766-9.
3. Galvin M, Jago-Byrne MC, Fitzsimons M, Grimes T. Clinical pharmacist's contribution to medication reconciliation on admission to hospital in Ireland. Int J Clin Pharm. 2013;35(1):14-21.
4. Vira T, Colquhoun M, Etchells E. Reconcilable differences: Correcting medication errors at hospital admission and discharge. Quality and Safety in Health Care. 2006;15(2):122-6.
5. Rognstad S, Straand J. [Do general practitioners know what medication community nurses give their shared patients?]. Tidsskr Nor Laegeforen. 2004;124(6):810-2.
6. Myhr R, Kimsas A. [Medication errors when transferring within health care services]. Tidsskr Nor Laegeforen. 1999;119(8):1087-91.

7. Hellstrom LM, Bondesson A, Hoglund P, Eriksson T. Errors in medication history at hospital admission: Prevalence and predicting factors. BMC Clin Pharmacol. 2012;12(9).
8. Scullin C, Scott MG, Hogg A, McElnay JC. An innovative approach to integrated medicines management. J Eval Clin Pract. 2007;13(5):781-8.
9. Kongkaew C, Noyce PR, Ashcroft DM. Hospital admissions associated with adverse drug reactions: a systematic review of prospective observational studies. Ann Pharmacother. 2008;42(7):1017-25.
10. Beijer HJ, de Blaey CJ. Hospitalisations caused by adverse drug reactions (ADR): a meta-analysis of observational studies. Pharm World Sci. 2002;24(2):46-54.
11. Howard RL, Avery AJ, Howard PD, Partridge M. Investigation into the reasons for preventable drug related admissions to a medical admissions unit: observational study. Quality & safety in health care. 2003;12(4):280-5.
12. 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.
13. Unroe KT, Pfeiffenberger T, Pharm SR, Jastrzembski J, Lokhnygina Y, Colon-Emeric C. Inpatient medication reconciliation at admission and discharge: A retrospective cohort study of age and other risk factors for medication discrepancies. American Journal Geriatric Pharmacotherapy. 2010;8(2):115-26.
14. Nester TM, Hale LS. Effectiveness of a pharmacist-acquired medication history in promoting patient safety. Am J Health Syst Pharm. 2002;59(22):2221-5.
15. Kramer JS, Hopkins PJ, Rosendale JC, Garrelts JC, Hale LS, Nester TM, et al. Implementation of an electronic system for medication reconciliation. Am J Health Syst Pharm. 2007;64(4):404-22.
16. Crook M, Ajdukovic M, Angley C, Soulsby N, Doecke C, Stupans I, et al. Eliciting comprehensive medication histories in the emergency department: The role of the pharmacist. Pharm Pract (Granada). 2007;5(2):78-84.
17. Walker PC, Bernstein SJ, Tucker Jones JN, Piersma J, Kim HW, Regal RE, et al. Impact of a pharmacist-facilitated hospital discharge program: A quasi-experimental study. Arch Intern Med. 2009;169(21):2003-10.
18. Forster AJ, Murff HJ, Peterson JF, Gandhi TK, Bates DW. Adverse drug events occurring following hospital discharge. J Gen Intern Med. 2005;20(4):317-23.
19. Field TS, Gurwitz JH, Harrold LR, Rothschild J, DeBellis KR, Seger AC, et al. Risk factors for adverse drug events among older adults in the ambulatory setting. J Am Geriatr Soc. 2004;52(8):1349-54.
20. Becerra-Camargo J, Martinez-Martinez F, Garcia-Jimenez E. A multicentre, double-blind, randomised, controlled, parallel-group study of the effectiveness of a pharmacist-acquired medication history in an emergency department. BMC Health Serv Res. 2013;13:337.
21. The Norwegian National Patient Safety Program; In safe hands, medication reconciliation: Programme secreteriate at the Norwegian Knowledge Centre for the Health Service and The Norwegian Directorate of Health; 2010. Available from: www.pasientsikkerhetsprogrammet.no.
22. Holte HH, Hafstad E, Vist GE Overview of reviews on effect of medication reconciliation: Nasjonalt Kunnskapssenter for helsetjenesten; 2015.
23. Blix HS, Viktil KK, Moger TA, Reikvam A. Characteristics of drug-related problems discussed by hospital pharmacists in multidisciplinary teams. Pharm World Sci. 2006;28(3):152-8.
24. Viktil KK, Blix HS. The impact of clinical pharmacists on drug-related problems and clinical outcomes. Basic Clin Pharmacol Toxicol. 2008;102(3):275-80.

25. Blix HS, Viktil KK, Reikvam A, Moger TA, Hjemaas BJ, Pretsch P, et al. The majority of hospitalised patients have drug-related problems: results from a prospective study in general hospitals. Eur J Clin Pharmacol. 2004;60(9):651-8.
26. Horne R, Weinman J, Hankins M. The beliefs about medicines questionnaire: the development and evaluation of a new method for assessing the cognitive representation of medication. Psychol Health. 1999(14):1–24.
27. Jonsdottir H, Friis S, Horne R, Pettersen KI, Reikvam A, Andreassen OA. Beliefs about medications: measurement and relationship to adherence in patients with severe mental disorders. Acta Psychiatr Scand. 2009;119(1):78-84.

Protocol amendments

September 9, 2016

- In the original trial protocol, it was proposed that written consent could be obtained from patients post-inclusion or from next of kin if the patient were not capable of providing this themselves during the emergency department stay. This was not approved by the Regional Committee for Medical and Health Research Ethics. A change in trial protocol were required for ethical approval.
  The inclusion criteria for the trial were changed to: *all patients arriving at the investigated emergency department, willing to/capable of providing written, informed consent.*
- Lasse Andreassen left the position as unit manager at the emergency department, Diakonhjemmet Hospital. Tord Kjesbu which were the new manager replaced Lasse Andreassen in the study group.

The change was approved by the Regional Committee for Medical and Health Research Ethics September 21, 2016.

March 14, 2017

After consultation with a statistician at department of Biostatistics and epidemiology at Oslo University Hospital, randomization procedure was altered. In the original protocol it was planned to randomise the data collection days and not patients, to reduce the spill over of methodology. However, the risk of selection bias when including intervention group patients and control group patients on different days, was considered higher than the risk of spill over of methodology. Hence, it was decided to randomize each patient at inclusion as described in the article.

March 17, 2017

- The start- and endpoint of the trial were changed, due to delay in financial support. Start of the trial was set to January 1, 2017, and endpoint March 31, 2021.
- In addition, a change in the original written consent scheme was necessary, this to clarify to participant what information the trial aimed to record and report.

The change was approved by the Regional Committee for Medical and Health Research Ethics March 21, 2017.

February-April 2017

Standard operation procedures were developed for:

- patient inclusion and randomization
- trial medication reconciliation and medication review
- registration of collected patient data

May 2017

The original protocol stated an exclusion criterion regarding terminal ill patients with short life expectancy. Sufficient information to clearly define these patients was not accessible in the fast-paced workflow in the emergency department. Hence, in May 2017 it was decided to include patients regardless of this exclusion criterion.

June 8, 2018

- A clarification regarding variables which should be harvested from the Norwegian Patient Registers was added to the protocol. The list of specified variables is listed below.

The clarification was approved by the Regional Committee for Medical and Health Research Ethics June 27, 2018.

List of specific variables harvested from the Norwegian Patient Registers approved by the Regional Committee for Medical and Health Research Ethics:

-Inndato og -tid for oppholdet (innDato / innTid) *(admission date and time)*
-Utskrivningsdato og –tid for oppholdet (utDato / utTid) *(discharge date and time)*
-Institusjonsnummer (org.nr) (institusjonID) *(institutional identification number of where patient was admitted)*
-Hvor pasienten kommer fra/ går til (fraSted / tilSted) *(indicator of where patients were admitted from and dicharged to)*
-Institusjonsnummer pasienten kommer fra/ går til (fraInstitusjonID / tilInstitusjonID) (*institutional identification number of what institution patient were admitted from and dicharged to)*
-Døgnopphold, dagopphold eller poliklinisk konsultasjon (omsorgsniva) *(indicator of the admission were an over-night stay, not an over-night stay or out-patient clinic contact)*
-Tidspunkt mht utskrivningsklar *(data when the patient treatment were completed during hospital stay)*
-Oppholdets liggetid *(length of stay)*
-Type kontakt, for polikliniske konsultasjoner/ dagbehandlinger (kontaktType)
-Klassifikasjonen av sykdommer og beslektede helseproblemer (ICD-10 diagnosekoder) *(ICD-10 code registered at discharge)*
-Angir om tilstanden er diagnostisert tidligere (nyTilstand) *(if the registered ICD-10 code was an earlier diagnosed condition)*
-Om oppholdet er et avdelings- eller sykehusopphold (niva) *(department or hospital stay)*
-Diagnoserelaterte grupper (drg) *(indicator of what condition were treated, used for economic analysis)*
-Korrigert vekt for drg poeng (korrvekt) *(indicator of what condition were treated, used for economic analysis)*
-Vekting av drg poeng (vekt) *(indicator of what condition were treated, used for economic analysis)*
-Antall liggedager innenfor aktuell DRG som er grunnlag for kostnadsvektberegninger
(trimpkt) *(indicator of length of stay for each treated condition, used for economic analysis)*
-Om DRG-en er medisinsk eller kirurgisk (M/K/blank) (drg_type) *(medical or surgical condition treated)*
-Kompliserende DRG (Ja/Nei) (komp_drg) *(complicating condisions)*
-Dagkirurgisk DRG (Ja/Nei) (dag_kir) *(surgical out-patient clinic conditions)*
-Spesifikk DRG (blank eller Ja) (spes_drg)
-Type rehabilitering (Vanling, komples eller sekundær) (rehabType) *(if admission could be classified as rehabilitation)*
-Gruppering av DRG-er til hoveddiagnosegruppe (hdg)
-Samtykkekompetanse *(if patient were competent of giving consent)*
-Informasjon om død og dødstidspunkt: død per 30. juni 2019? Dato for dødstidspunkt, dersom
død per juni 2019 *(information regarding death during follow-up)*

August 2018

The original protocol stated additional investigations of the study population and other investigations:

- Every 10th included patient (10%), and every 4th included patient (25%) retrospectively would be invited to participate in a group interview or fill out a survey, respectively. This to describe patients view on medication regimen, believes and concerns about medication (26, 27), medication lists and drug-related admissions.
- A survey amongst the involved physicians and other healthcare personnel at the emergency department and relevant hospital wards, should be conducted to describe workflow, information flow and multidisciplinary collaboration

Due to restricted resources, we were not able to perform these parts of the trial.
Workflow, information flow, and multidisciplinary collaboration was instead illustrated by implementation of pharmacists' recommendations by physicians.

March 2020

It was decided to add amendments in secondary outcome due to the relatively short intervention compared with the long follow-up time. The following secondary outcomes were added:

- Proportion of patients with an unplanned contact with hospital:
    - within 90 days after inclusion stay discharge.
    - within 30 days after inclusion stay discharge.

Timeline of the trial with milestones

May 2015: Original trial protocol written

June 2015-June 2016: Maternity leave PhD student

September 10, 2015: Ethical approval of the original trial protocol. The Regional Committee for Medical and Health Research Ethics (REC) approved the trial protocol. The trial was also approved by the Research Committee at Diakonhjemmet Hospital (September 2016).

January 1, 2017, to April 24, 2017: Pre-study period, practical planning of data inclusion period

April 2017: Registration and publication of the trial on clinicaltrials.gov`s website, based on the original trial protocol, Identifier: NCT03123640

April 24, 2017: patient inclusion started

May 16, 2018: patient inclusion completed

May 30, 2019: last day of follow-up on post-discharge outcomes

June 4, 2018: Application for harvesting outcome data was sent to the Norwegian Patient Registers**

April 2019 to February 2020: Maternity leave PhD student

January 15, 2020: Outcome data from the Norwegian Patient Registry was received

March 2020 to February 2021: Demographic data files prepared for analysis

February 2021 to June 2021: Outcome data files from Norwegian Patient registries prepared for analysis

August 2021 to November 2021: Outcome analyses conducted

**Huge workload at the Registers entails a very long processing time for outcome data.

S3 Appendix Detailed description of the drug-related problems categories

Table A. Description of drug-related problem categories. All drugs documented in the patients' reconciled drug lists were assessed according to these categories during medication review. The utilized drug-related problem categorization is based on a validated medication review-tool[1].

Drug-related problems categories	Detailed description
Drug monitoring	Therapeutic drug monitoring or laboratory monitoring was needed, for example for digoxin, warfarin, levothyroxine, antidiabetics, statins
Adherence issues	Intentionally, or unintentionally deviation from the intended usage of prescribed drugs
Adverse effects	Symptoms or changed laboratory values that seems to be associated with drug treatment
Drug-interactions	Clinically relevant drug-interactions (both drug-drug interactions and drug-supplements/herbal preparations interactions were included)
Non-optimal drug therapy	Adjustments in the patient's drug therapy (included both dose adjustments and temporarily stopping drug therapy) are needed due to: - the acute situation - reduced organ function (kidney failure, reduced liver function etc.) - contraindications
Unnecessary drug	Drug treatment without indication according to guidelines
Drug-related ED visit	Considering all the above-mentioned categories, study pharmacists assessed if the current ED visit could be connected to one or more of the drugs used by the patient at admission

1. Ruths S, Viktil KK, Blix HS. [Classification of drug-related problems]. Tidsskr Nor Laegeforen 2007; 127 (23):3073-3076.

S4 Appendix Sensitivity analyses and survival curves

Table A. Sensitivity analysis on inclusion stay data.

Inclusion stay endpoints		**Intervention group *n=405***	**Control group *n=402***	**P-value**
Patients not hospitalized	*Number (%)*	129 (31.9%)	130 (32.3%)	0.882 [a]
Length of emergency department stay	*Median, hours (IQR, range)*	3.1 (2.1, 0.6-10.6)	3.0 (1.9, 0.6-8.9)	0.060 [b]
	Mean, hours (±SD)	3.5 (±1.5)	3.3 (±1.4)	0.086 [c]
Length of hospital stay	*Median, days (IQR, range)*	1.1 (2.6, 0.0-37.8)	1.1 (2.7, 0.0-34.1)	0.636 [b]
	Mean, days (±SD)	2.1 (±4.1)	1.8 (±2.9)	0.054 [c]

Inclusion stay endpoints presented for all patients allocated to intervention or standard care, including patients who died during hospital stay.

[a] P-values generated with Pearson chi^2

[b] P-values generated with Mann-Whitney test

[c] P-values generated with negative binomial regression

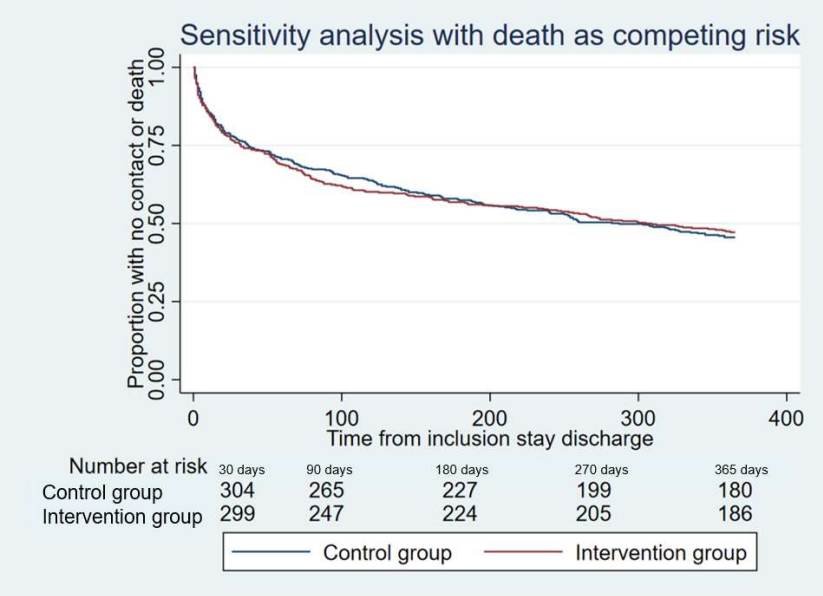


Fig A. Sensitivity *intention-to-treat* analysis with death as competing risk. All patients with follow-up data were included, intervention group n=394, control group n=395. Death during 12 months from inclusion stay discharge were treated as competing risk to unplanned contact with hospital. Median time to event (next unplanned contact with hospital or death) was 305 days for the intervention group and 287 days for the control group. This difference was not statistically significant (p=0.837, HR 0.98, 95% CI 0.81, 1.19.).

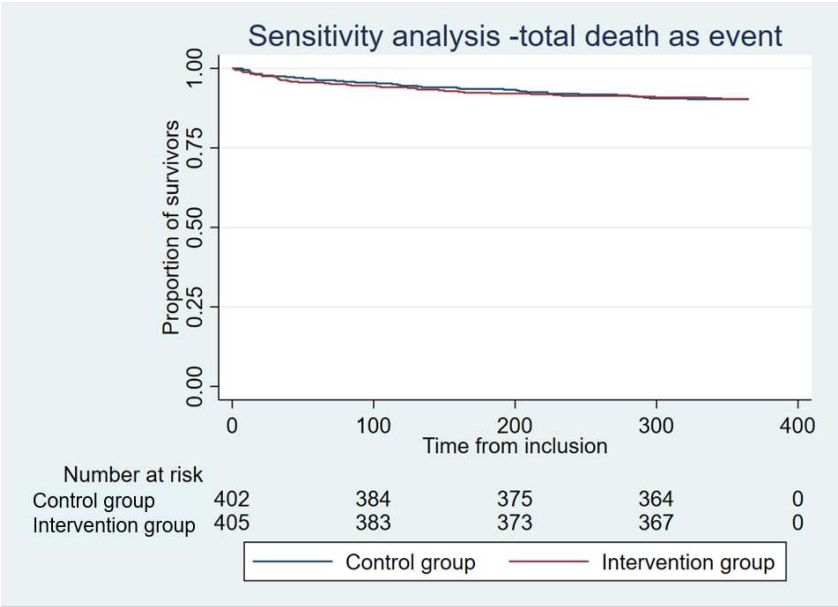


Fig B. Survival curve with death as event. All patients receiving allocated intervention or care were included. Overall death from inclusion stay admission were treated as event, i.e., both death during inclusion stay and during 12 months from hospital discharge. There was no difference between intervention- and control group regarding overall death (p=0.998, HR 1.00, 95% CI 0.64, 1.56).

Paper III

Internal and Emergency Medicine
https://doi.org/10.1007/s11739-022-02935-9

EM - ORIGINAL

Drug-related emergency department visits: prevalence and risk factors

Lisbeth Damlien Nymoen[1,2] · Malin Björk[3] · Trude Eline Flatebø[1] · Merethe Nilsen[1] · Aasmund Godø[4] · Erik Øie[5] · Kirsten Kilvik Viktil[1,2]

Received: 27 July 2021 / Accepted: 18 January 2022

Abstract
The study aimed to investigate the prevalence of drug-related emergency department (ED) visits and associated risk factors. This retrospective cohort study was conducted in the ED, Diakonhjemmet Hospital, Oslo, Norway. From April 2017 to May 2018, 402 patients allocated to the intervention group in a randomized controlled trial were included in this sub-study. During their ED visit, these patients received medication reconciliation and medication review conducted by study pharmacists, in addition to standard care. Retrospectively, an interdisciplinary team assessed the reconciled drug list and identified drug-related issues alongside demographics, final diagnosis, and laboratory tests for all patients to determine whether their ED visit was drug-related. The study population's median age was 67 years (IQR 27, range 19–96), and patients used a median of 4 regular drugs (IQR 6, range 0–19). In total, 79 (19.7%) patients had a drug-related ED visits, and identified risk factors were increasing age, increasing number of regular drugs and medical referral reason. Adverse effects (72.2%) and non-adherence (16.5%) were the most common causes of drug-related ED visits. Antithrombotic agents were most frequently involved in drug-related ED visits, while immunosuppressants had the highest relative frequency. Only 11.4% of the identified drug-related ED visits were documented by physicians during ED/hospital stay. In the investigated population, 19.7% had a drug-related ED visit, indicating that drug-related ED visits are a major concern. If not recognized and handled, this could be a threat against patient safety. Identified risk factors can be used to identify patients in need of additional attention regarding their drug list during the ED visit.

Keywords Emergency departments · Medication review · Medication reconciliation · Medication errors · Drug-related hospitalization

Introduction

A growing body of evidence suggests that emergency department (ED) physicians do not recognize drug-related ED visits in the fast-paced workflow [1–3]. During the ED visit, physicians evaluate a patient's symptoms and decide if hospitalization is needed, or if the patient could be discharged directly. If ED visits caused by drug-related issues are not identified during the stay in the ED, physicians might end up misdiagnosing and treating the symptoms instead of the actual problem [1]. Hence, identifying patients with a drug-related referral reason early in the admission process is crucial for the patient safety [1, 4, 5].

The prevalence of drug-related hospital admissions (DRHAs) has been investigated in several studies during the last decades, and the reported prevalence which is summarized in two systematic reviews varies between 1.3 and 41.3% [6, 7]. Recently, there has been a growing interest in investigating drug-related *ED visits* with studies reporting prevalence of 2.3–28.6% [1, 2, 8–11]. Definition of drug-related ED visits, method of identification and population-selection vary between these studies.

✉ Lisbeth Damlien Nymoen
lisbetd@student.matnat.uio.no

1 Diakonhjemmet Hospital Pharmacy, Oslo, Norway

2 Department of Pharmacy, University of Oslo, Oslo, Norway

3 Faculty of Pharmacy, Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden

4 Department of Anaesthesia and Intensive Care, Diakonhjemmet Hospital, Oslo, Norway

5 Department of Internal Medicine, Diakonhjemmet Hospital, Oslo, Norway

Published online: 07 February 2022

The main objective of this study was to investigate the prevalence of drug-related ED visits and risk factors associated with these visits, including involved drug-groups.

Methods

Study design

This retrospective cohort study investigated drug-related ED visits at Diakonhjemmet Hospital, a local urban, non-academic hospital in Oslo, Norway. The study was a sub-study of a randomized controlled trial (RCT), registered at ClinicalTrials.gov, Identifier: NCT03123640, investigating the patients allocated to the intervention group (Fig. 1). Patients were included consecutively in periods from April 2017 to May 2018. A manuscript reporting results from the RCT is in production.

The sub-study was approved by the institutional review board and the Norwegian Regional Committee for Medical and Health Research Ethics and conducted in accordance with the Helsinki Declaration. Written informed consent was obtained from all patients before inclusion. Further, the sub-study was designed and reported according to the STROBE Statement, utilizing the STROBE checklist in all stages of the study (planning, execution, and reporting).

Study setting

In Norway, patients are referred to a hospital's ED by health care personnel of the primary health care service e.g., general practitioner (GP), municipal emergency clinic, nursing home physician. GPs and the municipal emergency clinics have a gatekeeper function and handle less severe conditions. Yearly 13,500 patients with both medical and surgical referral reasons are referred to the ED at Diakonhjemmet Hospital. In 2018, the average length of stay in the ED was 3.2 h.

In the RCT, all patients 18 years or older, referred to the ED, and willing to/capable of providing written, informed consent were suitable for inclusion. Patients with both medical and surgical referral reason were included. Unconscious patients were not included e.g., severe intoxications. Further, patients aged ≥ 65 with hip fracture were not eligible for inclusion as they were admitted to a specialized ED at another location. Patients were included periodically by study pharmacists between 9:00 am and 10:00 pm, on weekdays and weekends. A total of 807 patients were included in the RCT. Of patients admitted to the ED during data collection periods, 43.7% were assessed for eligibility for inclusion; the remaining patients were not assessed due to ED crowding which exceeded study pharmacists' capacity. After inclusion, patients were randomized to intervention- or

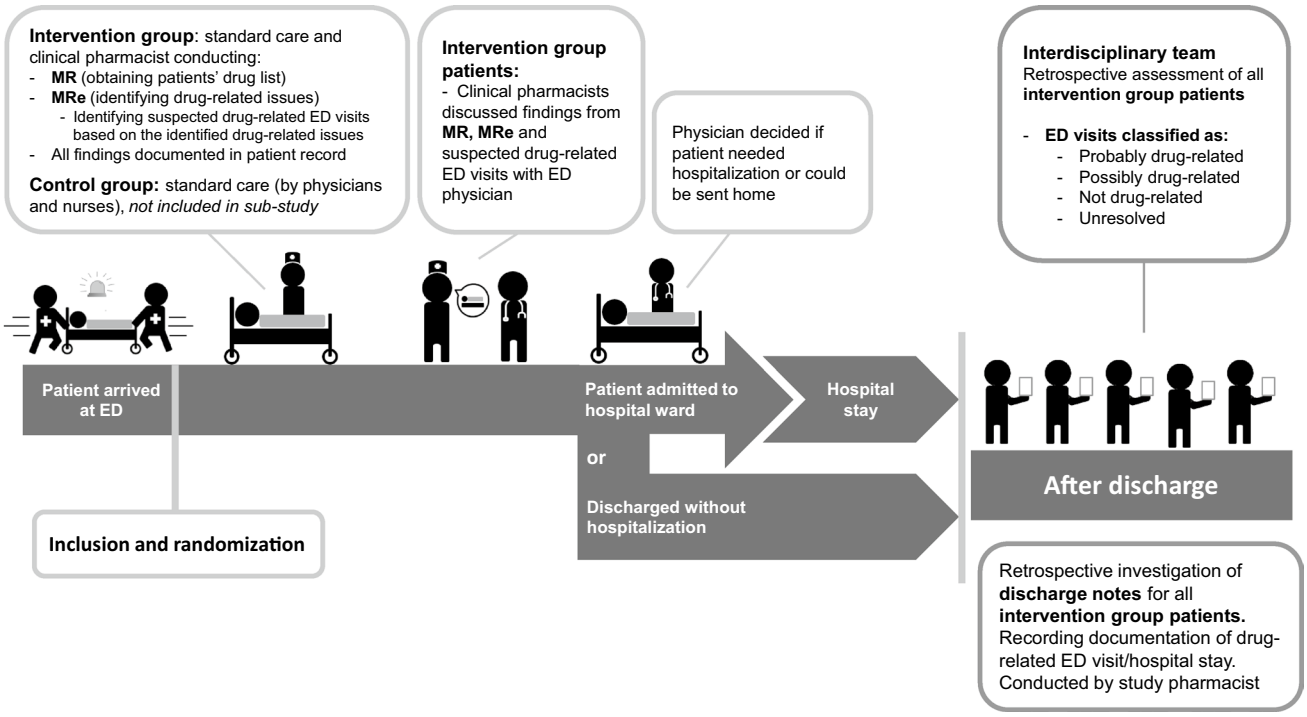


Fig. 1 Study design: retrospective cohort study of the intervention group. ED emergency department, MR medication reconciliation, MRe medication review

control-group (1:1) with prepacked randomization envelopes from Department of Biostatistics and Epidemiology at Oslo University Hospital.

The intervention group received, in addition to standard care, an intervention consisting of medication reconciliation and systematic medication review conducted by study pharmacists during the patients ED stay (Fig. 1). The intervention was based on the Integrated Medicine Management (IMM) model [12], adjusted to the fast-paced workflow ED-setting [13], and conducted by experienced clinical pharmacists. The medication reconciliation process consisted of a standardized interview of the patient/next of kin/health care personnel to obtain the patient's complete drug list. Further, written sources (electronical prescriptions, drug list of a multi-dose patient etc.) were checked to clarify and verify information from the interview, and GPs or pharmacies were contacted for complementary information when needed. The medication review was based on the reconciled drug list. In addition, referral notes, examinations in the ED, laboratory test, and computer resources, e.g., interaction databases, summary of product characteristics for drugs, medical databases, were reviewed. Drug-related issues were identified and registered. The study pharmacists documented the reconciled drug list and all clinically relevant drug-related issues, i.e., issues of importance for the patient treatment, including if they suspected the ED visits to be drug-related, in the electronic patient record. These findings were also communicated vocally to the responsible ED physician (Fig. 1). The control group received standard care by physicians and nurses during the ED stay, which did not include systematic medication reconciliation nor medication review.

Study population

The entire intervention group from the RCT was included in the present sub-study ($n = 402$). Control group patients ($n = 405$) were excluded as systematic medication reconciliation and medication review were not standard care. However, there was no statistical difference in demographics (gender, age, allocation of referral reason, earlier hospital admissions, and hospitalization rate) between the intervention and control groups.

Data collection

After discharge, a standardized de-identified patient scheme was created for each patient. The schemes included demographic data and results from completed laboratory tests. Further, the schemes included tentative referral reasons set by the referring health care personnel based on the patient's symptoms and initial examinations (before ED visit). The final diagnoses documented in the discharge note by the physician discharging the patient were also included in the schemes. And finally, the patient's drug list obtained through medication reconciliation and clinically relevant drug-related issues from the medication review performed in the ED were registered on the schemes (see template in Online Resource 1).

Clinically relevant drug-related issues identified during the medication review were categorized in the following categories: adverse effect: defined as a negative or harmful patient outcome that seemed to be associated with treatment [14]. Non-adherence: defined as deviation between patient's actual drug use and physician's prescription with respect to type of drug, dose, or scheme (both unintentional and intentional) [15]. Suboptimal dosing, suboptimal formulation, and need for additional drug treatment: defined as deviation between the patient's treatment and established national/international guidelines [15]. Inappropriate drug choice: defined as deviation between the patient's treatment and diagnosis/indication or absolute/relative contraindication [15].

Drugs were classified according to the Anatomical Therapeutic Chemical (ATC)-classification [16, 17]. In the ATC classification system, the active substances are grouped according to the organ or system on which they act (indicated by ATC-1st level), their therapeutic and pharmacological properties (indicated by ATC-2nd–3rd level) and finally their chemical properties (indicated by ATC-4th–5th level). In this study, drugs were reported at ATC classification 3rd level, hereafter called ATC-3 groups.

The patient schemes were presented to an interdisciplinary team (Fig. 1), consisting of two chief physicians and three experienced clinical pharmacists. The interdisciplinary team was blinded regarding if the patient was hospitalized or discharged directly from the ED, they were also blinded to the study pharmacist's opinion regarding drug-related ED visit. All patient schemes were first assessed and classified by each member of the interdisciplinary team individually. Further, six consensus meetings were arranged between November 2017 and February 2019. The interdisciplinary team classified each ED visit as probably drug-related, possibly drug-related, not drug-related, or unresolved, according to a set of criteria based on World Health Organization Uppsala Monitoring Centre criteria for causality [18] and inspired by Hallas' criteria for contribution [19]. In the present study, a drug-related ED visit was defined as an ED visit directly (probably) or indirectly (possibly) related to the patient's drug use prior to the visit. The association between patients' drug use and ED visits was determined by an interdisciplinary team retrospectively.

To investigate physicians' recognition of drug-related ED visits/hospital admissions, discharge notes written by physicians treating intervention group patients during ED visit/hospital stay were reviewed by a study pharmacist retrospectively (Fig. 1). It was registered that the treating physician

considered the ED visit/hospital admission drug-related if the physician explicitly stated (either through a description or a drug-related diagnosis code) in the discharge note that drugs could be the cause of the visit/admission.

Statistics

In comparative analysis, probably and possibly drug-related ED visits were treated as one group: drug-related ED visits. Patients not classified (Unresolved/No consensus reached) were not included in the comparative statistics. Data handling was conducted in Microsoft Office Excel 365. Statistical analyses were carried out in Stata SE version 16. Demographic statistics are given as median, interquartile range (IQR), and range for continuous variables and as percentage for categorical variables (group specific percentage when comparing groups). Wilcoxon rank-sum test was used in comparative analysis of continuous variables (due to skewness of data), and Pearson chi^2-test was used for categorical variables. Logistic regression was used to determine odds ratios of drug-related ED visits, 95% confidence interval (CI). The relative frequency of ATC3 groups was calculated as follows: how often a drug from the specified ATC-3 group was involved in drug-related ED visits divided by number of times drugs from that specific ATC-3 group was used. The tentative referral reasons were presented in text from referring health care personnel and not systematically categorized e.g., with ICD-10 [20]. Hence, the tentative referral reasons were grouped based on the presented text and similar symptoms/tentative diagnoses were grouped together to reduce diversity in data.

Results

Demographics of the 402 included patients are presented in Table 1. The interdisciplinary team classified 19.7% of the ED visits as drug-related (Table 2). Further, 4.2% of the ED visits were classified as probably drug-related, and 15.4% as possibly drug-related. ED visits could not be classified for 10 of the patients (2.5%), due to lack of necessary information or disagreement within the interdisciplinary team (Table 2).

Patients classified with a drug-related ED visit by the interdisciplinary team were significantly older and used more drugs regularly compared to patients classified with a non-drug-related ED visit (Table 3). The odds ratio of having a drug-related ED visit was higher in patients with medical referral reasons compared to patients with surgical referral reasons. Patients with a drug-related ED visit were more frequently admitted to hospital after the ED visit (Table 3); this was consistent even after adjusting for age (OR 1.91, 95%CI 1.04, 3.50, $p=0.04$). Further, referral reasons "hemorrhage or anemia" and "dizziness, syncope, or tendency to fall" were more frequently presented for patients

Table 1 Demographics of study population

	Study population $n=402$
Age	
Median (IQR, range)	67 (27, 19–96)
Patients ≥ 65 years %	54.7
Sex	
Female %	47.8
Male %	52.2
Referral reason allocation	
Medical %	69.7
Surgical %	30.4
Patients admitted to DH last 12 months before ED visit %	31.6
Number of prescribed drugs[a]	
Regular drugs, median (IQR, range)	4 (6, 0–19)
Patients using ≥ 5 regular drugs %	44.3
As needed drugs, median (IQR, range)	2 (3, 0–9)
Responsible for drug administration before ED visit	
Patient %	83.3
Other (next in kin/home care service/ nursing home) %	16.7
Hospitalized patients[b] %	67.9

DH Diakonhjemmet Hospital, *ED* emergency department

[a]Number of prescribed drugs obtained through medication reconciliation

[b]The other part was discharged directly from the ED

Table 2 Classification of emergency department (ED) visits by interdisciplinary team

Classification	Number of patients (%) $n=402$	Sub-classification	Number of patients (%) $n=402$
Drug-related ED visits	79 (19.7)	Probably drug-related	17 (4.2)
		Possibly drug-related	62 (15.4)
Non-drug-related ED visits	313 (77.9)	–	
Not classified patients	10 (2.5)	Unresolved	4 (1.0)
		No consensus reached	6 (1.5)

Table 3 Comparisons of demographics

	Drug-related ED visits ($n=79$)	Non-drug-related ED visits ($n=313$)	*P* value	OR (95% CI)
Sex				
Female %	54.4	45.7	0.16	1.42 (0.87, 2.33)
Male %	45.6	54.3		
Age				
Age, median (IQR, range)	73 (21, 26–93)	64 (28, 19–96)	< 0.01	1.03(1.01, 1.05)*
Patients ≥ 65 years %	73.4	49.2	< 0.01	2.85 (1.65, 4.92)*
Number of prescribed drugs[a]				
Regular drugs, median (IQR, range)	6 (4, 0–19)	3 (5, 0–15)	< 0.01	1.17 (1.09, 1.25)*
Patients using ≥ 5 regular drugs %	73.4	36.4	< 0.01	4.82 (2.78, 8.35)*
As needed drugs, median (IQR, range)	2 (3, 0–7)	2 (3, 0–9)	0.17	1.11 (0.96, 1.28)
Allocation referral reason				
Medical %	82.3	65.8	< 0.01	2.45 (1.31, 4.56)*
Surgical %	17.7	34.2		
Patients admitted to DH last 12 months %	35.4	30.0	0.35	1.28 (0.76, 2.15)
Responsible for drug administration before ED visit				
Patient %	79.8	84.7	0.29	0.71 (0.38, 1.34)
Other (next in kin/home care service/ nursing home) %	20.3	15.3		
Hospitalized patients %[b]	79.8	64.2	0.01	2.19 (1.21, 3.98)*
Referral reason				
"Hemorrhage or anemia" %	17.7	3.9	< 0.01	5.38 (2.38, 12.18)*
"Malfunction or impaired general condition" %	10.1	4.5	0.05	2.40 (0.97, 5.94)
Dizziness, syncope, or tendency to fall" %	8.9	3.5	0.04	2.66 (1.00, 7.10)*

Patients with drug-related emergency department (ED) visits versus patients with non-drug-related ED visits in the classified study population ($n=392$)

DH Diakonhjemmet Hospital

[a]Number of prescribed drugs obtained through medication reconciliation

[b]The other part was discharged directly from the ED

*Statistically significant ($p<0.05$)

with a drug-related ED visit compared to patients with non-drug-related ED visits.

Adverse effects caused 72.2% of the drug-related ED visits. Further, non-adherence caused 16.5%, and suboptimal dosing caused 7.6% of the drug-related ED visits. Need for additional drug treatment, inappropriate drug choice and suboptimal formulation each caused 1.3% of the drug-related ED visits.

A total of 44 unique ATC-3 groups were found to be involved in drug-related ED visits. Antithrombotic agents were the ATC-3 group most frequently involved in drug-related ED visits (19.0%) (Table 4). Further, antiinflammatory and antirheumatic products, non-steroids (NSAIDs) and agents acting on the renin-angiotensin system (RAS-inhibitors) were each involved in 10.1% of drug-related ED visits. Immunosuppressants, urologicals (drugs for urinary

Table 4 ATC-3 groups involved in drug-related ED visits

ATC-3 group	Relative frequency of drug-related ED visits in ATC-3 groups[a] %	Proportion of drug-related ED visits caused by specific ATC-3 groups ($n=79$) %
Immunosuppressants	29.4	3.8
Urologicals (Only drugs for urinary frequency and incontinence were involved in drug-related ED visits)	18.2	5.1
Antidepressants	13.5	3.8
Corticosteroids for systemic use	11.6	6.3
High-ceiling diuretics (loop-diuretics)	10.9	6.3
Antithrombotic agents	10.2	19.0
Drugs for obstructive airway diseases, inhalants (both adrenergics and others)	10.2	7.6
Agents acting on the renin-angiotensin system, with or without thiazide (RAS-inhibitors)	8.2	10.1
Antiinflammatory and antirheumatic products, non-steroids (NSAIDs)	6.7	10.1
Beta blocking agents, with or without thiazide	5.1	6.3

Included ATC-3 groups in the table: either contributed to 5 or more drug-related ED visits, have a relative frequency > 10%, or both. ATC-3 codes of the presented ATC-3 groups can be found at www.whocc.no/atc_ddd_index/

ATC Anatomical Therapeutic Chemical classification of drugs

A single drug-related ED visit could involve drugs from multiple ATC-3 groups, and also multiple drugs from the same ATC3-group.

[a]The relative frequency was calculated as follows: how often a drug from the specified ATC-3 group was involved in drug-related ED visits divided by number of times drugs from that specific ATC-3 group were used by the 392 classified patients

frequency and incontinence) and antidepressants were the ATC-3 groups with the highest relative frequency of drug-related ED visits (Table 4).

Physicians treating the patients during the ED visit/hospital admission had documented a drug-related ED visit/hospital admission in the discharge notes of 11 (2.7%) of the included patients ($n=402$). Of the 79 ED visits classified by the interdisciplinary team as drug-related, physicians had documented 11.4% in total, 29.4% of all the probably- and 6.5% of all the possibly drug-related ED visits. All discharge notes documenting drug-related ED visits/hospital admissions were written by medical physicians. Surgical physicians did not document any drug-related ED visits/hospital admissions, even though 14 surgical patients (Table 3) were classified with a drug-related ED visits by the interdisciplinary team. The study pharmacists conducting the intervention documented a suspected drug-related ED visit in 82% of the patients classified by the interdisciplinary team to have a drug-related ED visit.

Discussion

Prevalence of drug-related ED visits

In this study, 19.7% of the ED visits were classified as drug-related. The prevalence of drug-related ED visits/DRHAs in earlier studies varies between 1.3 and 41.3% [1, 2, 6–11]. The prevalence revealed in the present study is however, in line with one prior study investigating drug-related ED visits [2], reporting a prevalence of 22.5%.

One earlier study only identified ED visits caused by adverse drug reactions retrospectively classified based on documentation in electronic patient records and reported a prevalence of 2.3% [9], which is significantly lower than found in the present study. Even though adverse effects were the most frequently registered cause of drug-related ED visits in the present study, other drug-related issues for instance non-adherence and suboptimal dosing accounted for 27.8% of the drug-related visits, similar to prior studies [1, 8]. To estimate the total burden of drug-related ED visits, it is important to focus on more than adverse drug reactions/adverse effects.

Several earlier studies only included hospitalized patients in their population, hence investigating DRHAs [4–7, 21, 22]. In the present study, 20% of the patients classified with a drug-related ED visit were discharged directly from the ED, thus not admitted to hospital. These patients are important to recognize as they also stress the health care service and require adequate evaluation of their drug lists before discharge. Further, some of the DRHA studies only investigated select patient groups, such as patients from specified hospital ward, only patients older than 65 years or using more than five drugs [6, 21, 22].

The difference in patient population between the present study and the above-mentioned DRHA studies makes comparison of prevalence challenging.

National differences in health care systems should also be considered when comparing the prevalence of drug-related ED visits. All patients included in this study were referred to the ED by health care personnel of the primary health care service, which leads to a selected patient population presenting to the ED [23]. A Norwegian study revealed a slightly higher percentage of high-level acute patients (based on triage) presenting to the ED and a higher percentage of patients being hospitalized after the ED stay, compared to EDs in other countries [24]. Further, it was reported that 49.7% of patients admitted to the ED were aged over 65 years [24]. The organizing of the Norwegian health care system could explain why the study population in the present study was older compared to populations of most of the earlier studies investigating drug-related ED visits [1, 8–10], with reported prevalence 2.3–12%. Two earlier studies investigated drug-related ED visits in populations with average age over 60 years and reported prevalence at 22.5–28.6% [2, 11]. This could indicate that the age diversity in the investigated populations may be more important than national differences in health care systems regarding the reported prevalence of drug-related ED visits.

Some of the previous studies investigating drug-related ED visits have used pharmacists to obtain the drug list and reveal drug-related issues [1, 2, 8]. In these studies, the pharmacists classified whether the ED visit was drug-related or not, and independent reviewers were only used when the pharmacist assessments were inconclusive. Prevalence of drug-related ED visits in these studies was reported to be 8.3–22.5%. One earlier study relied on ED physicians' assessment and documentation in electronic patient records to determine the prevalence of drug-related ED visits, with a reported prevalence of only 3.4% [10]. Another study utilized prospective classification of drug reaction-related ED visits and reported a prevalence of 28.6% [11]. This illustrates the importance of methodology when investigating drug-related ED visits. The present study is the first study combining pharmacist intervention with a retrospective assessment by an interdisciplinary team assessing all patients to determine the prevalence of drug-related ED visits. The combination of prospective intervention and retrospective assessment eliminates several of the limitations of using either of these study designs in an isolated fashion [7, 25]. In addition, utilizing an interdisciplinary team to determine the prevalence, balanced any inter-professional and inter-individual differences of opinion.

Recognizing drug-related ED visits

To assess drug-related ED visits and DRHAs, it is vital to have a reconciled drug list. To obtain this communication with the patient, next of kin/home care service/nursing home is essential. A study conducted at the same ED as the present study revealed that 62% of the patients had a clinically relevant medication discrepancy between the drug list registered in the hospital's electronic patient record and the drug list actually in use before visiting the ED [13]. Alongside a reconciled drug list, the interdisciplinary team in the present study was provided essential information from the medication review about non-adherence, suboptimal dosing, and adverse effects, which enabled a thorough assessment of the association between present drug use and the ED visit.

In the present study, only 11.4% of the drug-related ED visits classified by the interdisciplinary team were documented in the discharge notes. This finding is in line with earlier studies raising concerns regarding physicians not recognizing drug-related ED visits/DRHAs [1–3]. Results from this study indicate that physicians are more likely to document an ED visit/hospital stay as drug-related if there is a direct and undoubtedly association (classified as probably) to the patient's drug use. Only documenting definite drug-related ED visit/hospital admission can lead to neglect of patients who need an adequate evaluation of their drug list. In addition, interpretation of data from the presented study indicates that physicians tend to not document expected events, that is, events that may be interpreted as not preventable in the clinical setting. For instance, none of the infections in patients treated with immunosuppressants were documented to be drug-related by the treating physicians. Patients often depend on follow-up from several different physicians, hence also documenting expected drug-related events are important to alert the next level of care. In addition, documentation can better inform the patient about the risk associated with certain drugs and encourage them to contact health care personnel at an early stage in future.

The preventability of the identified drug-related ED visits was not investigated in the present study. Prior studies have however revealed that between 57.3 and 70.7% of drug-related ED visits may be preventable [5, 8, 10]. According to these studies, ED visits caused by non-compliance, suboptimal dosing, and need for additional drug treatment were most frequently found preventable [8, 10]. Even though all drug-related ED visits may not preventable, it is essential to increase the overall recognition and documentation to be able to avoid the ones that are preventable [8]. Acknowledgment and documentation of suspected/possible drug-related ED visits will increase recognition of drug-related ED visits/hospital admissions.

To identify suspected drug-related ED visits early in the admissions process, this study found that pharmacists can be a valuable resource, which is in line with earlier studies [1, 2]. Additional research is needed to reveal why physicians did not document drug-related ED visits in patients where study pharmacists had documented and communicated their suspicion.

Patients classified with a drug-related ED visit in the present study were more frequently admitted to hospital following their ED stay compared to patients classified with a non-drug-related ED visit. This has also been reported by other studies [2, 8]. A suggested explanation is that identified drug-related issues often require monitored observation to decide on further treatment; hence, hospital admission may therefore be necessary for a greater proportion of patients with drug-related ED visits [8]. In the present study, majority of the drug-related ED visits were not recognized by the treating physicians, which potentially could have delayed the assessment of the patients' symptoms. The present study revealed that the increased hospitalization rate was not an age-dependent effect; however, there may be some relevant confounding variables which were not controlled for instance triage status and comorbidity. Hence, additional research is needed to determine whether the increased hospitalization rate related to drug-related ED visit patients represents an association, a causation, or both.

Risk factors for drug-related ED visits

According to the results of the presented study, the risk of having a drug-related ED visit increased with increasing age and increasing number of regular drugs, this is consistent with earlier studies [8, 11]. These risk factors are also in line with the inclusion criteria utilized in some of the prior studies investigating DRHAs [6, 21, 22]. Regarding the aim of the present study, it was, however, essential to include patients without such criteria to identify relevant risk factors. Identifying age as a risk factor also partly explains the higher prevalence revealed in the present study, compared to prior studies with younger populations [1, 8–10]. It is noteworthy that even though a patient aged over 65 years had a significantly higher odds of having a drug-related ED visit, 26.6% of patients classified with a drug-related ED visit were younger than 65 years. And further, 35% of patients classified with a drug-related ED visit used less than five drugs, although patients using more than five drugs had a significantly higher odds of having a drug-related ED visit. This indicates that age and number of regular drugs must be combined with other risk factors to identify all high-risk patients presenting with drug-related ED visits.

In line with the results of this study, medical referral reason was identified as a risk factor for DRHA in one earlier study [26]. The present study did also reveal that none of the identified drug-related ED visits regarding patients with a surgical referral reason were documented by surgical physicians. In earlier studies, surgical referral reasons have been identified to be a risk factor for medication discrepancies [13, 27]. This may indicate that surgeons have more focus on the acute surgical issue rather than reconciling the patients' drug list, which is essential to reveal drug-related ED visits. Personnel dedicated to conduct medication reconciliation and to identify suspected drug-related ED visits is highly needed in patients with surgical referral reasons.

Immunosuppressants and antidepressants have been identified as risk-drug groups in prior studies [10, 25]. All drug-related ED visits involving immunosuppressants in the present study were infection related (an adverse effect), which is a known complication of the treatment. Infections were however, not found to be more frequent among patients with a drug-related ED visit in this study. Thus, infections were a common referral reason, while relatively few patients used immunosuppressants. Urologicals (drugs for urinary frequency and incontinence) have not been identified as a risk-drug group related to drug-related ED visits/DRHAs in prior studies. However, this group of drugs is capable of causing antimuscarinic side effects, especially in older patients [28]. The antimuscarinic drug burden is increased if combining several antimuscarinic drugs, for instance combination of urologicals and antidepressants [28]. This finding corresponds to identification of "dizziness, syncope, or tendency to fall" as a frequently registered referral reason in patients with a drug-related ED visit. Identifying antithrombotic agents and NSAIDs as risk-drug-groups can correspond to the finding of "hemorrhage or anemia" as the most frequent referral reason for patients classified with a drug-related ED visit. These findings are in line with other studies [2, 3, 25]. RAS inhibitors in older patients can contribute to dizziness and tendency to fall, especially when combined with other blood pressure regulating agents, such as high-ceiling diuretics or beta-blocking agents.

The identified risk factors can be used as screening tools for patients admitted to the ED to prioritize patients in need of a thorough evaluation of their drug list. Older patients with polypharmacy and one of the risk-referral reasons or using drugs from one or more of the risk-drug groups may need extra attention in the ED to assess if the ED visit can be related to their drug use. In addition, the identified risk factors can be used to prevent future drug-related ED visits, as it could alert health care providers in primary health care to perform a systematic medication review to reveal for instance adverse effects, non-adherence, or suboptimal dosage in patients with risk factors.

Limitations

Given the single study location, in one specific health care system (where patients are referred to the ED by health care personnel of the primary health care system), the results are not necessarily generalizable to other hospital EDs. The revealed prevalence is, however, consistent with other studies investigating study populations with the same age diversity. In addition, most of the identified risk factors are in line with other studies. Indicating that the risk factors may be more generalizable than the prevalence due to the methodology utilized to identify them.

Selection bias cannot be ruled out as only 43.7% of patients admitted to the ED were assessed for eligibility for inclusion to the RCT. However, study pharmacists had no specific criteria for which patients to include in case of ED crowding. And further, summary statistics from 2017 to 2018 in Diakonhjemmet Hospital reveal that 57.2% of patients admitted to the ED were aged over 65 years, hence similar to the age-distribution of the study population in the present study.

A total of 19.7% of the included patients had a drug-related ED visit, indicating that drug-related ED visits are a major concern. The identified risk factors from this study can be used to identify patients in need of extra attention during an ED stay to reveal whether the ED visit is drug-related. Further, the risk factors can also indicate which patients who can benefit from a systematic medication review in the primary health care, which can prevent future drug-related ED visits. Only a minor part of discharge notes written by physicians documented that the ED visit/hospital stay was drug-related, illustrating that this topic needs to be highlighted and an increased awareness regarding possibly drug-related events is needed.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11739-022-02935-9.

Acknowledgements The authors want to thank master students Therese Tran and Ingrid Kinne Tunestveit who contributed to gathering, handling and analysing parts of the data.

Author contributions LDN, KKV, EØ conceived the study, and designed the trial. KKV, and LDN obtained research funding. LDN and TEF included and randomized patients, and further conducted the intervention. TEF, MN, EØ, AG and KKV constituted the interdisciplinary team. LDN retrospectively assessed discharge notes. MB and LDN handled and analyzed the data, with statistical guidance from Oslo Center for Biostatistics and Epidemiology. LDN drafted the manuscript, and all authors contributed substantially to its revision. All authors read and approved the final manuscript and take responsibility for the paper as a whole.

Funding Open access funding provided by University of Oslo (incl Oslo University Hospital). The study is funded by Diakonhjemmet Hospital Pharmacy, Diakonhjemmet Hospital fund for research, innovation and professional development and Diakonhjemmet Foundation.

Data availability The data that support the findings are not publicly available due to them containing information that could compromise research participant consent (the patient consent form was approved by the Norwegian Regional Committee for Medical and Health Research Ethics in 2017 and did not include consent to data-sharing). The data are de-identified and stored at the password protected research server at Diakonhjemmet Hospital. Anonymized data are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Ethical approval The study was approved by the institutional review board and the Norwegian Regional Committee for Medical and Health Research Ethics (Case number: 2015/1356/REK Helse sør-øst A).

Consent to participate Written informed consent was obtained from all patients before inclusion.

Consent for publication.

Consent to publication Written informed consent was obtained from all patients before inclusion and the institutional review board.

References

1. Hohl CM, Zed PJ, Brubacher JR, Abu-Laban RB, Loewen PS, Purssell RA (2010) Do emergency physicians attribute drug-related emergency department visits to medication-related problems? Ann Emerg Med 55(6):493-502.e4
2. Roulet L, Ballereau F, Hardouin JB, Chiffoleau A, Moret L, Potel G et al (2013) Assessment of adverse drug event recognition by emergency physicians in a French teaching hospital. Emerg Med J 30(1):63–67
3. Roulet LBF, Hardouin JB, Chiffoleau A, Potel G, Asseray N (2014) Adverse drug event nonrecognition in emergency departments: an exploratory study on factors related to patients and drugs. J Emerg Med 46(6):857–864
4. Bénard-Laribière A, Miremont-Salamé G, Pérault-Pochat MC, Noize P, Haramburu F, centres ESGobotFnop (2015) Incidence of hospital admissions due to adverse drug reactions in France: the EMIR study. Fundam Clin Pharmacol 29(1):106–111

5. Ahern F, Sahm LJ, Lynch D, McCarthy S (2014) Determining the frequency and preventability of adverse drug reaction-related admissions to an Irish University Hospital: a cross-sectional study. Emerg Med J 31(1):24–29
6. Ayalew MB, Tegegn HG, Abdela OA (2019) Drug related hospital admissions; a systematic review of the recent literatures. Bull Emerg Trauma 7(4):339–346
7. Alhawassi TM, Krass I, Bajorek BV, Pont LG (2014) A systematic review of the prevalence and risk factors for adverse drug reactions in the elderly in the acute care setting. Clin Interv Aging 9:2079–2086
8. Zed PJ, Abu-Laban RB, Balen RM, Loewen PS, Hohl CM, Brubacher JR et al (2008) Incidence, severity and preventability of medication-related visits to the emergency department: a prospective study. CMAJ 178(12):1563–1569
9. de Almeida SM, Romualdo A, de Abreu FA, Zelezoglo GR, Marra AR, Edmond MB (2017) Use of a trigger tool to detect adverse drug reactions in an emergency department. BMC Pharmacol Toxicol 18(1):71
10. Lo Giudice I, Mocciaro E, Giardina C, Barbieri MA, Cicala G, Gioffrè-Florio M et al (2019) Characterization and preventability of adverse drug events as cause of emergency department visits: a prospective 1-year observational study. BMC Pharmacol Toxicol 20(1):21
11. McLachlan CY, Yi M, Ling A, Jardine DL (2014) Adverse drug events are a major cause of acute medical admission. Intern Med J 44(7):633–638
12. Scullin C, Scott MG, Hogg A, McElnay JC (2007) An innovative approach to integrated medicines management. J Eval Clin Pract 13(5):781–788
13. Damlien L, Davidsen N, Nilsen M, Godø A, Moger TA, Viktil KK (2017) Drug safety at admission to emergency department: an innovative model for PRIOritizing patients for MEdication reconciliation (PRIOMER). Eur J Emerg Med 24(5):333–339
14. Uppsala monitoring centre, glossary of pharmacovigilance team. https://www.who-umc.org/global-pharmacovigilance/publications/glossary/. Accessed 05 July 2021
15. Ruths S, Viktil KK, Blix HS (2007) Classification of drug-related problems. Tidsskr Nor Laegeforen 127(23):3073–3076
16. World Health Organization, Anatomical Therapeutic Chemical (ATC) classification. https://www.who.int/tools/atc-ddd-toolkit/atc-classification. Accessed 26 Feb 2021
17. WHO. (2021) Collaborating centre for drug Statistics Methodology, ATC/DDD Index. https://www.whocc.no/atc_ddd_index/. Accessed 01 Sept 2021
18. WHO. Causality assessment.pdf. https://www.who.int/medicines/areas/quality_safety/safety_efficacy/WHOcausality_assessment.pdf. Accessed 20 Jan 2021
19. Hallas J, Harvald B, Gram LF, Grodum E, Brøsen K, Haghfelt T et al (1990) Drug related hospital admissions: the role of definitions and intensity of data collection and the possibility of prevention. J Intern Med 228(2):83–90
20. World Health Organization (2015) International statistical classification of diseases and related health problems, 10th revision, Fifth edition, 2016. World Health Organization. https://www.who.int/standards/classifications/classification-of-diseases
21. Lea M, Mowe M, Mathiesen L, Kvernrød K, Skovlund E, Molden E (2019) Prevalence and risk factors of drug-related hospitalizations in multimorbid patients admitted to an internal medicine ward. PLoS ONE 14(7):e0220071
22. Gustafsson M, Sjölander M, Pfister B, Jonsson J, Schneede J, Lövheim H (2016) Drug-related hospital admissions among old people with dementia. Eur J Clin Pharmacol 72(9):1143–1153
23. Mentzoni I, Bogstrand ST, Faiz KW (2019) Emergency department crowding and length of stay before and after an increased catchment area. BMC Health Serv Res 19(1):506
24. Bjørnsen LP, Uleberg O, Dale J (2013) Patient visits to the emergency department at a norwegian university hospital: variations in patient gender and age, timing of visits, and patient acuity. Emerg Med J 30(6):462–466
25. Parameswaran Nair N, Chalmers L, Peterson GM, Bereznicki BJ, Curtain CM, Bereznicki LR (2018) Prospective identification versus administrative coding of adverse drug reaction-related hospitalizations in the elderly: a comparative analysis. Pharmacoepidemiol Drug Saf 27(11):1281–1285
26. Kongkaew C, Hann M, Mandal J, Williams SD, Metcalfe D, Noyce PR et al (2013) Risk factors for hospital admissions associated with adverse drug events. Pharmacotherapy 33(8):827–837
27. Unroe KT, Pfeiffenberger T, Riegelhaupt S, Jastrzembski J, Lokhnygina Y, Colón-Emeric C (2010) Inpatient medication reconciliation at admission and discharge: a retrospective cohort study of age and other risk factors for medication discrepancies. Am J Geriatr Pharmacother 8(2):115–126
28. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P (2015) STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age Ageing 44(2):213–218

Appendix 1 paper III

Reproduction of Supplementary information

Drug-related emergency department visits -prevalence and risk factors, European Journal of Clinical Pharmacology

L. D. Nymoen [1, 2], M. Björk[3], T. E. Flatebø[1], M. Nilsen[1], A. Godø[4], E. Øie[5], K. K. Viktil[1, 2]

[1] Diakonhjemmet Hospital Pharmacy, Oslo, Norway [2] Department of Pharmacy, University of Oslo, Oslo, Norway [3]Department of Pharmaceutical Biosciences, Faculty of Pharmacy, Uppsala University, Uppsala, Sweden [4], Department of Anaesthesia and Intensive Care, Diakonhjemmet Hospital, Oslo, Norway [5] Department of Internal Medicine, Diakonhjemmet Hospital, Oslo, Norway

Assessment of drug-related emergency department (ED) visits and clinical relevance of drug-related problems[1]

Patient ID			
Gender:	**Age** (year)**:**	**Department:**	**Triage** (at admission to ED)**:**
Earlier admitted to Diakonhjemmet Hospital (yes/no and number of times)**:**			
Registered adverse drug reactions/CAVE (drug and reaction)**:**			
Drug handling before admission:		**Drug handling problems:**	

Tentative referral cause (set by referring physician)	
Final diagnosis (from discharge note)	

MEDICAL HISTORY (earlier registered diagnoses)

OTHER RELEVANT INFORMATION

Additional information about the patient was given, for instance:

- Non-adherence
- Social circumstances
- Help from homecare service
- Alcohol abuse

Results from laboratory tests at admission to ED (adjusted according to what was relevant for each patient)	
CRP	
Leucocytes	
Neutrophiles	
Lymphocytes	
Hemoglobin	
s-Sodium	
s-Potassium	
s-Calcium	
s-Glucose	
Bilirubin	
Urea	
Creatinine	
GFR	
S-Troponin T	
Pulse	
Blood pressure	

USED REGULAR DRUGS (revealed through medication reconciliation)

Drug	**Strength/ dosage**	**Indication**	**Other comments**
Number of rows were adjusted to the findings			

USED AS NEEDED DRUGS (revealed through medication reconciliation)

Drug	**Strength/ dosage**	**Indication**	**Other comments**
Number of rows were adjusted to the findings			

[1] The standardized patient scheme was originally in Norwegian, translated for publication

Drug-related problem (DRP) nr.	Description of DRP	Actions/ additional comments
DRP 1	Number of rows were adjusted to the findings (all identified DRPs were listed here, regardless of association with a potential drug-related ED-visit)	
DRP 2		
DRP 3		

ASSESSMENTS (this part were filled out by the interdisciplinary team)

IS THE ED VISIT DRUG-RELATED? (MARK WITH X):			
PROBABLY	**POSSIBLY**	**NO**	**UNRESOLVED**
Rationale and suspected drug, associated DRP (free text):			

WHEN WAS THE INFORMATION OBTAINED IN MENTIONED DRPs CLINICALLY RELEVANT?				
	IN THE ED	**DURING THE HOSPITAL STAY**	**NOT RELEVANT DURING THE HOSPITAL STAY**	**NOT A DRP**
LRP 1				
LRP 2				
LRP 3				

Paper IV

International Journal of Clinical Pharmacy
https://doi.org/10.1007/s11096-021-01364-6

RESEARCH ARTICLE

Emergency department physicians' distribution of time in the fast paced-workflow-a novel time-motion study of drug-related activities

Lisbeth D. Nymoen[1,2] · Therese Tran[2] · Scott R. Walter[3] · Elin C. Lehnbom[4,5] · Ingrid K. Tunestveit[2] · Erik Øie[6] · Kirsten K. Viktil[1,2]

Received: 4 August 2021 / Accepted: 7 December 2021

Abstract

Background In the emergency department physicians are forced to distribute their time to ensure that all admitted patients receive appropriate emergency care. Previous studies have raised concerns about medication discrepancies in patient's drug lists at admission to the emergency department. Thus, it is important to study how emergency department physicians distribute their time, to highlight where workflow redesign can be needed.

Aim to quantify how emergency department physicians distribute their time between various task categories, with particular focus on drug-related tasks.

Method Direct observation, time-motion study of emergency department physicians at Diakonhjemmet Hospital, Oslo, Norway. Physicians' activities were categorized in discrete categories and data were collected with the validated method of Work Observation Method By Activity Timing between October 2018 to January 2019. Bootstrap analysis determined 95% confidence intervals for proportions and interruption rates.

Results During the observation time of 91.4 h, 31 emergency department physicians were observed. In total, physicians spent majority of their time gathering information (36.5%), communicating (26.3%), and documenting (24.2%). Further, physicians spent 17.8% (95% CI 16.8%, 19.3%) of their time on drug-related tasks. On average, physicians spent 7.8 min (95% CI 7.2, 8.6) per hour to obtain and document patients' drug lists.

Conclusion Emergency department physicians are required to conduct numerous essential tasks and distributes a minor proportion of their time on drug-related tasks. More efficient information flow regarding drugs should be facilitated at transitions of care. The presence of healthcare personnel dedicated to obtaining drug lists in the emergency department should be considered.

Keywords Emergency service hospital · Medication reconciliation · Medication errors · Practice management medical · Time and motion studies · Time management

✉ Lisbeth D. Nymoen
lisbetd@student.matnat.uio.no

1 Diakonhjemmet Hospital Pharmacy AS, Postbox 40 Vinderen, 0319 Oslo, Norway

2 Department of Pharmacy, University of Oslo, Oslo, Norway

3 Centre for Health Systems and Safety Research, Australian Institute of Health Innovation, Macquarie University, Sydney, Australia

4 Department of Pharmacy, UiT The Arctic University of Norway, Tromsø, Norway

5 Department of Health and Caring Sciences, Linnaeus University, Kalmar, Sweden

6 Department of Internal Medicine, Diakonhjemmet Hospital, Oslo, Norway

Impacts on practice

- Physicians spend under eight minutes per hour on average to obtain and document patients' drug lists at admission. This must be taken into consideration when using these lists as basis for further drug treatment during the hospital stay.
- This study has provided baseline data which is required to evaluate future quality improvements and work efficiencies regarding drug-related tasks conducted by emergency department physicians.
- This study highlights a need for a more seamless drug information flow for patients admitted to hospital.

Published online: 23 December 2021

Introduction

Crowding is an increasing challenge in the fast-paced workflow of the emergency department (ED) [1]. Physicians are forced to distribute their time to ensure that all admitted patients receive adequate emergency care. In several countries, obtaining and documenting patients' medication histories at ED admission are tasks assigned to ED physicians [2–7]. However, there is concerning evidence that approximately 60% of patients are registered with an incorrect drug list on admission [5, 8, 9]. And further, it has been indicated that obtaining drugs-lists is down-prioritized by physicians when the ED is crowded [7], Around half of the medication errors identified in hospitals occur on admission or at discharge [10], and up to 27% of hospital prescribing errors can be linked to inaccurate or incomplete ED drug lists obtained at admission [11]. Several studies have reported that dedicated personnel, such as pharmacists or pharmacy technicians obtain more complete and accurate drug lists in the ED setting compared to physicians [2–4].

Work tasks performed by ED physicians have been investigated in previous time-motion studies; however, these have focussed on length of stay, communication patterns, interruptions, multitasking, and time dedicated to direct patient care [12, 13]. There is a lack of studies focusing on what drug-related tasks ED physicians' conduct and their time distribution between drug-related and non-drug-related tasks. As essential drug-related tasks at ED admission are assigned to physicians in several countries, it is important to investigate their work patterns, to highlight where workflow redesign is needed to improve patient safety regarding for instance medication discrepancies.

Aim

The aim of this study was to quantify how ED physicians distributed their time between various task categories, with particular focus on the time spent on drug-related activities.

Ethics approval

The study protocol was approved by the institutional review board. The Regional Committee for Medical and Health Research Ethics (Reference number: 2015/1356/REK South-East A) approved the study protocol August 8, 2018. Written informed consent was obtained from all participating physicians before inclusion.

Method

Study design

A continuous observational time-motion study of physicians in the ED at Diakonhjemmet Hospital (non-academic, urban), Oslo, Norway. The study was designed and reported according to the "Suggested Time And Motion Procedures (STAMP)" guidelines [14] and the STROBE statement [15]. Two observers (LDN -experienced clinical pharmacist, TT -pharmacy master student) performed direct observations between October 16, 2018, to January 8, 2019.

The validated method of Work Observation Method By Activity Timing (WOMBAT) [16, 17] was used to collect data. WOMBAT was developed to provide a reliable method for investigating the complexity of clinical work patterns. The method enables recording of multiple dimensions (*what, where, how*, and with *whom*) simultaneously, interruptions and multitasking, and thus chosen as the method in this study. Data were collected using a Samsung Galaxy 8 tablet running version 2 of the licenced WOMBAT software [16, 17].

Study setting

In Norway patients are referred to the ED from healthcare personnel in the primary healthcare service e.g., general practitioner (GP) and municipal emergency clinic. The referring healthcare personnel set a tentative referral reason after assessing the patient's symptoms and conducting an initial examination (before the ED admission). Every year around 14,000 patients are referred to the ED at Diakonhjemmet Hospital. The average length of stay in the ED is 3.2 h (2018). During this time physicians decide if the patient needs to be hospitalized or not. Emergency Medicine (EM) was first established as a physician speciality in Norway in 2017 and there are few EM specialists in Norway. Hence, physicians working at the ED, Diakonhjemmet Hospital are physicians from other specialities, rostered to cover shifts in the ED. Based on the tentative referral reason patients are allocated to see a physician from the Department of Internal Medicine (Medical physicians), or a physician from the Department of Surgery (Surgical physicians) at admission to the investigated ED. Medical physicians handle approximately 70% of referred patients and Surgical physicians handles 30% of patients.

In addition to physicians, the clinical ED staff at Diakonhjemmet Hospital consists of nurses triaging patients at arrival to the ED, taking measurements (e.g., blood pressure, temperature, echocardiography), monitoring symptoms, preparing, and administering drugs. A secretary handles administrative matters such as payment for foreign patients,

obtaining discharge notes from earlier hospital stay at other hospitals or drug lists from GPs. Clinical pharmacists cover a 0.5 full-time equivalent pharmacist position (approximately 19 h per week) in the ED and primarily conducts medication reconciliation. When clinical pharmacists have conducted a medication reconciliation, the ED physician responsible for the patient is alerted. The physician utilizes the information obtained through medication reconciliation when taking medication history, and further document the drug list in the medication chart. Due to the limited pharmacist-coverage, majority of medication histories is obtained by physicians without pharmacists conducting medication reconciliation.

Study population and sample size

During the data collection period 4-6 physicians were present in the ED at all times, 3-4 Medical physicians, and 1-2 Surgical physicians. Due to the roster-based affiliation of physicians to the ED the physician staff shifted frequently, hence inclusion and randomization of physicians were conducted consecutively before each observation session. All physicians present in the ED at the pre-set observation session time were eligible for inclusion. The observers randomized (by draw) which of the available physicians to observe. First a draw of affiliation (3:1, medical or surgical, due to the skewed distribution of physicians present in the ED), further a draw of experience level (1:1, experienced or inexperienced). Affiliation (Medical or Surgical) and experience level (inexperienced: interns and junior residents; experienced: senior consultants) was recorded for all included physicians.

The number of observation hours was selected based on previous time- and motion studies where approximately 62-137 h of observations were recorded [12, 18–20]. According to the aim of this study 90 h of observations were considered sufficient to accurately describe physicians work pattern.

Data collection

Once included, the physician was continuously observed for one session (two hours), where observers recorded all conducted tasks (automatically time stamped by the WOMBAT-software). Each physician was observed for a maximum of two sessions. Observation sessions were two hours long to minimize participant and observer fatigue. The sessions were conducted according to a time schedule set by the observers, to ensure the data collection covered all hours between 9:00 am to 9:00 pm (80% of patients admitted to the ED arrive within this timeframe), both weekdays and weekends. The observation sessions were independent of the length of stay for patients treated by the observed physicians.

No previous time-motion study of ED physicians has defined drug-related tasks separately, therefore the discrete categories used in this study were conceptualised and structured based on the findings from a pre-study period. In the pre-study period ED physicians were followed and all conducted activities were recorded in plain text, including tasks conducted (*what)*, the locations physicians were in when conducting the task (*where*), the tools they used to conduct the tasks (*how*) and other persons involved in the conducted tasks (*who*). Further the recorded text was grouped in discrete categories and structured under four dimensions (*what, where, how, and who*) in line with earlier studies [20, 21]. The identified task categories for the *what* dimension (Table 1) were reviewed by an experience clinical pharmacist (KKV) and a chief physician (EØ). Thereafter categories in all dimensions were tested and evaluated during a pilot study before data collection, to ensure that all physician tasks were covered by the conceptualised categories. A detailed overview of categories within *where, how* and *who* dimensions is presented in electronic supplementary material 1.

Interruptions, defined as stopping the current task to respond to an external stimulus (e.g., a telephone call), and multitasking, defined as performing two (or more) tasks simultaneously, were recorded with the WOMBAT software.

To test the observers' agreement on data collection categories (all dimensions, and timestamping), inter-rater reliability testing (IRR) was performed. The observers followed the same physician and independently recorded data for three separate sessions of 30 min each, once before data collection and twice during the data collection period. The IRR observation data were analysed after each session using a multivariate chance-adjusted agreement method (the iota score, a multivariate generalisation of Cohen's kappa) [22, 23], applied to the data in the format of one second time windows. The average iota score was 0.76 (before data collection: 0.781, during data collection: 0.622 and 0.867), indicating substantial agreement [24] between observers.

Patients were not observed in this study, however the number of patients treated by the observed physicians was recorded. Patients were classified as "new" or "follow-up". Patients were classified as new when no one had taken their medical history, including medication history, prior to when the observed physician met the patient. Patients were classified as follow-up if a medical history, including a medication history, had already been obtained when the observed physician met the patient.

Data analysis

Proportions of total observation time were defined as the time spent on each task category, accounting for any multitasking, divided by the total observation time. Proportions

Table 1 Work task categories (***What***), subcategories, definitions, and examples. Drug-related: all conversations, reading or writing that included information about the patients' drugs or drug use. Non-drug-related: all other conversations, activities, reading and writing. Where, how and with whom the observed physicians conducted tasks presented in the table, was specified by categories in *where, how* and *who* dimensions in the WOMBAT-tool (Electronic supplementary material 1)

Task category	Subcategories	Definition	Examples
Examination/ Treatment		Direct, physical examination/treatment of the patient[1]	Examination of patient Taking samples (e.g., fecal occult blood test, arterial blood gas) Relocating shoulder, suture a wound Monitoring patients' symptoms
Gather information	Drug-related	Gather drug-related information related to patients/ patient treatment	Physician obtained information about patients' medication history by talking directly or by telephone to patients, next of kin, other hospitals, reading on computer or paper referral letters.
	Non-drug-related	Gather non-drug-related information related to patients/ patient treatment	Physician obtained information about patients' medical history by talking directly or by telephone to patients, next of kin, other hospitals, reading on computer or paper referral letters.
Documentation	Drug-related	Documentation of drug-related patient information	Physician documented drug-related information on paper or on computer Prescribing drugs in medical chart/ Prescription Intermediary
	Non-drug-related	Documentation of non-drug-related patient information	Physician documented non-drug-related information on paper or on computer
Professional communication	Drug-related	Professional communication with other healthcare personnel/ patients/ next of kin about drug-related matters relevant to patients' treatment	Physician communicated direct or via telephone with other healthcare personnel about patient drug-related treatment Physician informed patient, next of kin about further drug-treatment
	Non-drug-related	Professional communication with other healthcare personnel/ patients/ next of kin about non-drug-related matters relevant to patients' treatment	Physician communicated direct or via telephone with other healthcare personnel about patient-related matters Physician informed patient, next of kin about further non- drug-related treatment
Social	Professional	Professionally relevant activities or communication not directly linked to patient treatment/ information	Digital courses Reading procedures (not directly regarding patient treatment) Send professional e-mail
	Non-professional	Social activities or communication (not professionally relevant)	Personal phone calls/ texting/ e-mailing Bathroom breaks Meal break
Unknown		Activities that could not be observed	Physician treated a patient in an infection isolated room (droplet- or airborne infections)
Hygiene		Activities to prevent communicable diseases	Physician washed/ disinfected hands
Movement		Movement between locations (***Where***)	Physician walked between locations (where categories)
Outside emergency department		Activities conducted outside the defined area of the emergency department	Physician were called on to assist patient on hospital ward (left the emergency department)

[1]During observation time physicians did not administer drugs to patients, hence only non-drug-related treatment and examination were recorded

specific for physician groups and specific drug-related and non-drug-related time were calculated similarly, although the denominators were group specific (considering any overlap in time due to multitasking). The field of analyzing proportions of continuous time measures are scarcely investigated, hence a bootstrapping approach was used to generate 95% confidence intervals (CIs) for the proportions and interruption rates. Monte Carlo testing was applied for comparing drug-related task time between different physician groups: medical vs. surgical physicians, experienced vs. inexperienced physicians, significance level 0.05. Both bootstrapping and Monte Carlo testing were chosen to avoid the reliance on parametric assumptions which were not met by this data.

Descriptive statistics comprised the number of registered tasks and observed total task time. Data preparation was conducted in Microsoft Office Excel. Data were analysed using the SAS system for Windows, version 9.4, and IBM SPSS software, version 25.

Results

A total of 31 physicians were observed to obtain a total observation time of 91.4 h, (Fig. 1), 14 of the physicians were observed for two sessions.

During each two-hour session, physicians attended to 2.7 patients on average (95% CI 2.3, 3.1). Of these, 2.0 patients (95% CI 1.6, 2.4) were new patients while 0.7 patients (95% CI 0.4, 1.0) were follow-up. Hence, physicians saw on average one new patient per hour in addition to follow-up patients.

Physicians spent 17.8% of their time conducting drug-related tasks and 83.3% conducting non-drug-related tasks (Table 2). Proportions add up to over 100% due to multitasking. Physicians multitasked for 17.4% (95% CI 14.8, 20.5) of the drug-related task time and 9.8% (95% CI 9.0, 10.7) of the non-drug-related task time ($p<0.01$).

Overall (both drug-related and non-drug-related) gathering information (36.5%), professional communication (26.3%) and documentation (24.2%) were the most time-consuming tasks. Gathering information was also the most time-consuming drug-related task (7.0% of total observation time, Table 2).

When combining the most time-consuming task categories, with how tasks were conducted *(how)* and other personnel involved *(who)* (Table 3), gathering information on computer was the most time-consuming task combination overall, including both drug-related and non-drug-related (19.0% of total task time). Documentation on paper and computer was the most time-consuming drug-related tasks, 3.2% and 3.1% of total task time respectively (Table 3).

Obtaining and documenting a patient's drug lists in the hospital systems was found to be a complex process consisting of a series of tasks (Table 3-highlighted cells (Italic)). This process occupied 12.9% (95% CI 11.9, 14.3) of ED physicians' time, equivalent to 7.8 min (95% CI 7.2, 8.6) per hour on average. The process was fragmented through the patient's stay in the ED (Fig. 2). Documentation on paper (medication chart) and computer/dictaphone (electronic patient journal) occupied approximately 4.0 min of the time spent on this process (documentation in both were required). An average of 1.7 min per hour was spent questioning the patient or next of kin about drugs, and an additional 2.0 min were spent gathering drug-related information on computer (including checking the Prescription Intermediary) or paper.

Physicians were interrupted 368 times during the total observation time, which translates to an overall average interruption rate of 4.0 (95% CI 3.6, 4.4) times per hour. Interruption rate during drug-related task time were 4.3 (95% CI 3.0, 5.2) times per hour ($p = 0.81$, compared to the interruption rate for non-drug-related task time). The most

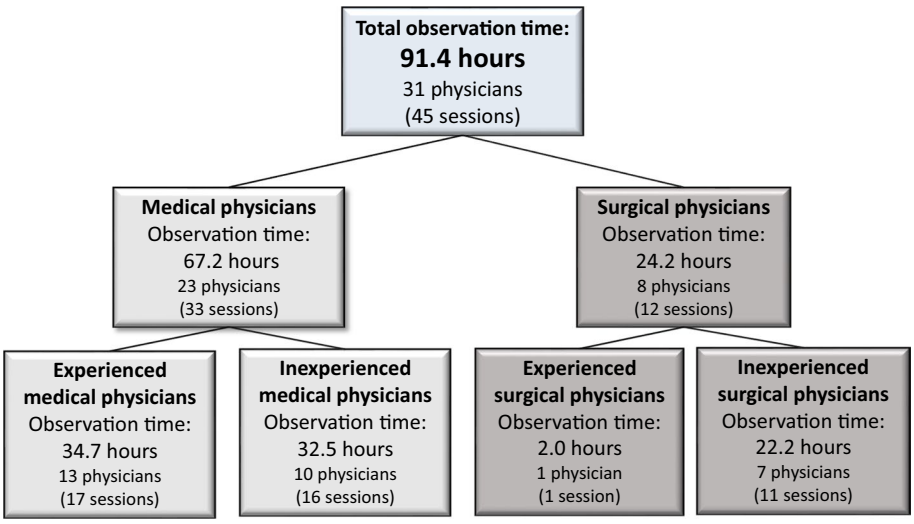


Fig. 1 Distribution of included physicians. Observation time is reported as absolute observation time in hours. Experienced and inexperienced physicians were included from both Department of Internal Medicine (medical physicians) and Department of Surgery (surgical physicians)

Table 2 Physicians' distribution of task time. Data on gathering information, documentation, and professional communication is specified by subcategories non-drug-related and drug-related

Task type	Number of recorded tasks	Observed total task time, hours	Proportion of time on task %[1, 2] (95% CI)
Non-drug-related			83.3% (95% CI 80.0%, 86.6%)
Examination	253	5.2	5.6 (4.8, 6.6)
Professional communication	1664	18.7	20.3 (19.0, 21.9)
Gather information	1678	27.1	29.4 (27.7, 31.5)
Documentation	551	16.3	17.7 (15.9, 19.6)
Unknown	11	0.7	0.8 (0.2, 1.6)
Social (both professional and non-professional)	507	6.1	6.7 (5.9, 7.6)
Hygiene	180	0.9	1.0 (0.8, 1.2)
Movement	925	5.4	5.9 (5.5, 6.3)
Outside ED	68	2.5	2.7 (1.8, 4.5)
Drug-related			17.8% (95% CI 16.8%, 19.3%)
Professional communication	504	5.5	5.9 (5.3, 6.6)
Gather information	491	6.5	7.0 (6.2, 7.9)
Documentation	376	6.1	6.6 (5.8, 7.5)

[1]Proportion of total observation time spent on task

[2]The proportions add up to more than 100% due to multitasking

Table 3 With whom and how physicians conducted work tasks. Gather information, documentation, and professional communication (*what* with sub-categories *drug-related* vs. *non-drug-related,* combined with *who-* and *how)*. Highlighted cells (Italic) represent tasks included in the complex process of obtaining and documenting the patients' drug lists

Task conducted with (WHO)	How task was conducted (HOW)	Drug-related tasks		Non-drug-related tasks	
		Number of recorded tasks	Proportion of time on task %[1, 2] (95% CI)	Number of recorded tasks	Proportion of time on task %[1, 2] (95% CI)
Professional communication					
Patient	Direct	84	1.08 (0.77, 1.56)	211	2.66 (2.09, 3.35)
Next of kin	Direct	19	0.25 (0.13, 0.40)	30	0.37 (0.19, 0.65)
Another physician	Direct/telephone	260	3.05 (2.64, 3.49)	730	9.82 (9.01, 10.65)
Nurse	Direct/telephone	119	1.07 (0.86, 1.35)	489	3.66 (3.30, 4.04)
Pharmacist	Direct	6	0.04 (0.01, 0.09)	-	-
Other hospital	Telephone	7	0.15 (0.06, 0.29)	16	0.68 (0.44, 1.00)
Unknown	Direct/telephone	15	0.40 (0.25, 0.62)	109	1.63 (1.30, 2.04)
Others	Direct/telephone	9	0.10 (0.05, 0.17)	82	1.59 (1.05, 2.43)
General Practitioner	Telephone	0	–	1	0.02
Gather information					
Patient	Direct	*200*	*2.57 (2.10, 3.11)*	400	8.42 (7.26, 9.53)
Next of kin	Direct	*22*	*0.21 (0.13, 0.34)*	53	0.65 (0.44, 0.93)
Another physician	Direct	1	0.01 (0.00, 0.02)	4	0.05 (0.01, 0.15)
Nurse	Direct	1	0.01 (0.00, 0.03)	3	0.02 (0.00, 0.07)
–	On paper	*57*	*1.08 (0.73, 1.58)*	253	2.91 (2.47, 3.37)
–	On computer	*153*	*1.80 (1.45, 2.20)*	961	17.22 (15.84, 18.66)
–	On smartphone	54	1.04 (0.76, 1.41)	12	0.21 (0.09, 0.40)
–	With Prescription Intermediary	*21*	*0.46 (0.26, 0.75)*	–	–
Documentation					
–	On paper	*144*	*3.19 (2.57, 3.83)*	83	0.67 (0.54, 0.83)
–	On computer	*186*	*3.09 (2.51, 3.67)*	400	15.12 (13.52, 17.03)
–	With dictaphone	*40*	*0.27 (0.16, 0.42)*	62	1.81 (1.28, 2.38)
–	With Prescription Intermediary	2	0.07 (0.02, 0.14)	–	–

[1]Proportion of total observation time spent on task

[2]Summarized proportion in this table exceeds proportions reported in Table 2 due to multitask

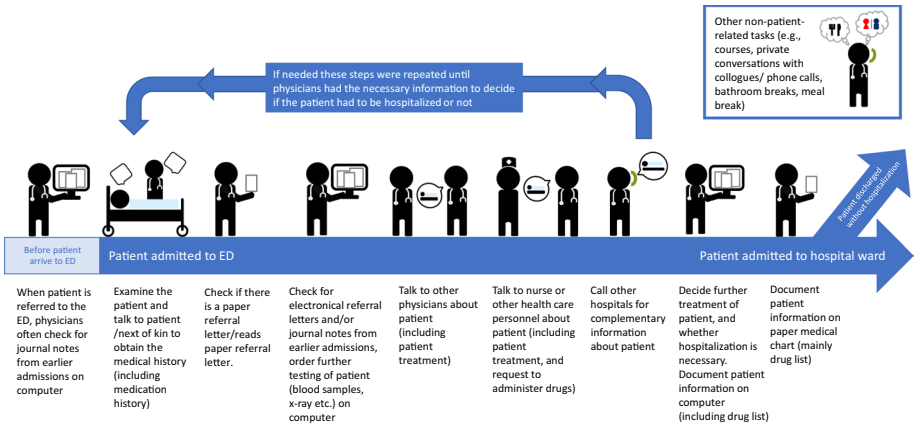


Fig. 2 Illustration of physician tasks conducted during a typical emergency department (ED) visit (for one patient). Typically, the initial examination and communication with the patient were the most extensive, follow-up communication was more brief. Documentation in the electronic patient record was important for accessible information about the admission for healthcare personnel at hospital wards and documentation of the emergency department visit if patient was not hospitalized. Documentation on paper medical chart (mainly drug list) was used during the hospital stay e.g., by nurses at hospital wards to dispense drugs. Tasks present in the illustration is based on the collected data. Observation sessions were independent of the patient pathway. ED: emergency department

interrupted drug-related task was documentation (55.6% of tasks with at least one interruption, during the time physicians conducted drug-related task). Professional communication was the most common reason for interruption of drug-related documentation (82.5% of interruptions).

Medical physicians spent more time than surgical physicians on drug-related tasks overall (19.1% (95%CI 17.5, 20.6) vs. 15.1% (95%CI 13.1, 17.2), $p = 0.01$), as well as for drug-related gathering information (7.7%, (95%CI 6.6, 8.8) vs. 5.4%, (95%CI 4.1, 6.9), $p = 0.03$) and drug-related professional communication (6.7% (95%CI 5.9, 7.4) vs. 4.5% (95%CI 3.7, 5.8), $p = 0.01$). There was no evidence of differences in time spent on any of the specific drug-related tasks, nor drug-related tasks overall between experienced and inexperienced physicians (17.8% (95%CI 16.0, 19.6) vs. 18.2 (95%CI 16.6, 20.0), $p = 0.73$).

Discussion

Statement of key findings

Among the nine conceptualized task categories gathering information, documentation, and professional communication were the most time-consuming for ED physicians in this study. ED physicians spend 17.8% of their time on drug-related tasks, and gathering information was the most time-consuming drug-related task. On average, physicians spent 7.8 min per hour on the complex process of obtaining and documenting patients' drug lists. The ED physicians multitasked more during drug-related task time compared to non-drug-related tasks time. The overall interruption rate was 4.0 times per hour, there were no difference between drug-related task time and non-drug-related task time regarding interruption rates.

Strengths and weaknesses

A validated method was used to perform the study [17] and high inter-rater agreement was achieved and maintained throughout the data collection period. WOMBAT utilized predefined categories. The discrete categories conceptualised and applied in this study were a compromise between the desire to collect as detailed data as possible and the practical feasibility of the study.

The number of observation hours (which is the sample size of concern in these kind of studies) are comparable to other time-motion studies aiming to describe work patterns [12, 18–20]. Due to the roster-based affiliation of physicians to the ED the proportion of physicians enrolled from the total number of available physicians were not calculated. However, observers randomized which of the available physicians to include and observed physicians with different affiliation, experience level, at different hours, and across a time-period of approximately 3 months. This provides the study with solid power regarding inter-individual variability. The study can therefore provide useful baseline information for future studies.

Data were collected between 9am and 9pm and may not be representable of night-time activities in the ED. However, the results represent the time distribution of physicians during the treatment of 80% of patients admitted to the investigated ED.

This study only involved one ED, thus potentially reduce the generalisability of the results. No other studies have investigating ED physicians' drug-related task time. Hence, it is challenging to consider if the findings are representative of other EDs. Although, when looking at the results overall, they match many of the findings in a Danish ED study[12]. In Norway obtaining and documenting medication history is a physician task, hence the results from this study are not generalizable to EDs which have personnel specifically dedicated to obtaining medication history e.g., pharmacy technicians, pharmacists, or nurses.

Interpretation

Physicians' time distribution

ED physicians' time distribution in the present study underlines the purpose of the ED and are similar to earlier studies [12, 18]. Gathering information is important to elucidate the patients' presented symptoms, and to decide if the patient needs hospitalization. Documentation is important to inform the next level of care e.g., hospital ward or healthcare personnel in the primary healthcare. And professional communication with the patient and colleagues is essential among other to ensure safe and efficient treatment of the ED patient.

This is the first study of ED physicians quantifying time spent on all conducted drug-related tasks separately. Compared to physicians in hospital wards at an Australian hospital [25], physicians in the present study spent more time on drug-related tasks (7 vs. 17.8%, respectively). This is not surprising, normally a patient's medication history is documented at admission to the ED. Hence, when the patient arrives at the hospital ward gathering of information and documentation of a patient's drugs are already completed.

Obtaining and documenting patients' drug lists

Gathering information about a patient's medication history and current drug list is important as the drug list documented in the ED is used to decide further drug treatment during the hospital stay and after discharge.

The present study did not assess the quality of the obtained drug lists, it therefore remains undetermined whether the 7.8 min per hour (per patient as one new patient was assessed by physicians per hour on average) are sufficient to obtain a correct and complete drug list at admission. However, several prior studies have reported that ED drug lists frequently do not reflect the patients' drug use prior to admission [3, 5, 8, 26]. According to the results from the present study physicians conduct numerous essential tasks during the patients ED stay, obtaining and documenting drug lists are only two of these tasks. This may explain that healthcare personnel in the ED dedicated to obtaining patients drug lists e.g., pharmacists, pharmacy technicians, document more accurate drug lists than physicians [2–4], as they focus on this specific task. Comparing the time spent by physicians obtaining and documenting drug lists in the present study with a systematic review on pharmacists conducting medication reconciliation in the ED setting, shows that the latter spend more time, reported 13.9-30 min per patient [8]. Further, it was also reported that medication discrepancies were reduced by 88% when ED pharmacists performed the medication reconciliation [8], indicating that the time spent and the systematic approach through medication reconciliation were worthwhile. As ED crowding is an increasing challenge, it should be considered to include healthcare personnel in the ED dedicated to obtaining patients drug lists. This can contribute to decrease ED physicians' workload in the fast-paced workflow. However, the most important benefit is the potential decrease in medication discrepancies, especially for complex patients where the time spent by physicians may not be sufficient to obtain their complete and correct drug list.

Interruptions and multitasking

A German study reported that physicians were most frequently interrupted during documentation [27], and a Canadian study found that professional communication was the most common reason for interruption, which is in line with the results of the present study. In the present study interruption rates during drug-related and non-drug-related task time were equal. However, the frequency of multitasking was higher during drug-related task time compared to non-drug-related task time. According to an Australian study, multitasking and interruptions were associated with a higher rate of prescribing errors per medication order [13]. Interruptions and multitasking which result in prescribing errors at admission to ED can be a hazard against patient safety through the entire hospital stay and even after discharge [11].

Gather information in transition of care

Overall, the physicians in the present study spent approximately the same amount of time on documentation and communication as the ED physicians in a Danish study [12]. However, the physicians in the present study spent more time gathering information. The difference in study methods and definitions must be considered, although there may also be differences in accessibility of patient information between countries.

During the data collection period the only common electronic system between primary and secondary healthcare in Norway were the Prescription Intermediary, a

nationwide electronic prescription database which includes information about patients' prescribed drugs [28]. Another database has been implemented after the study were conducted, the "Summary care record", which include a short summary of information needed in emergency care, e.g., information about critical adverse drug reactions and prescribed drugs. However, there are still no common patient record for primary and secondary healthcare with complete information about a patient's medical and medication history. Physicians in the study had to use multiple sources to obtain this information. This can explain why no differences between drug-related time spent by experienced and inexperienced physicians were found, as checking multiple sources are equally time-consuming regardless of experience. The Prescription Intermediary was only checked for approximately every fourth patient. This was a surprising and noteworthy finding. Conclusions on why physicians did not take advantage of this easily accessible source cannot be drawn from the results. However, reliability can be a factor, as the database have to be manually updated the content in the Prescription Intermediary (and also the "Summary care record") is not always trustworthy. With a short average length of stay in the ED, it is essential that electronic support tools are trustworthy to ensure that physicians' limited time are used efficiently.

Medical physicians spent more time gathering drug-related information than surgical physicians. This may contribute to explain that earlier studies identified surgical admission/referral as a risk factor for clinically relevant medication discrepancies [2, 5].

Multidisciplinary interactions

Observed physicians in this study spent more time interacting (including both *professional communication* and *gathering information)* with other healthcare personnel than admitted patients, which is in line with another study[12]. Communication between colleague physicians and between physicians and nurses, are vital to ensure safe and efficient treatment of the ED patient. Although this cannot be quantified from the data (due to the discrete categories), it was noticed by the observers that some drug-related tasks were not conducted by physicians themselves but delegated to other health professions in the ED. Nurses were requested during *professional communication* with the observed physician to administer drugs to patients. And the secretary (*others*) was requested during *professional communication* to obtain information about patients' drug lists from GP or nursing home.

Due to the limited pharmacist coverage in the investigated ED, it was not surprising that physicians only communicated with pharmacists 6 times during the data collection period. For instance, some observations sessions occurred when there was no pharmacist present. However, with adequate coordinating (e.g., a referral system or more resources), pharmacists could contribute to the process of obtaining and documenting correct and complete drug lists in the ED, as reported in prior studies [2, 3, 5].

Further research

The findings in this study raises some interesting questions regarding whether the time spent by ED physicians is sufficient to obtain a correct and complete drug list for admitted patients. And further, it could be explored if the interruptions during drug-related documentation could affect the quality of the drug lists. To answer this, future studies should combine time-motion observations with quality assessments of the obtained drug lists. In addition, further research could focus on how to optimize implementation of dedicated personnel to obtain drug-lists at admission e.g., pharmacists or pharmacy technicians, in the multidisciplinary team in the ED, and how this implementation could impact physicians' time distribution.

Conclusion

This is the first study to perform a detailed quantitative assessment of time spent on all drug-related tasks performed by ED physicians, in addition to the time distribution across other conducted tasks. Overall, 17.8% of ED physicians' time was spent on drug-related tasks, and 7.8 min per hour (i.e., per patient) was spent on the complex process of obtaining and documenting the patients' drug lists. This study adds important information that can be used for redesigning and optimising work- and information flow in transition of care when patients are admitted to the ED. In addition, it provides a useful baseline for future studies.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11096-021-01364-6.

Acknowledgements The authors would like to thank all the included physicians and the Emergency Department at Diakonhjemmet Hospital.

Funding Open access funding provided by University of Oslo (incl Oslo University Hospital). The project is funded by Diakonhjemmet Hospital Pharmacy AS, Diakonhjemmet Hospital fund for research, innovation and professional development and Diakonhjemmet Foundation.

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

References

1. Mentzoni I, Bogstrand ST, Faiz KW. Emergency department crowding and length of stay before and after an increased catchment area. BMC Health Serv Res. 2019;19(1):506.
2. Reeder TA, Mutnick A. Pharmacist- versus physician-obtained medication histories. Am J Health Syst Pharm. 2008;65(9):857–60.
3. Hatch J, Becker T, Fish JT. Difference between pharmacist-obtained and physician-obtained medication histories in the intensive care unit. Hospital Pharmacy. 2011;46(4):262–8.
4. Henriksen JP, Noerregaard S, Buck TC, et al. Medication histories by pharmacy technicians and physicians in an emergency department. Int J Clin Pharm. 2015;37(6):1121–7.
5. Damlien L, Davidsen N, Nilsen M, et al. Drug safety at admission to emergency department: an innovative model for PRIOritizing patients for MEdication Reconciliation (PRIOMER). Eur J Emerg Med. 2017;24(5):333–9.
6. Caglar S, Henneman PL, Blank FS, et al. Emergency department medication lists are not accurate. J Emerg Med. 2011;40(6):613–6.
7. Welch S, Finckh A. Prescribing errors in emergency department medication history taking: will electronic medication management systems help?. J Pharm Pract Res, (2019) 49: 400–402.
8. Choi YJ, Kim H. Effect of pharmacy-led medication reconciliation in emergency departments: A systematic review and meta-analysis. J Clin Pharm Ther. 2019;44(6):932–45.
9. Hohl CM, Zed PJ, Brubacher JR, et al. Do emergency physicians attribute drug-related emergency department visits to medication-related problems? Ann Emerg Med. 2010;55(6):493-502.e4.
10. Sullivan C, Gleason KM, Rooney D, et al. Medication reconciliation in the acute care setting: opportunity and challenge for nursing. J Nurs Care Qual. 2005;20(2):95–8.
11. Santell JP. Reconciliation failures lead to medication errors. Jt Comm J Qual Patient Saf. 2006;32(4):225–9.
12. Füchtbauer LM, Nørgaard B, Mogensen CB. Emergency department physicians spend only 25% of their working time on direct patient care. Dan Med J. 2013;60(1):A4558.
13. Westbrook JI, Raban MZ, Walter SR, et al. Task errors by emergency physicians are associated with interruptions, multitasking, fatigue and working memory capacity: a prospective, direct observation study. BMJ Qual Saf. 2018;27(8):655–63.
14. Zheng K, Guo MH, Hanauer DA. Using the time and motion method to study clinical work processes and workflow: methodological inconsistencies and a call for standardized research. J Am Med Inform Assoc. 2011;18(5):704–10.
15. von Elm E, Altman DG, Egger M, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ. 2007;335(7624):806–8.
16. Westbrook JI, Ampt A. Design, application and testing of the Work Observation Method by Activity Timing (WOMBAT) to measure clinicians' patterns of work and communication. Int J Med Inform. 2009;78 Suppl 1:S25-33.
17. Ballermann MA, Shaw NT, Mayes DC, et al. Validation of the Work Observation Method By Activity Timing (WOMBAT) method of conducting time-motion observations in critical care settings: an observational study. BMC Med Inform Decis Mak. 2011;11:32.
18. Richardson LC, Lehnbom EC, Baysari MT, et al. time and motion study of junior doctor work patterns on the weekend: a potential contributor to the weekend effect? Intern Med J. 2016;46(7):819–25.
19. Hefter Y, Madahar P, Eisen LA, et al. A time-motion study of ICU workflow and the impact of strain. Crit Care Med. 2016;44(8):1482–9.
20. Lehnbom EC, Li L, Prgomet M, et al. Little things matter: a time and motion study of pharmacists' activities in a paediatric hospital. Stud Health Technol Inform. 2016;227:80–6.
21. Schofield B, Cresswel K, Westbrook J, et al. The impact of electronic prescribing systems on pharmacists' time and workflow: protocol for a time-and-motion study in English NHS hospitals. BMJ Open. 2015;5(10):e008785.
22. Walter SR, Dunsmuir WTM, Westbrook JI. Inter-observer agreement and reliability assessment for observational studies of clinical work. J Biomed Inform. 2019;100:103317.
23. Janson H, Olsson, U. A Measure of Agreement for Interval or Nominal Multivariate Observations. Educational and Psychological Measurement. 2001;61 (2):277–89.
24. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977;33(1):159–74.
25. Westbrook JI, Ampt A, Kearney L, et al. All in a day's work: an observational study to quantify how and with whom doctors on hospital wards spend their time. Med J Aust. 2008;188(9):506–9.
26. Tong EY, Roman CP, Mitra B, et al. Reducing medication errors in hospital discharge summaries: a randomised controlled trial. Med J Aust. 2017;206(1):36–9.
27. Weigl M, Müller A, Zupanc A, et al. Hospital doctors' workflow interruptions and activities: an observation study. BMJ Qual Saf. 2011;20(6):491–7.
28. The Norwegian health network, What is e-prescription?, 2019, Available at: https://helsenorge.no/other-languages/english/what-is-e-prescription?redirect=false. Accessed 11.03.2020.

Appendix 1, paper IV
Reproduction of Electronic supplementary material 1

Emergency department physicians' distribution of time in the fast paced-workflow- a novel time-motion study of drug-related activities

Lisbeth D. Nymoen[1,2], Therese Tran[2], Scott R. Walter[3], Elin C. Lehnbom[4,5], Ingrid K. Tunestveit[2], Erik Øie[6], Kirsten K. Viktil[1,2]

1 Diakonhjemmet Hospital Pharmacy, Oslo, Norway, 2 Department of Pharmacy, University of Oslo, Oslo, Norway, 3 Centre for Health Systems and Safety Research, Australian Institute of Health Innovation, Macquarie University, Sydney, Australia, 4 Department of Pharmacy, UiT The Arctic University of Norway, Tromsø, Norway, 5 Department of Health and Caring Sciences, Linnæus University, Kalmar, Sweden, 6 Department of Internal Medicine, Diakonhjemmet Hospital, Oslo, Norway

Corresponding author: Lisbeth Damlien Nymoen
Postal address: Diakonhjemmet Hospital Pharmacy AS, Postbox 40 Vinderen, 0319 Oslo, Norway
E-mail: lisbetd@student.matnat.uio.no
ORCID (corresponding author): 0000-0001-9330-3374
Journal: International Journal of Clinical Pharmacy

Screenshot of the WOMBAT data collection tool with four dimensions.

During direct observation of emergency department physicians, data were systematically registered using a Samsung Galaxy 8 tablet running version 2 of the licenced WOMBAT software(1, 2). Data were registered in predefined discrete categories organised under four dimensions: *WHAT, WHERE, HOW, AND WHO*. And were automatically time-stamped by the WOMBAT software i.e., recording the exact time for the start of the task and recording the time until a new task was started (either due to finishing the task or getting interrupted).

WHAT

The *WHAT* dimension described the work tasks conducted by the observed emergency physician. This dimension was mandatory. Categories, sub-categories, definitions, and examples of work tasks, *WHAT* dimension is presented in Table 1 in the article.

Explanation of truncated words in the figure:
Treatment; treatment/examination,
Gather info.; gather information
Document; documentation
Proff.com; professional communication

WHERE

The *WHERE* dimension was utilized to record where the observed emergency physician conducted the recorded task. This dimension was mandatory (connected to every recorded work task, *WHAT*).

Physician room (Physicianro)**:** the office of the emergency department physicians
Patient room (Patientroom)**:** rooms dedicated to patients admitted to the emergency department
Corridor: the corridor in the emergency department, leading to physician room and all patient rooms
Break room (Breakroom)**:** room for meal breaks and socialising
Hospital ward (Hospitalwar.)**:** hospital wards at Diakonhjemmet Hospital
Outside emergency department (OutsideED)**:** when emergency department physicians left the emergency department for whatever reason

As the aim of this study was to investigate emergency department activities, work tasks recorded as performed at hospital wards and outside emergency department were merged to one work task category, under the *WHAT* dimension called *outside emergency department* see article.

HOW

The *HOW* dimension was utilized to record how the observed emergency physician conducted the recorded task. This dimension was not mandatory as some work tasks did not require this dimension, e.g., hygiene, movement. However, this dimension was recorded connected to recorded work task, *WHAT* whenever appropriate.

Direct: face-to-face interaction
Data: reading or writing on computer
Telephone: talking on the work telephone, each emergency department physician on call have a work phone available
Paper: reading or writing on paper
Dictaphone: recording via dictaphone information which was transcribed to text by transcribers employed at Diakonhjemmet Hospital, some of the emergency department physicians utilized this instead of writing the admission note in the electronically patient record
The prescription intermediary (Reseptform.)**:** a nationwide electronic prescription database which is available both to primary and secondary healthcare and contain information about patients' prescribed drugs
Smart phone: checking apps for professional information, talking on the telephone, answering private texts

WHO

The *WHO* dimension was utilized to record with whom the observed emergency physician conducted the recorded task. This dimension was not mandatory as some work tasks did not require this dimension, e.g., documentation, hygiene, movement. However, this dimension was recorded connected to recorded work task, *WHAT* whenever appropriate.

Patient: observed physician interacted with a patient
Next of kin: observed physician interacted with next of kin of an admitted patient
Nurse: observed physician interacted with nurse
Physician: observed physician interacted with another physician
Pharmacist: observed physician interacted with a pharmacist
Primary healthcare service (Primary HC)**:** observed physician interacted with healthcare personnel in the primary healthcare service, general practitioner (GP), nursing home, municipal emergency clinic
Other hospitals (Other hospi.)**:** observed physician interacted with healthcare personnel at another hospital
Unknown: observed physician interacted with someone which could not be identified by the observers
Other: observed physician interacted with other persons which were not covered by the pre-set categories e.g., emergency department secretary, personnel from the hospital laboratory

Examples of data collection:

Observation	WHAT	WHERE	HOW	WHO
Physician taking medication history with the patient in the patient room	Gather information, drug-related (subcategory)	Patient room	Direct	Patient
Physician writing background information about a patient's medical history on computer in the physician office	Documentation, non-drug-related (subcategory)	Physician room	Data	-
Physician examining the patient in the patient room	Treatment/Examination	Patient room	Direct	Patient
Physician discussing the patients drug treatment with a colleague physician and a nurse in the physician office	Professional communication, drug-related (subcategory)	Physician room	Direct	Physician & Nurse
Physician writes patients drug list, and further drug-treatment for the hospital stay on the hospital medication chart while in the physician office	Documentation, drug-related (subcategory)	Physician room	Paper	-
Physician walks from patient room to physician office	Movement	Corridor	-	-
Physician asks nurse (in the corridor) to administer a drug to a patient	Professional communication, drug-related (subcategory)	Corridor	Direct	Nurse
Physician asks secretary (in the physician room) to obtain drug-list from the patients GP	Professional communication, drug-related (subcategory)	Physician room	Direct	Other

REFERENCES

1. Westbrook JI, Ampt A. Design, application and testing of the Work Observation Method by Activity Timing (WOMBAT) to measure clinicians' patterns of work and communication. Int J Med Inform. 2009;78 Suppl 1:S25-33.

2. Ballermann MA, Shaw NT, Mayes DC, Gibney RT, Westbrook JI. Validation of the Work Observation Method By Activity Timing (WOMBAT) method of conducting time-motion observations in critical care settings: an observational study. BMC Med Inform Decis Mak. 2011;11:32.