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SEVERE MEDICATION ERRORS – A CHALLENGE FOR PATIENT SAFETY

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DOCTORAL DISSERTATION

To be presented for public examination with the permission of the Faculty of Pharmacy of the University of Helsinki, in Auditorium Tekla Hultin, University Main Building, on the 3rd of November, 2023 at 13 o'clock.

Helsinki 2023

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Publisher: University of Helsinki, Finland
Series: Dissertationes Universitatis Helsingiensis 45/2023

ISBN 978-951-51-9124-3 (print)
ISBN 978-951-51-9125-0 (online)
ISSN 2954-2898 (print)
ISSN 2954-2952 (online)

PunaMusta
Joensuu 2023

ABSTRACT

A medication error (ME) is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Severe medication errors are the most unwanted outcome of the medication use process causing severe harm or even being fatal to the patient. Considering how common intervention medication treatment is in health care, and how many people use medicines daily, severe MEs are relatively rare. Still, they are an untenable global burden from individual patient and professional, public health, and economic perspectives. Although severe MEs typically occur because of complex error processes, including multiple errors and contributing factors, their preventability may have great potential. For successful prevention, we need to understand error processes and learn from them using different kinds of ME data and analysis methods to build up safer practices and systemic defenses for prospective risk management.

This doctoral thesis study aimed to have insights into severe MEs to find ways to learn from them and prevent them. The thesis consists of three studies, two focusing on analyzing and developing methods to investigate severe ME data derived from a national authority register (Studies I, II). The third study evaluated the implementation process of selected safe medication practices in hospitals within 11 EU countries, focusing on facilitators and barriers to implementation (Study III). System-based risk management approach to human error by Reason was applied as a theoretical framework.

Studies I and II were based on retrospective document analysis of medication-related complaints and authoritative statements investigated by the National Supervisory Authority for Welfare and Health (Valvira) in Finland in 2013-2017 (n=58). The goal was to evaluate how the extensive incident documentation gathered for authority purposes applies to learning from severe MEs. Study I investigated characteristics of severe MEs reported to Valvira, the error processes, settings, and the preventability of errors. The majority (83%, n=48/58) of the incidents concerned patients over 60 years. Most likely the errors occurred in prescribing (n=38; 47%), followed by administration (n=15, 19%) and monitoring (n=14, 17%). The error process often included multiple failures (n=24; 41%) or health care professionals (n=16; 28%). Antithrombotic agents (n=17; 13%), opioids (n=10, 8%), and antipsychotics (n=10, 8%) were the therapeutic groups most involved in the errors. Almost all error cases (91%, n=53) were assessed as likely or potentially preventable. In 60% (n=35) of the cases, the organization reported actions taken to improve medication safety after the occurrence of the investigated incident.

Although several classification systems for MEs have been established, they do not apply well to classifying severe MEs. Therefore, Study II focused on

exploring the applicability of a cause-based drug-related problem (DRP) classification system by Basger et al. (2015) for classifying severe MEs. In total, 100 MEs were identified from Valvira's ME case reports (n=58) by using the Basger et al. DRP classification system. In 53% (n=31) of the cases, more than one ME was identified, with the mean number of MEs identified being 1.7 per case. It was possible to classify all MEs according to aggregated DRP system, and only a small proportion (8%, n=8) were classified in the category "Other," indicating that the cause of the ME could not be classified as a specific cause-based category.

Study III was carried out as part of the European Network for Patient Safety (EUNetPas) project in 2008-2010. The objective was to evaluate transferability and the implementation process of seven selected medication safety practices (MSPs). The selected practices were: two different versions of medicine bed dispensation; safety vest; discharge medication list for patients; medication reconciliation at patient discharge; medication reconciliation at patient admission and patient discharge; and sleep card. The MSPs were implemented across 55 hospitals within 11 European Union countries that participated in the project. The participating hospitals submitted an evaluation report (n=75) describing the implementation process of a chosen practice(s) in their organization. The reports were analyzed with qualitative inductive content analysis. Of those hospitals that started the implementation, 78% (n=52) reported that they were able to implement the practice as described or as modified within the given timeframe. The major reported general barrier to implementation was difficulties encountered in changing the work processes because of the new practice. Facilitators for successful implementation were especially the existence of a safety culture, national guidelines and projects, expert support, sufficient resources, electronic patient records, and interprofessional cooperation. Practice specific facilitators and barriers were also recognized.

As demonstrated in this doctoral study, MEs reported to a national health care supervisory authority are valuable and unique information sources of severe errors, and this data should be regarded as a part of national incident reporting and learning systems. Analysis of severe MEs with complex processes has a great potential to develop health care organizations´ systems, processes, resources, and competencies, if we have adequate methods to investigate the existing ME data. The aggregated DRP classification system with some modifications has the potential for analyzing and describing MEs and their causes, specially producing more sensitive and selective information for learning from severe MEs. The other part of the study demonstrated that medication safety practices are transferable across different organizations and countries. However, successful implementation requires selecting the right practice for the right medication safety risk, the presence of a safety culture, and sufficient resources and professionals.

TIIVISTELMÄ

Lääkityspoikkeamalla tarkoitetaan mitä tahansa estettävissä olevaa tapahtumaa, joka voi aiheuttaa tai johtaa lääkkeen epäasianmukaiseen käyttöön tai haittaan potilaalla, kun lääkityksestä vastaa terveydenhuollon ammattilainen tai potilas itse. Vakavissa lääkityspoikkeamissa haitta potilaalle on vakava tai jopa kuolemaan johtava, ja siksi ne ovatkin lääkehoitoprosessin epätoivotuin lopputulos. Ottaen huomioon lääkehoidon yleisyyden osana potilaiden hoitoa ja kuinka paljon lääkkeitä päivittäin käytetään, vakavat lääkityspoikkeamat ovat suhteellisen harvinaisia. Vakavat lääkityspoikkeamat ovat kuitenkin merkittävä maailmanlaajuinen haaste yksittäisten potilaiden, terveydenhuollon ammattilaisten ja terveydenhuoltojärjestelmien näkökulmasta. Vakavat lääkityspoikkeamat ovat tyypillisesti kompleksisia, useita virheitä ja myötävaikuttavia tekijöitä sisältäviä prosesseja, joiden tapahtumista voidaan kuitenkin estää. Lääkityspoikkeamien estäminen ja niistä oppiminen vaatii kuitenkin ymmärrystä tapahtuneesta poikkeamaprosessista. Ymmärtämällä ja analysoimalla lääkityspoikkeamia erilaisissa vaaratapahtuma-aineistoissa luodaan edellytykset turvallisten käytäntöjen ja järjestelmälähtöisten suojausten rakentamiselle osana lääkityspoikkeamien ennakoivaa riskienhallintaa.

Tämän väitöskirjatutkimuksen tavoitteena oli tutkia millaisia ovat vakavat lääkityspoikkeamat sekä löytää keinoja niistä oppimiseen ja niiden estämiseen. Väitöskirja koostuu kolmesta tutkimuksesta, joista kaksi keskittyy vakavien lääkityspoikkeamien analysointiin kansallisesta viranomaisaineistosta sekä analysointimenetelmän pilotointiin (Tutkimukset I, II). Kolmas tutkimus arvioi lääkitysturvallisuuskäytänteiden implementointiprosessia 11 EU-maan sairaaloissa keskittyen erityisesti implementaatiota edistäviin ja estäviin tekijöihin (Tutkimus III). Järjestelmälähtöinen riskien hallinta inhimillisten virheiden ymmärtämisen näkökulmasta toimi tutkimuksen teoreettisena viitekehyksenä.

Tutkimukset I ja II perustuivat Sosiaali- ja terveysalan lupa- ja valvontavirasto Valviran lääkehoitoon liittyvien kanteluiden ja viranomaislausuntojen retrospektiiviseen dokumenttianalyysiin ajanjaksolta 2013-2017 (n=58). Tavoitteena oli arvioida, kuinka ensisijaisesti valvontatarkoituksiin kerätty viranomaisaineisto soveltuu vakavista lääkityspoikkeamista oppimiseen. Tutkimus I tutki Valviran aineiston ja vakavien lääkityspoikkeamien taustatekijöitä, lääkityspoikkeamien luonnetta, poikkeaman toimintaympäristöä sekä arvioi poikkeamien ennalta estettävyyttä. Pääosa lääkityspoikkeamista (83%, n=48/58) koski yli 60-vuotiaita potilaita. Lääkityspoikkeamat liittyivät yleisimmin lääkkeen määräämiseen (n=38; 47%), lääkkeenantoon (n=15, 19%) ja lääkehoidon seurantaan (n=14, 17%). Lääkityspoikkeamaprosessit sisälsivät usein

epäonnistumisia useissa lääkehoitoprosessin vaiheissa (n=24; 41%) tai useita terveydenhuollon ammattilaisia (n=16; 28%). Antitromboottiset lääkeaineet (n=17; 13%), opioidit (n=10, 8%), ja antipsykootit (n=10, 8%) olivat lääkityspoikkeamissa yleisimmin toistuneet lääkeaineryhmät. Lähes kaikki poikkeamatapaukset (91%, n=53) arvioitiin todennäköisesti tai mahdollisesti estettäviksi. Yhteensä 60%:ssa tapauksista (n=35) organisaatio oli raportoinut Valviralle tehneensä lääkitysturvallisuuden kehittämistoimenpiteitä vastaavan tilanteen toistumisen estämiseksi.

Vaikka lääkityspoikkeamille on olemassa useita erilaisia luokittelumenetelmiä, ne eivät optimaalisesti ja riittävän informatiivisesti sovellu kuvaamaan vakavia lääkityspoikkeamia. Tämän vuoksi Tutkimuksessa II tutkittiin, voisiko Basgerin ym. (2015) lääkehoidon ongelmien luokitteluun kehittämää syypohjaista luokittelumenetelmää soveltaa vakavien lääkityspoikkeamien luokitteluun. Luokittelua käyttäen Valviran tapauskuvauksista (n=58) tunnistettiin yhteensä 100 lääkityspoikkeamaa. Yhteensä 53%:ssa (n=31) tapauksista tunnistettiin useampi kuin yksi lääkityspoikkeama (keskiarvo 1,7 lääkityspoikkeamaa tapauskuvausta kohden). Kaikki tunnistetut lääkityspoikkeamat pystyttiin luokittelemaan lääkehoidon ongelmille tarkoitetulla luokittelulla. Vain pieni osuus poikkeamista (8%, n=8) jouduttiin luokittelemaan kategoriaan “Muut”, jonne sijoittuivat ne lääkityspoikkeamat, joille ei ollut löydettävissä selkeää omaa spesifiä luokkaa.

Tutkimus III toteutettiin osana Euroopan Unionin ”European Network for Patient Safety (EUNetPas)” potilasturvallisuusprojektia, joka toimi vuosina 2008–2010. Tutkimuksen III tavoitteena oli tunnistaa valitun seitsemän lääkitysturvallisuuskäytännön (kaksi erilaista käytäntöä lääkkeiden jakamisesta potilaan vierellä; lääkkeidenjakoliivi; kotiutusvaiheen lääkelista; lääkityksen ajantasaistaminen potilaan kotiutuessa; lääkityksen ajantasaistaminen potilaan saapuessa ja kotiutuessa; unilääkkeiden käyttöprotokolla) implementointia sairaaloissa edistäneitä ja estäneitä tekijöitä sekä tutkia käytäntöjen siirrettävyyttä eri maihin ja sairaaloihin. Lääkitysturvallisuuskäytäntöjä implementoitiin projektissa 55 sairaalassa 11 eri EU-maassa. Projektiin osallistuneet sairaalat toimittivat arviointiraportin (n=75) käytännön implementointiprosessista. Nämä arviointiraportit analysoitiin laadullisella, induktiivisella sisällön analyysillä. Niistä sairaaloista, jotka olivat aloittaneet implementoinnin, 78% (n=52) raportoi onnistuneensa implementoimaan käytännön joko sellaisenaan tai muokattuna projektissa annetussa aikataulussa. Yksi yleisimmistä implementointia estäneistä tekijöistä oli haasteet työprosessien muuttamisessa. Implementointia edistäneitä tekijöitä olivat erityisesti olemassa oleva turvallisuuskulttuuri, kansalliset suositukset ja projektit, asiantuntijatuki, riittävät resurssit, elektroniset potilastietojärjestelmät ja moniammatillinen yhteistyö. Arviointiraporteista tunnistettiin myös implementointia edistäneitä ja estäneistä tekijöitä, jotka olivat spesifejä tietyille lääkitysturvallisuustyökaluille.

Kuten tässä väitöskirjatutkimuksessa on osoitettu, kansalliselle sosiaali- ja terveydenhuollon valvontaviranomaiselle kertyy sellaista tietoa vakavista lääkityspoikkeamista, jota tulisi hyödyntää yhtenä osana kansallista vaaratapahtumien raportointia yhteisen oppimisen ja kehittämisen varmistamiseksi. Vakavista ja kompleksisista lääkityspoikkeamista oppimisella voidaan kehittää sosiaali- ja terveydenhuollon organisaatioiden prosesseja, resursseja ja osaamista, edellyttäen että meillä on luotettavat menetelmät tiedon analysoimiseksi ja hyödyntämiseksi. Lääkehoidon ongelmien luokittelumenetelmä voisi pienin muutoksin olla yksi potentiaalinen tapa jatkossa analysoida ja kuvata lääkityspoikkeamia sekä niiden syitä, erityisesti kun on tarve saada aiempaa tarkempaa tietoa vakavista lääkityspoikkeamista oppimiseksi. Tutkimuskokonaisuuden toinen osio osoitti, että lääkitysturvallisuuskäytäntöjä voidaan siirtää organisaatiosta tai maasta toiseen. Onnistunut implementointi vaatii kuitenkin oikein valitun työkalun, turvallisuuskulttuurin sekä asianmukaisia resursseja ja ammattilaisia.

ACKNOWLEDGEMENTS

It all started as a pharmacy student who was afraid of making errors. With a wisdom of my main supervisor professor Marja Airaksinen, this fear was formed as a research topic on how medication errors are reported. I am incredibly grateful for her that she already then realized the need for medication safety as new research area in Finland. After my bachelor´s thesis, she guided me on studying severe medication errors in Valvira as my master's thesis, which was also the start for my PhD studies and a career in medication safety field.

Completing the dissertation has been longer journey than I assumed over ten years ago when starting the process. I have been privileged to join many medication safety projects and working positions that have been launched in international, national, and organizational levels making them the priority in my life and making delays in completing my doctoral training. Still, without those projects and working experience, this thesis would be quite different and the perspective narrower. I would like to thank all those who asked me to join those opportunities to develop my knowledge and competence in medication safety.

Assistant professor Anna-Riia Holmström has been my close friend for years and I am grateful for her supervision in the last years of my dissertation journey. Although there were many points where I was almost ready to give up, she first finalized her own PhD and then guided me through the same path. This dissertation would not have been finalized without her support.

I am privileged to have Docent Timo Keistinen as my opponent. You have been key person and promoter in Finnish patient safety work, and it is a privilege to defend and discuss my study with you. I want to express my deepest thanks to MD Pirjo Pennanen who had vital role starting medication safety work in Finland. She also opened my way to international research and her contribution was essential in Study III.

I am also grateful for the reviewers of this doctoral thesis, Docent Liisa-Maria Voipio-Pulkki and Dr Ramesh Walpola who gave me valuable feedback to improve and finalize it. The dissertation would not have been possible without Docent Virpi Talman being the faculty representative in the grading committee.

I am grateful for Valvira for long-term cooperation starting from my early research stages and seeing the need for studying and using their data. Studies I and II would not have been possible without Anna Takala, MSc (Pharm), who collected the study data in Valvira. You are one of my most talented master students and it was a pleasure to supervise your thesis and cooperate with you.

There are no words to express how lucky I am to work in HUS Pharmacy, which is the best workplace to do medication safety research and implement it into practice. This is mainly because of the vision created by the Director of

HUS Pharmacy Kerstin Carlsson, MSc (Pharm). I want to thank all members of HUS Pharmacy Research Center but especially Hanna Tolonen, PhD, Sini Kuitunen, PhD, and Kirsi Kvarnström, PhD who were in the same PhD train and kept me on track. Only you felt the pain of the PhD student and helped to see the bright waiting after all setbacks experienced during the PhD journey. Hanna has also been the most supporting superior enabling research breaks in my work. Special thanks for Lotta Schepel, PhD, who has always supported me as a medication safety researcher and specialist. I appreciate that HUS Pharmacy Medication Safety team was always understanding and supporting when I had some research deadlines that were impossible to reach at the same time with work deadlines. Many PhD students and colleagues in social pharmacy have been the peer-support and inspiration to finalize my thesis and I like to warmly thank you all.

The financial support of the Finnish Cultural Foundation and the Helsinki University Pharmacy (Yliopiston Apteekki) has been important enabling research periods during hectic work and family life.

Finally, I want to thank my family for standing with me this decade lasting period when there were no holidays without some research work included. You understood the difficulty to combine full-time work, family, research, and endless enthusiasm for medication safety. The most grateful I am for my husband Mika who make it possible to find moments for my research in a family with children. Thank you for being the greatest dad for our children.

Hyvinkää, October 2023

Carita Linden-Lahti

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications, referred to in the text by their Roman numerals (I-III):

I **Linden-Lahti C**, Takala A, Holmström A-R, Airaksinen M. What severe medication errors reported to health care supervisory authority tell about medication safety? *J Patient Saf* 2021;17:e1179-e1185. doi: 10.1097/PTS.0000000000000914 (Open Access)

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II **Linden-Lahti C**, Takala A, Holmström A-R, Airaksinen M. Applicability of drug-related problem (DRP) classification system for classifying severe medication errors. *BMC Health Serv Res* 2023;23:743. doi: 10.1186/s12913-023-09763-3 (Open Access)

III **Linden-Lahti C**, Holmström A-R, Pennanen P, Airaksinen M. Facilitators and barriers in implementing medication safety practices across hospitals within 11 European Union countries. *Pharm Pract (Granada)* 2019;17:1583. doi: 10.18549/PharmPract.2019.4.1583 (Open Access)

The publications are referred to in the text by their Roman numerals.

DEFINITIONS OF THE KEY CONCEPTS

Adverse event (AE)

An incident that resulted in harm to a patient (World Health Organization 2009).

Adverse drug event (ADE)

Any injury due to medication (Bates et al. 1995, Morimoto et al. 2004, Committee of Experts on Management on Safety and Quality in Health Care and Expert Group on Safe Medication Practices 2005, World Health Organization 2009). This includes both adverse drug reactions in which no error occurred and complications resulting from medication errors (World Health Organization 2019).

Adverse drug reaction (ADR)

Noxious and unintended effects resulting not only from the authorized use of a medicinal product at normal doses but also from medication errors (Ferner and Aronson 2006, Directive 2010/84/EU).

Barrier

In the patient safety context, barriers refer to health care structures and approaches, such as a lack of resources or safety culture, which may prevent, e.g., safety practice implementation (Vrbnjak et al. 2016).

Contributing factor

A circumstance, action, or influence which is thought to have played a part in the origin or development of an incident or to increase the risk of an incident (Reason 1990, World Health Organization 2009).

Drug-related problem (DRP)

An event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes (Pharmaceutical Care Network Europe 2020). Drug-related problems can be caused by medication errors, but there might be no error involved. A medication error does not necessarily lead to a drug-related problem; there can be no problem or a potential problem.

Error

A failure to carry out a planned action as intended or application of an incorrect plan (World Health Organization 2009). It may be caused by doing the wrong thing (commission) or failing to do the right thing (omission).

Facilitator

In the patient safety context, facilitators refer to health care structures and approaches that may facilitate, e.g., safety practice implementation.

High-alert medication

High-alert medications are medicines with a heightened risk of causing significant patient harm when used in error (Institute for Safe Medication Practices 2018, World Health Organization 2019c, Institute for Safe Medication Practices 2021a, Institute for Safe Medication Practices 2021b). Although mistakes may or may not be more common with these medicines, the consequences of an error are clearly more devastating to patients. High-risk medication is sometimes used as a synonym.

Human factors

Study of the interrelationships between humans, the tools, equipment, and methods they use, and the environments in which they live and work (Reason 1990, World Health Organization 2009).

Incident

Any deviation from usual medical care that causes an injury to the patient or poses a risk of harm (World Health Organization 2009).

Medication error (ME)

A medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer (National Coordinating Council for Medication Error Reporting and Prevention 2023). Such events may be related to professional practice, health care products, procedures, and systems, including prescribing, order communication, product labelling, packaging, and nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use.

Medication safety

Freedom from accidental injury during medication use; activities to avoid, prevent, or correct adverse drug events that may result from the use of medications (Committee of Experts on Management on Safety and Quality in Health Care and Expert Group on Safe Medication Practices 2005, Council of Europe 2006, World Health Organization 2009).

Medication safety practice (MSP)

Applied to the definition of patient safety practices, medication safety practices refer to interventions, strategies, or approaches intended to prevent or mitigate unintended consequences of the delivery of medication use and to improve medication safety (Shekelle et al. 2010). Safe medication practices can be used as synonym (Committee of Experts on Management on Safety and Quality in Health Care and Expert Group on Safe Medication Practices 2005, Council of Europe 2006).

Medication use process

The multistep process in the use of medications by or for patients, including prescribing, ordering, storage, dispensing, preparation, administration and/or monitoring (Hepler and Strand 1990, World Health Organization 2019c).

Near miss

An incident that did not reach the patient (Reason 1990, World Health Organization 2009). Close call is sometimes used as synonym.

Patient Safety

A framework of organized activities that creates cultures, processes, procedures, behaviors, technologies, and environments in health care that consistently and sustainably lower risks, reduce the occurrence of avoidable harm, make the error less likely and reduce the impact of harm when it does occur (World Health Organization 2021).

Pharmacovigilance

Pharmacovigilance is the science and activities relating to detecting, assessing, understanding, and preventing adverse drug effects or any other medicine/vaccine-related problem (Directive 2010/84/EU, European Medicines Agency 2015, World Health Organization 2023).

Potential adverse drug event

Those adverse drug events that did not cause an injury to a patient, but which had the potential to harm (Otero and Schmitt 2005). A potential adverse drug event is a medication error with the potential to cause an injury, but which does not actually cause any injury, either because of specific circumstances, chance, or because the error is intercepted and corrected (Morimoto et al. 2004, Committee of Experts on Management on Safety and Quality in Health Care and Expert Group on Safe Medication Practices 2005, Council of Europe 2006).

Process

A series of related actions to achieve a defined outcome (World Health Organization 2009). A course of action, or sequence of steps, including what and how it is done.

Risk

The probability of danger, loss, or injury within the health care system (World Health Organization 2009).

Root cause

The most fundamental reason an event has occurred (World Health Organization 2009, VHA National Center for Patient Safety 2021).

Safety culture

The safety culture of an organization is the product of individual and group values, attitudes, perceptions, competencies, and patterns of behavior that determine the characteristics of the organization's health and safety management (American College of Healthcare Executives and Institute for Healthcare Improvement 2017). Organizations with a positive safety culture are characterized by communications based on mutual trust, shared perceptions of the importance of safety, and by confidence in the efficacy of preventive measures.

Safety of medicine use

The safety of medicine use consists of medication safety (the safety of process) and drug safety (the safety of product) (STAKES and Rohto 2006).

Severe medication error

The definitions of severe patient safety incidents vary greatly (Hegarty et al. 2021). In this study, severe medication errors refer to the errors that are causing severe harm or have the potential to cause severe harm. Harm for the patient is defined as severe when the error had been life-threatening, led to hospitalization or prolonged hospitalization, or caused permanent or significant injury with incapacity (Gates et al. 2019). Serious medication error is sometimes used as synonym.

Systemic defenses

Systemic defenses (or safety barriers) are functions in the process to protect patients from potential hazards and they can include engineered mechanisms (e.g., alarms, physical barriers), people (e.g., in-depth knowledge), procedural or administrative controls (e.g., patient identification verifications) (Reason 1990, Ternov 2011).

ABBREVIATIONS

AI	Artificial Intelligence
AVI	Regional State Administrative Agency (Finland)
CPOE	Computerized physician order entry
CoE	Council of Europe
DRP	Drug-related problem
EMA	European Medicines Agency
EU	European Union
Fimea	Finnish Medicines Agency
FMEA	Failure Mode and Effect Analysis
IOM	Institute of Medicine
ISMP	Institute for Safe Medication Practices
ME	Medication error
MERS	Medication error reporting system
MMU	Medication Use and Management
MSAH	Ministry of Social Affairs and Health (STM, Finland)
MSP	Medication Safety Practice
NCCMERP	National Coordinating Council for Medication Error Reporting and Prevention (USA)
OTKES	Safety Investigation Authority, Finland
PCNE	Pharmaceutical Care Network Europe
RCA	Root cause analysis
Rohto	National Pharmacotherapy Development Centre (Finland, 2002-2009)
THL	National Institute for Health and Welfare (Finland)
Valvira	National Supervisory Authority for Welfare and Health (Finland)
WHO	World Health Organization
e.g.,	exempli gratia

1 INTRODUCTION

It all started in 2000 when the Institute of Medicine (IOM) published its report on the state of patient safety in the United States (US) (Kohn et al. 2000). It alarmed health care systems globally to realize that they cause harm or even death for thousands of people every day; not because patients are not treated but because they are. Especially medication errors (MEs) were among the most jeopardizing risks to patient safety (Institute of Medicine 2001, Aspden et al. 2007). In addition to the harm that was caused to patients, the IOM report highlighted costs of poor patient safety that were found to be high and to form a remarkable financial burden (Aspden et al. 2007, Walsh et al. 2017, Elliot et al. 2021, World Health Organization 2021). The most recent estimate by the World Health Organization (WHO) is that globally the cost associated with MEs is USD 42 billion annually (World Health Organization 2017).

The above-mentioned reports by IOM (Kohn et al. 2000, Institute of Medicine 2001) started a global patient safety movement. The movement has been globally promoted and coordinated by WHO since 2004, when the Global Patient Safety Alliance was formed (World Health Organization 2021). In Europe, the Council of Europe was the first multinational organization to investigate the patient safety situation in Europe by establishing a ministerial-level expert group in 2003 and another expert group assisting the ministerial level work in medication safety issues. The Council of Europe published its first medication safety vision paper in 2003 (Council of Europe Committee of Experts on Pharmaceutical Questions 2003) and the ministerial level patient safety recommendations with special strategic emphasis on medication safety in 2006 (Council of Europe 2006, Expert Group on Safe Medication Practices 2007). As a Council of Europe member country, these recommendations laid the foundation for the systemic patient and medication safety work in Finland. They also laid the foundation for developing medication safety as an integral part of patient safety, not a separate entity.

In Finland, medication safety initiatives were among the first when the national systemic patient safety work started in the mid-2000s (Ministry of Social Affairs and Health 2006, Airaksinen et al. 2012, Holmström 2017, Schepel 2018). From the beginning, the strategic choice has been to encourage health care organizations to set up their own safe medication practices and to provide them with tools to identify high-risk practices and situations to make their processes and practices safer. Thus, the long-term goal has been prospective medication risk management.

This doctoral thesis has its origins in the early phase steps taken in Finland to start nationally organizing patient and medication safety work according to the recommendations by the Council of Europe and European Union, as well as international organizations (Kohn et al. 2000, Institute of Medicine 2001,

Council of Europe Committee of Experts on Pharmaceutical Questions 2003, European Commission DG Health and Consumer Protection 2005, Council of Europe 2006, Aspden et al. 2007, Council of the European Union 2009). As there was no national or otherwise widely used medical incident or medication error reporting systems implemented in Finland at that time, the first medication safety working group coordinated by the National Pharmacotherapy Development Centre (Rohto) started to identify potential sources of information on risk situations caused by medications. The Finnish National Supervisory Authority for Welfare and Health (Valvira) was identified among potential sources having information on severe MEs because of its function as the national authority investigating patient safety incidents that have led to severe harm or death of a patient because of inappropriate care (National Supervisory Authority for Welfare and Health 2023). Our early phase research based on the documentation on severe MEs by Valvira made us realize that we need to develop a methodology applicable to this kind of documentary data and ME classification suitable for severe MEs (Linden 2007, Linden-Lahti et al. 2009). These methodological development needs were confirmed with other studies focusing on medication-related patient injury claims reported to the Finnish Patient Insurance Centre that had caused harm to patients (Pitkä 2009, Eronen 2016).

As severe MEs are the most unwanted outcome in the medication use process, causing severe harm or even death to patients (World Health Organization 2017), it is important to have a more comprehensive understanding of why severe MEs happen and how they can be prevented. However, the research on severe MEs is still limited. Therefore, this doctoral thesis focused on severe MEs, seeking ways to learn from and prevent them, and successfully implement new medication safety practices to support prospective risk management.

2 REVIEW OF THE LITERATURE

2.1 KEY MEDICATION SAFETY CONCEPTS AND EVOLUTION OF THEIR DEFINITIONS

Globally, current patient and medication safety work is based on systems thinking introduced in the health systems context since the 1990s (Reason 1990, Hepler and Strand 1990, Leape 1994). This chapter will first introduce the concept of medication use process, which is fundamental for understanding the context in which MEs can happen. It provides a ground to explain the key concepts related to medication safety risks and their prevention from a systems approach.

2.1.1 MEDICATION USE PROCESS

The medication use process means a multistep process from prescribing to using medicines and monitoring their effects (Hepler and Strand 1990, World Health Organization 2019c). Even though the medication use process has the same steps regardless of the medication use setting in health care, it has nuances according to context, e.g., whether medicines are used in an inpatient or outpatient setting. Figure 1 illustrates typical steps in the medication use process in a hospital setting (inpatient care), including prescribing, ordering, storage, dispensing, preparation, administration, and monitoring (World Health Organization 2019c). Transitions of the patient (admission and transfer/discharge) are also typical for patient care in all settings (World Health Organization 2019b). The complexity of medication use process in outpatient care is formed of multiple interfaces of social and health care organizations and professionals, and the role of the patient as a care team member responsible for the medication self-management (Ministry of Social Affairs and Health 2018, Mononen et al. 2020, Finnish Medicines Agency 2021).

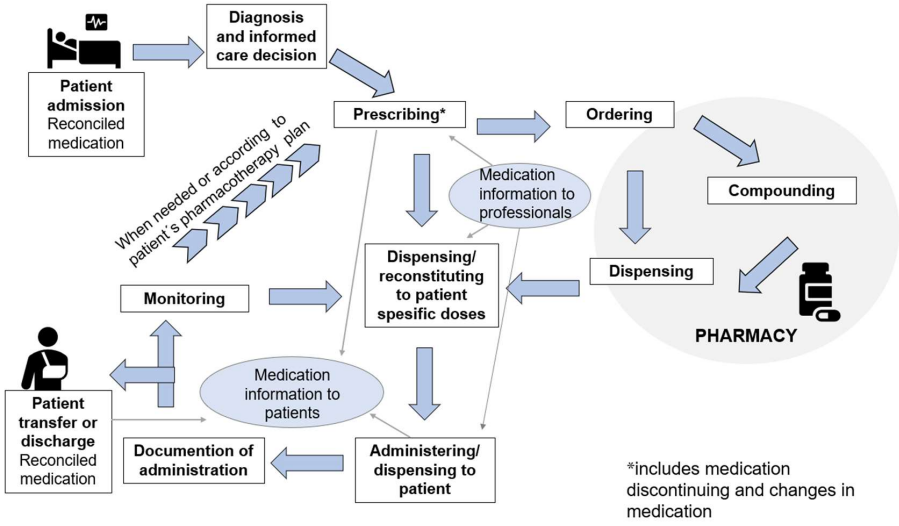

Figure 1 Medication use process with typical process steps in a hospital setting.

Regardless of the setting, the medication use process is one of the most complex processes in health care, and it has been estimated to include even 40 to 60 steps (Botwinick et al. 2006). Even though the medication use process presented in Figure 1 looks complicated, it is a simplified version of the real-life medication use process that includes, e.g., hospital formulary, distribution, stocking and dispensing systems, medicines information services, medication information systems, and other technical medication management systems. Therefore, medication management and use process (MMU) is a commonly used broad term for medication use process especially in hospital settings (Joint Commission International 2021).

2.1.2 SAFE USE OF MEDICINES AS A KEY DIMENSION OF PATIENT SAFETY

Patient safety aims to have organized activities that create cultures, processes, procedures, behaviors, technologies, and environments in health care that consistently and sustainably lower risks, reduce the occurrence of avoidable harm, make the error less likely and reduce the impact of harm when it does occur (World Health Organization 2021). This aim also includes preventing harm and errors in the medication use process. Thus, the safe use of medicines is one of the key dimensions and global objectives of patient safety in clinical processes and practices (Figure 2, World Health Organization 2021). Safe use of medicines is also closely related to other patient safety key dimensions, such as safety in transitions of care.

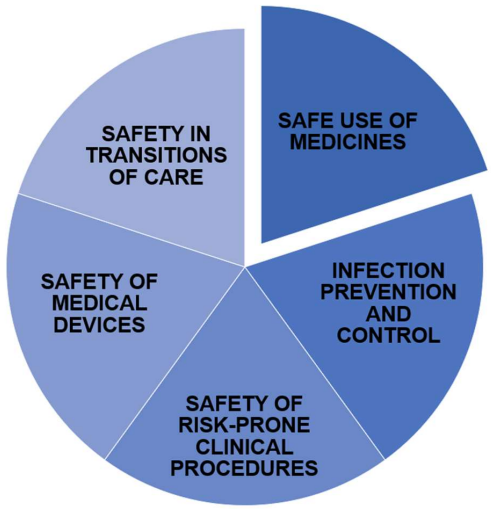

Figure 2 Key global patient safety dimensions and objectives of clinical processes and practices (World Health Organization 2021). Safe use of medicines is one of the key dimensions but is also closely related to the safety of other key dimensions.

Safe use of medicines consists of 1) drug safety referring to the safety of medicinal products, and 2) medication safety referring to the safety of the medication use process (Figure 3, STAKES and Rohto 2006). In practice, this division to drug and medication safety is sometimes explicit but merely overlapping, e.g., the medicinal product's properties can influence how safely it can be used and how complex medication use process is required for implementing the therapy safely in clinical practice. There still needs to be clarity between drug and medication safety definitions and how they possibly overlap (Falconer et al. 2019, Monni 2022). The limited understanding of this overlapping terminology is a challenge for research, practice, and policy development.

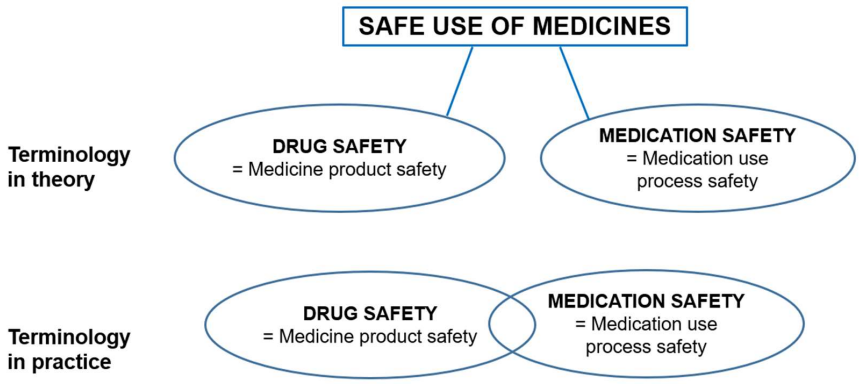

Figure 3 Safe use of medicines consists of the combination of drug safety and medication safety (STAKES and Rohto 2006). In theory, both concepts have distinct application areas, but in practice, they partially overlap.

2.1.3 RELATIONSHIP BETWEEN THE CONCEPTS OF ADVERSE DRUG EVENTS, MEDICATION ERRORS, AND DRUG-RELATED PROBLEMS

Any safety risks, problems, or deficiencies in medication use can cause harm or potential harm to the patient. An adverse drug event (ADE) is any injury for the patient due to medication (Figure 4, Bates et al. 1995, Morimoto et al. 2004, Committee of Experts on Management on Safety and Quality in Health Care and Expert Group on Safe Medication Practices 2005, Council of Europe 2006, World Health Organization 2009). This includes adverse drug reactions (ADRs) in which no error occurred and complications resulting from MEs (World Health Organization 2019). ME is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer (National Coordinating Council for Medication Error Reporting and Prevention 2023). Such events may be related in medication use process to professional practice, health care products, procedures, and systems, including prescribing, order communication, product labeling, packaging, and nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use.

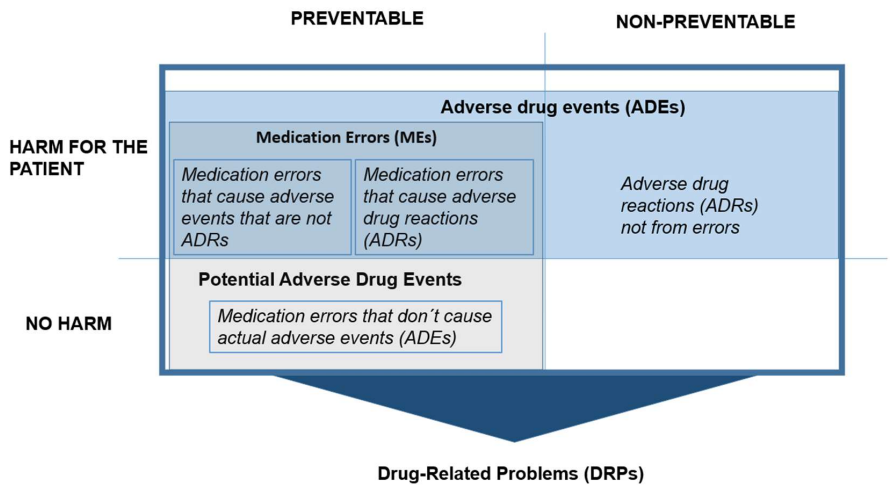

Figure 4 Relationship between the definitions of adverse drug events, medication errors and drug-related problems (summarized and modified from Bates et al. 1995, Morimoto et al. 2004, Otero and Schmitt 2005, Ferner and Aronson 2006, Directive 2010/84/EU, Pharmaceutical Care Network Europe 2020, National Coordinating Council for Medication Error Reporting and Prevention 2020, European Medicines Agency 2023).

MEs can cause ADRs (e.g., shortness of breath in accidental opioid overdose). Still, the harm can also be something other than ADR (e.g., embolism because of omission in antithrombotic medication) (Figure 4). In a potential ADE, there is no injury for the patient, but there was a potential to harm (Morimoto et al. 2005, Otero and Schmitt 2005). In a potential ADE, the harm was prevented because of specific circumstances, chance, or because the error was intercepted and corrected (Morimoto et al. 2004). Non-preventable ADRs and MEs can cause drug-related problems (DRPs), that are events or circumstances involving drug therapy that actually or potentially interferes with desired health outcomes (Pharmaceutical Care Network Europe 2020). DRPs occur or have the potential to occur because of a prior event or events that perform as a cause or causes of the DRP (e.g., failures associated with the medication use process).

MEs can be divided into the following three main categories based on whether they reach the patient and cause harm (World Health Organization 2009, World Health Organization 2020):

1) Near miss (ME did not reach the patient, and no harm resulted).
2) No harm ME (ME reached the patient, but no discernable harm resulted).
3) Harmful ME (ME that resulted in harm to the patient).

The harm or potential harm that ME causes to the patient (no harm, minor, moderate, serious, severe) can be assessed, e.g., according to The Harm Associated with Medication Errors Classification (HAMEC) (Gates et al. 2019).

2.1.4 THE EVOLUTION OF MEDICATION SAFETY TERMINOLOGY

Definitions related to medication safety have great variability (Aronson 2009, Lisby et al. 2010, Pintor-Marmol 2012, Hegarty et al. 2021, Biro et al. 2022). In particular, international consensus should be reached on the relationship of ADE, ADR and ME terminology and if omissions should be excluded from the definitions of ADE and ADR (Falconer et al. 2019). It is known that vague terminology can easily lead to methodological challenges. Thus, differences in definitions can partly explain why it is difficult to investigate and assess medication safety and MEs (Ferner 2009, Pintor-Mármol et al. 2012, Walsh et al. 2017).

The evolution of medication safety terminology started in 1994 when US researchers introduced MEs as a prevalent type of medical errors (Leape 1994). Internationally, the most widely used definition for ME is the definition by the US National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) (Lisby et al. 2010). Their definition was first launched in 1998, and it has been used e.g., in the patient safety glossaries of WHO and Council of Europe (Council of Europe 2006, World Health Organization 2009).

The most remarkable recent changes in medication safety definitions have occurred in Europe when European Union regulations started to regard MEs as a more integral part of pharmacovigilance work and one cause of adverse drug reactions (European Parliament and Council of Europe directive 2010/84/EU). According to the directive, the definition of the term adverse reaction should be amended to ensure that it covers noxious and unintended effects resulting not only from the authorized use of a medicinal product at normal doses but also from MEs and uses outside the terms of the marketing authorization, including the misuse and abuse of the medicinal product. This change in terminology was confusing regarding other international definitions in which ADRs are clearly separate from MEs (e.g., World Health Organization 2009, Falconer et al. 2019, World Health Organization 2020). Therefore, international standardization and terminology consensus are still urgently needed as the next step in evolving medication safety terminology (Falconer et al. 2019).

2.2 EVOLUTION OF SYSTEMS THINKING APPLIED TO PATIENT AND MEDICATION SAFETY

2.2.1 SYSTEM-BASED RISK MANAGEMENT OF HUMAN ERROR

The principles of accident system theory, called Human Error Theory, were first introduced by James Reason (1990). The theory states that errors in complex systems (such as health care) happen because active and latent failures are present in the process (Reason 1990, 2000). The errors are primarily failures of the system, not failures of an individual. Active failures are those that have a direct impact on patient safety (e.g., prescribing the wrong drug), and latent failures are usually invisible until they cause an error (e.g., the structure or process of the organization, training, and allocating resources) (World Health Organization 2009). This system-based theory can also be called human factors approach to safety, which focuses on human action in complex sociotechnical systems (Vincent et al. 1998).

The systems approach is closely related to the concept of high-reliability organizations (HROs), which operate under difficult conditions with potential for errors but experience fewer accidents than anticipated in high-risk work (Dlugacz and Spath 2011). HROs use systems approach to proactively evaluate and design safety (Patient Safety Network 2019). At the same time, HROs understand that safety is a dynamic feature of an organization requiring safety resilience. However, most health care organizations are not considered to be HROs, because they lack a systematic approach to safety.

2.2.1.1 Swiss Cheese Model (Reason)

Reason's theory has been visualized as the "Swiss Cheese Model" where the holes in cheese layers provide a dynamic window of opportunity for an accident or error to occur in the process (Reason 1990, Wiegmann et al. 2022, Figure 5). The model also gives a framework to understand that there may not be only one error, but a chain of errors before it reaches the patient (Reason 1990, Huckels-Baumgart and Manser 2014). If the error(s) are not recognized or prevented in any of the process steps (or cheese layers), the error will reach the patient. It has been estimated that approximately 80 percent of errors in patient care are system-derived (Leonard et al. 2004). The estimate is still relevant as the systems and processes in health care have become even more complex (World Health Organization 2013).

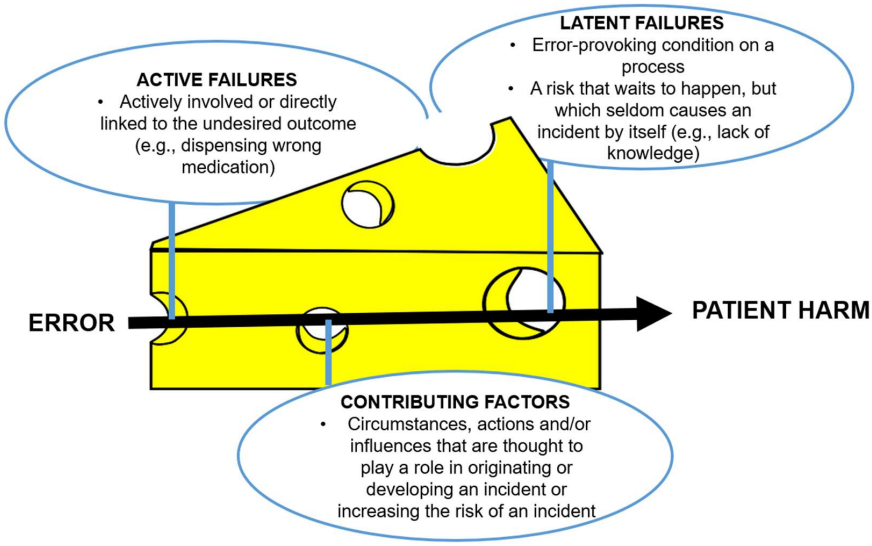

Figure 5 A modified illustration of the Swiss Cheese Model and factors that enable errors in a process (modified from Reason 1990, Reason 2000, Parker and Lawton 2006, World Health Organization 2009, Wiegmann et al. 2022).

According to Reason (1990, 2000), as humans, we are susceptible to different types of human errors, such as:

- Skill-based errors in routine work (slips and lapses).
- Rule-based errors when reading the situation or choosing the wrong procedure (mistakes).
- Knowledge-based errors when lacking the knowledge needed for the task or operation (mistakes).

With understanding these different types of errors in human performance, we can design the processes, implement defenses, and manage typical risks in our work environment (Reason 1990, Reason 2000, Phillips et al. 2001). Systemic defenses (or safety barriers) can be implemented as functions (e.g., alarms, verifications) in the process (Ternov 2011).

2.2.1.2 Recognizing latent failures (Vincent et al.)

In addition to Reason (1990), Vincent et al. (1998) have evolved systems thinking and identified factors influencing clinical practice that should be considered possible latent failures when analyzing why the error happened (Figure 6). Until the latent factors are recognized, they pose a risk for active failures. Situational factors (unlucky circumstances) and contributing factors activate several latent failures and cause an active failure (Reason 1990, Reason 2000, Ternov 2011).

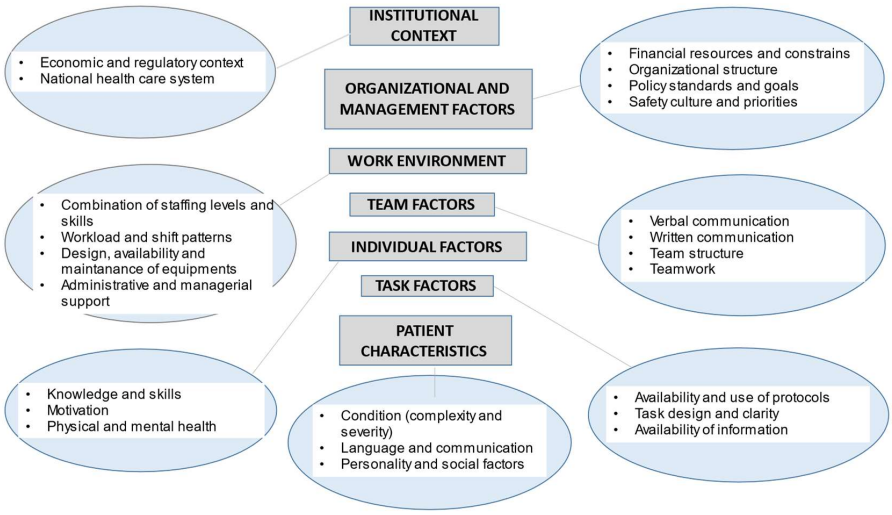

Figure 6 Illustration of factors influencing clinical practice that should be considered possible latent failures (modified from Vincent et al. 1998).

2.2.1.3 Errors in complex sociotechnical systems and patient journey: SEIPS Model (Carayon et al.)

In complex working environments, as in health care, it is not only about human performance. Instead, these environments comprise complex sociotechnical systems where human(s), tasks, tools and technologies, physical environment, and organizational conditions interact and influence each other (Carayon et al. 2006, Holden et al. 2013). This phenomenon can be described as human factors, which refer to interrelationships between humans, tools, equipments, and methods used, and the environments in which humans live and work (World Health Organization 2009). These relationships can be further described with the Systems Engineering Initiative for Patient Safety (SEIPS) model that has been developed based on recognized limitations in the Human Error Theory and the model of health care quality (Donabedian 1988, Carayon et al. 2006, Holden et al. 2013, Carayon et al. 2014).

The SEIPS model specifies the system components that can contribute to the causes and control of adverse events, showing the nature of the interactions between the components (Figure 7). It follows the Donabedian´s (1988) thinking of quality that has the same three components: structure, process, and outcomes. SEIPS explains how the design of the work system can impact not only the safety of patients but also employees and organizational outcomes. Consequently, the SEIPS model provides a framework for working

system's different aspects, interactions, and possible outcomes. The most recent development in this model has been the understanding that in health care, we usually need to develop single process and a multi-organizational patient journey (Carayon et al. 2020). This journey is characterized by the human-centered design of sociotechnical systems to improve patient safety.

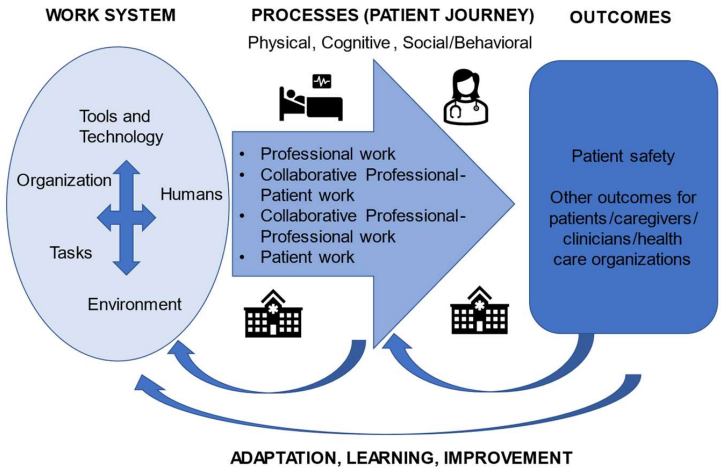

Figure 7 Systems Engineering Initiative for Patient Safety (SEIPS) model (modified from Holden et al. 2013, Carayon et al. 2020).

2.2.2 SAFETY CULTURE AS A BASIS FOR PATIENT AND MEDICATION SAFETY

Safety culture is the ability and willingness of the organization (and its members) to understand what safe performance means, what kind of risks are involved in actions and how the risks can be managed or even prevented (Reiman et al. 2008, Halligan and Zecevic 2011, Figure 8). Safety culture also involves the ability and willingness to act safely and promote safety in all safety culture dimensions. Hence, the safety culture is as much how we act as we think about safety. In a positive safety culture, professionals share perceptions of the importance of safety, communication is open, and information flows fluently. Moreover, errors and near misses are recognized and seen as an opportunity for organizational, non-blame learning and risks are identified proactively (Kirk et al. 2006, Halligan and Zecevic 2011). Patient safety culture is the extent to which an organization's safety culture supports and promotes patient safety (Agency for Healthcare Research and Quality 2022).

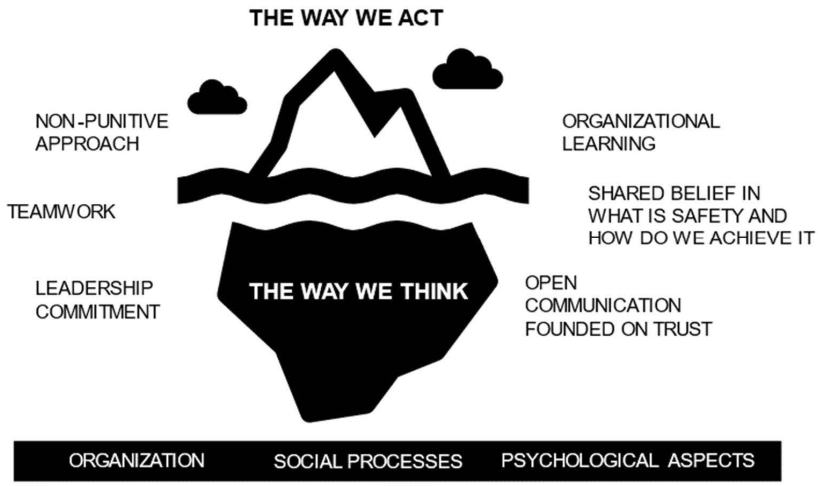

Figure 8 Dimensions of safety culture (modified from Reiman et al. 2008, Halligan and Zecevic 2011).

The basis for patient and medication safety in organizations is the existing safety culture where people understand the system-based approach to patient safety, e.g., systems thinking (Dean et al. 2002, Botwinick et al. 2006, World Health Organization 2011, Holmström et al. 2015, Ridelberg et al. 2020). In health care organizations, patient safety culture must be seen as multi-level safety culture (e.g., hospital, department, care unit) (Deilkås and Hofoss 2010, Agency for Healthcare Research and Quality 2022). Leadership support for safety, well-organized patient safety work, long-term commitment to patient safety, and organizational culture positive to patient safety seem to be the key elements for successful patient and medication safety work (Botwinick et al. 2006, Kirk et al. 2006, Holmström et al. 2015, Ridelberg et al. 2017). It has been found that positive safety culture in an organization is closely related to better patient outcomes and it can be improved with organizational and care unit level interventions (DiCuccio 2015, Weaver et al. 2013, Braithwaite et al. 2017).

Patient safety incident reporting systems, including medication error reporting systems (MERS), are tools to identify patient and medication safety risks and coordinate systematic, non-punitive investigations and development actions to manage observed risks (Holmström 2017, World Health Organization 2020). In an organization with a safety culture, reporting systems generate standardized settings to learn from errors and near misses in reducing future harm. In an advanced safety culture, the focus is on proactive and shared learning as a part of constant improvement (Parker et al. 2002). According to previous research, feedback mechanisms and communication of improvements are required to support a safety culture and make voluntary-based error reporting effective (Burlison et al. 2020).

2.2.3 EVOLUTION OF SAFETY CULTURE AND LEARNING FROM ERRORS

It has been argued that we should not talk about errors or failures but about deviation from an expected outcome, which helps us to understand the key cause of errors, human behavior (Conklin 2013). Additionally, it has been criticized that we describe and assess patient safety mainly according to the number of errors (Hollnagel 2014, Reason 2000). Paradoxically, low-level of reported adverse events do not mean the organization is safe (Reason 2000). Instead, it can be a sign of problems in safety culture, e.g., due to the staff experiencing fear of reporting.

Instead of focusing on errors and failures, we could focus on successes in care practices, which comprises most of the care. When improving patient safety according to systems thinking, we should also evaluate and learn from positive incidents and understand what keeps patients safe in the complex sociotechnical systems we work daily in health care (Hollnagel 2014, Braithwaite et al. 2015).

A theoretical framework that encourages seeing errors as unexpected variability of everyday performance is called Safety II (as a distinction of Human Error Theory, Safety I, Figure 9). Everyday work in practice (Work as Done) is often something else that we have presumed (Work as Imagined) and still the outcome succeeds more often than fails (Hollnagel 2014). Accordingly, we should facilitate the resilience in health care and support circumstances that enable things to go right (Braithwaite et al. 2015).

Figure 9 Key features and differences in Safety I and Safety II approaches in systems-based error management (Reason 1990, 2000, Hollnagel 2014).

With the contribution of Safety II, the recent focus in safety culture has been shifting towards "Just Culture" which is an atmosphere of trust in which people are encouraged to provide essential safety-related information but in which they are also aware of the line drawn between acceptable and unacceptable behavior (Hollnagel 2014, Rogers et al. 2017). Just Culture is defined as an environment that seeks to balance the need to learn from mistakes and the need to take disciplinary action when applicable (World Health Organization 2009).

In Just Culture, it is essential to understand that humans make different kinds of behavioral choices and human errors (Institute for Safe Medication Practices 2020). At-risk and reckless behavior should be managed from different perspectives. In at-risk behavior, individuals decide unsafe acts as they have lost the perception of risk associated with the choice or mistakenly believe the risk to be insignificant or justified. In reckless behavior, the decision of an unsafe act is conscious and unjustified. The individuals know the risk they are taking and understand that it is substantial. In a Just Culture, reckless behavior is seen as unacceptable behavior. Managing at-risk behaviors requires changes in safe choices, removing the rewards for at-risk behaviors, and coaching individuals to see the risk associated with their at-risk choices.

2.3 MEDICATION SAFETY AS A PART OF INTERNATIONAL, NATIONAL AND ORGANIZATIONAL PATIENT SAFETY STRATEGIES AND INITIATIVES

After the IOM report "To Err is Human" was published in the US, systems thinking in quality and patient safety became more notable in health care strategies (Zuckerman 2012). The general strategic goal in patient and medication safety is to make patient care safer and increase health care quality. The strategies to reach these goals have been developed at different levels:

1. Global strategies (e.g., International Medication Safety Network 2019, World Health Organization WHO 2021)
2. International strategies (e.g., Council of Europe 2006, European Commission 2014)
3. National strategies (e.g., Finnish Ministry of Social Affairs and Health 2022a, Institute for Safe Medication Practices 2022)
4. Organizational strategies (e.g., Helsinki University Hospital 2023)

In the strategy implementation, it is essential that the implementation responsibilities and tasks are assigned and mandated, there is enough information and communication between actors, implementation progress is monitored, and the strategy is updated regularly (American Hospital Association, Health Research and Educational Trust and Institute for Safe Medication Practices 2002, Zuckerman 2012). The prerequisite for the strategy to meet the operational level is that the implementation process is managed and coordinated. Similarly, the implementation is more likely to fail if resources are lacking. When patient and medication safety is seen as a strategic goal, there should be safety measures in structures, processes, and outcomes levels to indicate whether the goals are achieved (Nigam et al. 2008, Ferraco and Spath 2011, Smeulers et al. 2018).

Examples of different level patient and medication safety strategies are described later in this chapter. As the empirical part of this doctoral thesis concentrates on the settings in Europe and Finland, the focus is on their strategies.

2.3.1 GLOBAL MEDICATION SAFETY STRATEGIES – WHO

Since 2002, the World Health Organization (WHO) has been promoting the need for global patient safety improvement (World Health Organization 2021). In cooperation with other international patient safety networks and Member States, WHO works for patient safety improvements in general but also by focusing on some special high-risk patient safety areas (World Health Organization 2021). Figure 10 describes some major milestones in global

patient safety initiatives by the WHO after the launch of the IOM landmark report: "To Err is Human" (2000). Together these initiatives have contributed to the emergence of the global "patient safety wave."

Figure 10 The key patient safety programs and initiatives launched by WHO after global awareness was created by the Institute of Medicine "To Err is Human" report (Kohn et al. 2000). Together these initiatives have contributed to the emergence of the global "patient safety wave."

During the last few decades, WHO has launched three global patient safety challenges for the most urgent patient safety risks (Figure 10). The latest one, the third global patient safety challenge, focused on medication safety (World Health Organization 2017). The challenge called Medication Without Harm aimed to reduce the level of severe, avoidable medication-related harm globally by 50% over five years starting in 2017. The strategic framework for the medication safety challenge consisted of four domains: patients and the public; health care professionals; medicines; and systems and practices of medication (Figure 11). The key action areas were polypharmacy, high-risk situations, and transitions of care. WHO has also published the Patient Safety Curriculum Guide to promote incorporation of patient safety core contents in all health care professionals' education (World Health Organization 2011).

Figure 11 The Strategic Framework of the WHO Global Patient Safety Challenge "Medication Without Harm" (Source: World Health Organization 2018).

The current global action plan for patient safety by WHO is for the years 2021-2030. It includes specific strategic goals for medication safety (Figure 12, World Health Organization 2021). Although the timeline for the global challenge for Medication Without Harm has been closed, medication safety actions are still globally needed. Therefore, WHO's current strategic goal for medication safety is to implement a program to transform the safety of medication management and use based on the Medication Without Harm challenge. Other strategic goals in the WHO´s patient safety action plan closely relate to and support also the development of medication safety.

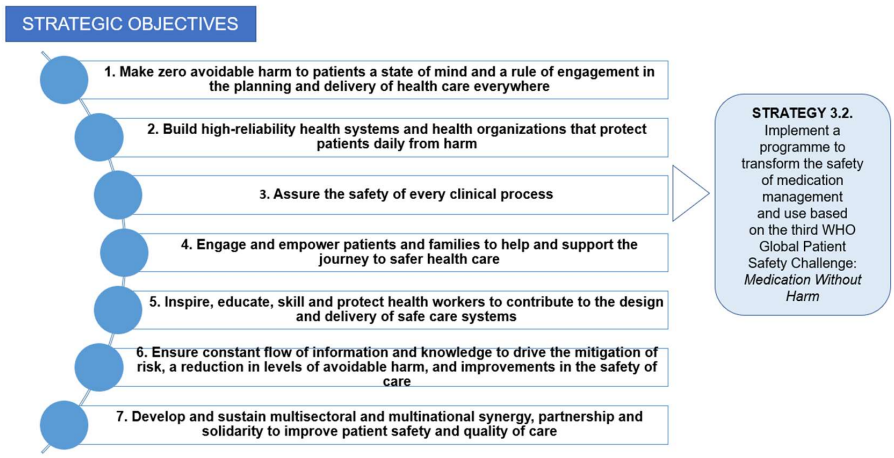

Figure 12 Strategic goals of the most current WHO Patient Safety Action Plan for 2021-2030 (World Health Organization 2021).

WHO has also a Regional Committee for Europe. As part of the European policy framework and strategy for 21st century, it has identified the need to commit more strongly to safety culture and improving the quality of public health and health care services, e.g., using medicines appropriately (World Health Organization 2013).

In addition to or in cooperation with WHO, some international medication safety, pharmacovigilance, and professional networks and organizations have introduced global medication safety targets and initiatives (International Medication Safety Network 2019, International Pharmaceutical Federation 2020, Council for International Organizations of Medical Sciences 2022, International Society of Pharmacovigilance 2023). These include, e.g., goals to reduce specific MEs in high-alert medicines or enhance patient involvement in ensuring medication safety.

2.3.2 INTERNATIONAL MEDICATION SAFETY STRATEGIES – EUROPE

The evolution of patient safety initiatives was also catalyzed in Europe by the US "To Err Is Human" report (Kohn et al. 2000). Shortly after that, a high political level commitment to patient and medication safety was achieved first in the Council of Europe and then in the European Union (McGill 2009). The key policy documents that defined and facilitated patient and medication safety work in Europe are summarized in Table 1. The policy documents were mainly published by the Council of Europe (46 Member States) and the European Union (27 Member States) during the years 2003-2014 (Table 1). Three policy documents concentrated solely on medication safety (Table 1, Council of Europe 2003, Council of Europe 2007, European Medicines Agency

2015). A comprehensive patient and medication safety glossary was launched as part of the Council of Europe's medication safety recommendations (Council of Europe 2006). The glossary had an essential role in implementing strategy work and recommendations for action by introducing common safety terminology. Implementing medication safety recommendations in Europe has been also supported by actors outside Europe, such as the International Network for Safe Medication Practice Centers (2008). From the perspective of medication safety, the emphasis in recommendations and statements has been on recognizing medication safety as a priority, creating a safety culture, assuring a national focal point, establishing MERS to learn from errors, and implementing medication safety practices.

Table 1 *Key policy documents and their objectives that have guided the evolution of European patient and medication safety initiatives since 2003.*

Policy document and year of publication	Objectives for patient and/or medication safety initiatives
2003 Council of Europe Committee of Experts on Pharmaceutical Questions - Vision statement	1. All European Health Authorities should recognize medication safety as a priority. 2. Medication safety comprises both adverse drug reactions and medication errors and that a clear distinction has to be made between them. 3. Medication errors, responsible of preventable events, be recognized as an important system-based public health issue. 4. The approach to safe medication practices should be multidisciplinary and should include patients, professionals and their organizations and all other stakeholders involved in the medication use system. 5. Medication safety should be considered as an essential element in the development and design of medicinal products, technology and medical devices including nomenclature, packaging and labelling. 6. Medication safety should proactively focus on prescribing, dispensing, administration, monitoring and information in outpatient and inpatient settings and their interfaces. 7. A recognized national focal point for safe medication practices be designated in each country in a collaborative and complementary way with pharmacovigilance systems based on a national system for reporting medication errors, analyzing causes and disseminating information on risk reduction and prevention. 8. An assessment at national level and funding of research of the frequency, nature and causes of medication errors and preventable adverse events is needed. 9. There should be Europe-wide standards for safe medication practices. 10. Local targets are valuable in implementing safe medication practices and sharing and disseminating of data and strategies for prevention and risk reduction between countries. 11.Medication safety culture should be a part of under and post graduate and continuous education of health professionals. 12.The public should be integrated in safe medication practice.
2005 European Commission DG Health and Consumer Protection: Luxembourg Declaration on Patient Safety	1. To establish an EU forum with participation by relevant stakeholders to discuss European and national activities regarding patient safety. 2. To work in alliance with WHO Alliance towards a common understanding on patient safety issues, and to establish an “EU solution bank” with “best practice” examples and standards. 3. To create the possibility of support mechanisms for national initiatives regarding patient safety projects, acknowledging that patient safety is in the program of DG Health and Consumer Protection. 4. To ensure that EU regulations with regard to medical goods and related services are designed with patient safety in mind. 5. To encourage the development of international standards for the safety and performance of medical technology. 6. To ensure that the European regulatory framework protects the privacy and confidentiality of patient records in the best interests of the patient, while at the same time ensuring that relevant patient information is readily available to health care professionals.

	7. To provide patients with full and free access to their personal health information whilst ensuring data accuracy and that patients fully understand their treatment. It is acknowledged that “informed patients” are well positioned to safeguard their own health. 8. To consider the benefits of a national voluntary confidential reporting systems of adverse events and near misses. 9. To work towards the introduction of risk management routines, for example, by developing guidelines and indicators as a part of a quality assessment system in the health care sector. 10. To optimize the use of new technologies, for example, by introducing electronic patient records. Such records would include the personal medical profile and decision-making support programs for health professionals with a view to reducing medication errors and increasing compliance rates. 11. To establish national fora, with participation by relevant stakeholders, to discuss patient safety and national activities. 12. To safeguard working conditions for all health care professions and to ensure that policies on recruitment and retention are linked to patient safety. 13. To recognize and support the user training provided by medical devices, tools and appliances manufacturers thereby ensuring the safe use of new medical technology and surgical techniques. 14. To include patient safety in the standard training of health professionals combined with integrated methods and procedures that are embedded in a culture of continuous learning and improvement. 15. To ensure that national regulatory framework protects the privacy and confidentiality of patient records in the best interests of the patient, while at the same time ensuring that relevant patient information is readily available to health care professionals. 16. To create a culture that focuses on learning from near misses and adverse events as opposed to concentrating on “blame and shame” and subsequent punishment. 17. To facilitate a collaborative care approach between health professionals and health care providers, aimed at enhancing patient safety. 18. To implement workplace projects focusing on patient safety and to establish an open culture to deal with errors and omissions more effectively. 19. To initiate a co-operation between patients/relatives and health care professionals in order that patients/relatives are aware of near misses and adverse events.

2006 Council of Europe Committee of Ministers: Recommendation Rec (2006)7 of the Committee of Ministers to member states on management of patient safety and prevention of adverse events in health care	1. Ensure patient safety is the cornerstone of relevant health policy. 2. Promote the development of a reporting systems for patient safety incidents in order to enhance patient safety by learning from such incidents. 3. Develop a coherent and comprehensive patient safety policy framework. 4. Review the role of other data sources such patient complaints and compensation systems, clinical databases and monitoring systems as a complementary data source of information on patient safety. 5.Promote the development of educational programs for all relevant healthcare personnel, including managers, to improve the understanding of clinical decision making, safety, risk management and appropriate approaches in the case of patient safety incidents. 6. Develop reliable and valid indicators of patient safety for various health care settings that can be used to identify safety problems, evaluate effective new interventions aimed at improving safety, and facilitate international comparisons. 7. Co-operate internationally to build a platform for the mutual exchange of experience and knowledge of all aspects of health-care safety. 8. Promote research on patient safety. 9. Produce regular reports on actions taken nationally to improve patient safety. ***Recommendation Appendix E: Medication safety - A specific strategy to promote patient safety*** 1. Medication errors are the most common single preventable cause of adverse events and European health authorities should consider them as an important public health issue. 2. Medication safety comprises both adverse drug reactions and medication errors. A clear distinction has to be made between them. 3. A medication error is defined as follows: “Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing; order communication; product labelling; packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.” 4. Key dimensions (organization and structures; patient-safety culture; indicators; ongoing observation) in the provision of care should be taken into account in order to prevent medication errors. 5. A recognized national focal point for safe medication practices should be designated in each country in a collaborative and complementary way with pharmacovigilance systems for reporting medication errors, analyzing caused and disseminating information on risk reduction and prevention. 6. European health authorities should recognize medication safety as a priority, promoting Europe-wide standards for safe medication practices and share and disseminate data and strategies for prevention and risk reduction between countries. 7. The nature, causes, frequency and clinical consequences of medication errors in hospitals and home-care settings in Europe should be assessed. 8. The improvement of the system of medication use requires the prevention of medication errors at every stage (including packaging and labelling; selection and procurement of medicines; storage in clinical areas; prescribing; medicine preparation; dispensing; administration; monitoring; information; patient education, and communication). 9. In this context, reference is made to an ongoing project of the Committee of experts on pharmaceutical questions (P-SP-PH) on safe medication practices.

2007 Council of Europe Expert Group on Safe Medication Practices: Creation of better medication safety culture in Europe: building up safe medication practices	1. Establish medication error reporting systems. 2. Establish and use common terminology concerning harm to patients caused by medication and promote a common taxonomy to facilitate the sharing of safety information in Europe. 3. Create culture of safety. 4. Set up a nationally recognized focal point for safe medication practices. 5. Update the European legislative framework applied by the European Medicines Agency and National Drug Regulatory Authorities to take into account the need for good design with a view to minimizing the risks of medication errors when using medicinal products in practice, as well as to include a requirement that packaging and labelling should be subject to specific human factor assessment and user testing including medicine information in the hospital/ ambulatory setting by the manufacturers prior to marketing authorization. 6. Update the national and European legislative framework to require pharmacies and other persons authorized for dispensing medicines to ambulatory patients to put a typewritten label on the container of the medicinal product at dispensation. 7. Update the national and European legislative framework to require complete and unambiguous labelling of every single unit of use of all licensed medicines products, including the international nonproprietary name (INN), trade name, strength, expiry date, batch number and a data matrix bar code. 8.Update the national and European legislative framework dealing with professional (datasheet, summary of product characteristics) and patient information. 9. Support national centers for safe medication practices which should be identified through post-marketing monitoring problems. 10. Include multidisciplinary medication practice procedures in undergraduate education, induction and refresher training for all health care staff responsible for using medicines. 11. Put into practice the concept of concordance wherever possible. 12. Delegate the responsibility for the management of local medication use systems in both primary and secondary care to multidisciplinary safe medication practices committees. 13. Use systematically appropriate methods to detect medication incidents and evaluate the effect of safe medication practices and initiatives intended to minimize risks. 14. Develop multidisciplinary teams to develop working procedures on safe medication practices. 15. Affect on safe prescribing. 16. Use electronic prescribing systems. 17. Enable pharmacists to review on a regular basis medication orders and the patient health record before medication is dispensed. 18. Provide essential and up-to-date medicine information and therapeutic guidelines. 19. Promote the key role of complete and appropriate interpersonal and interdisciplinary, oral and written communication between health professionals and patients.

2007 European Parliament and the Council of the European Union: Establishing a second programme of Community action in the field of health (2008 - 2013)	Improve citizens' safety by 1. Support and enhance scientific advice and risk assessment by promoting the early identification of risks; analyze their potential impact; exchange information on hazards and exposure; foster integrated and harmonized approaches. 2. Help to enhance the safety and quality of organs and substances of human origin, blood, and blood derivatives; promote their availability, traceability and accessibility for medical use. 3. Promote measures to improve patient safety through high-quality and safe healthcare, including in relation to antibiotic resistance and nosocomial infections.
2009 Council of the European Union: Council recommendation on patient safety, including the prevention and control of healthcare associated infections (2009/C 151/01)	1. Support the establishment and development of national policies and programmes on patient safety. 2. Empower and inform citizens and patients. 3. Support the establishment or strengthen blame-free reporting and learning systems on adverse events. 4. Promote education and training of healthcare workers on patient safety. 5. Classify and measure patient safety at community and Commission level. 6. Share knowledge, experience and best practices. 7. Develop and promote research on patient safety.
2010 European Parliament and the Council of the European Union directive 2010/84/EU	For the sake of clarity, the definition of the term 'adverse reaction' should be amended to ensure that it covers noxious and unintended effects resulting not only from the authorized use of a medicinal product at normal doses, but also from medication errors and uses outside the terms of the marketing authorization, including the misuse and abuse of the medicinal product. The suspicion of an adverse drug reaction, meaning that there is at least a reasonable possibility of there being a causal relationship between a medicinal product and an adverse event, should be sufficient reason for reporting. Therefore, the term 'suspected adverse reaction' should be used when referring to reporting obligations. Without prejudice to the existing Union and national provisions and practices on medical confidentiality, Member States should ensure that reporting and processing of personal data related to suspected adverse reactions, including those associated with medication errors is carried out on a confidential basis.

2014 European Parliament and the Council of European Union: Establishment of third Programme for the Union's action in the field of health (2014 - 2020)	Strengthen collaboration on patient safety and quality of healthcare, through, inter alia, implementing the Council Recommendation of 9 June 2009 on patient safety, including the prevention and control of healthcare-associated infections; exchange good practices on quality assurance systems; develop guidelines and tools to promote quality and patient safety; increase the availability of information to patients on safety and quality, improve feedback and interaction between health providers and patients
2014 Council of the European Union: Council conclusions on patient safety and quality of care, including the prevention and control of healthcare-associated infections and antimicrobial resistance (2014/C 438/05)	1. Intensify efforts in implementing Recommendation 2009/C 151/01. 2. Identify, if not already done, the authorities in charge. 3. Consider the implementation of guidelines, recommendations and good practices on patient safety, the prevention and control of healthcare-associated infections and antimicrobial resistance, and the use of the WHO patient safety taxonomy. 4. Promote the education and training of healthcare staff on patient safety and healthcare associated infections. 5. Promote the collection of information on adverse events. 6. Encourage health professional organizations to build an inter-professional patient safety culture that comprises also just and blame-free reporting on adverse events. 7. Develop measures that allow just and blame-free reporting by health professionals or patients and support handling of errors and adverse events as well as learning from them. 8. Encourage the participation and empowerment of patients, families and their informal caregivers, as well as patient organizations. Develop EU guidance for patient/citizens´ involvement in strategies on patient safety. 9. Consider the opportunity of developing cost-effective evaluation of patient safety programmes and policies. 10. Reinforce programmes and plans for infection prevention and control. 11. Step up the prevention, diagnosis, monitoring and control of healthcare-associated infections. 12. Share experience on strategies to ensure patient safety and quality of care between and across all settings of care. 13. Develop professional guidelines on the prudent use of antibiotics. 14. Continue to devote special attention to antimicrobial resistance and further research and the cooperation with human health and the veterinary sectors. 15. Develop voluntary guidelines on how to establish standards and guidelines on patient safety. 16. Take account research results while developing policies and programmes and promoting further research on patient safety and quality of care. 17. Finalize by December 2016 a framework for a sustainable EU collaboration on patient safety and quality of care. 18. Commission continues supporting Member States in improving strategies and programmes, ensuring coordination of EU activities and monitoring developments in patient safety and healthcare-associated infections.

2014 European Commission - Expert panel on effective ways of investing in health: Future EU Agenda on quality of health care with special emphasis on patient safety	1. The utilization of a comprehensive conceptual framework in relation to quality and safety. 2. Guideline development and the interprofessional sharing of good practices. 3. Funding research related to quality and safety. 4. Economic issues related to the defined quality dimensions. 5. Education and training in relation to the new roles of both patients and health professionals. 6. Information technology and information systems significant for health quality and safety. 7. Quality and safety aspects of the burden of chronic diseases and inequalities in health. 8. The HTA network and increasing attention on Health System Impact Assessment.
2015 European Medicine Agency: Good practice guide on risk minimization and prevention of medication errors	1. The potential for medication errors should be considered at all stages of the product life cycle but particularly during product development. 2. To minimize the risk of medication errors: a) Careful consideration should be given to the name and pharmaceutical design of a medicinal product (including its type of dosage form, appearance and other formulation characteristics, packaging and labelling) in order to minimize the risk of mix-ups between different products; b) The product information should inform HCPs, patients and caregivers of the most appropriate use of the product. 3. Where medication errors result in adverse outcomes, corrective actions should be taken.
2021 The European Parliament and the Council of European Union: Establishment of a Programme for the Union's action in the field of health ('EU4Health Programme') for the period 2021-2027	1. Improving and fostering health in the Union to reduce the burden of communicable and non-communicable diseases, by supporting health promotion and disease prevention, by reducing health inequalities, by fostering healthy lifestyles and by promoting access to healthcare. 2. Protecting people in the Union from serious cross-border threats to health and strengthening the responsiveness of health systems and coordination among the Member States in order to cope with serious cross-border threats to health. 3. Improving the availability, accessibility and affordability of medicinal products and medical devices, and crisis-relevant products in the Union, and supporting innovation regarding such products. 4. Strengthening health systems by improving their resilience and resource efficiency, in particular through: a) supporting integrated and coordinated work between Member States; b) promoting the implementation of best practices and promoting data sharing; c) reinforcing the healthcare workforce; d) tackling the implications of demographic challenges; and e) advancing digital transformation.

Table 2 summarizes the key objectives of the European level patient and medication safety policy documents included in Table 1. To describe the evolution of objectives, they are presented according to the year when they were first mentioned in the policy documents. According to the summary, the following key objectives have been introduced in very early stages of the European patient and medication safety work: the need for shared definitions and terminology; use of error reporting systems and other data sources for learning purposes; educating health professionals on principles of patient and medication safety from a systems approach; safety culture; proactive focus; and research to inform patient and medication safety work. These key objectives have remained quite the same over time. However, the latest patient and medication safety objectives include new aspects of measuring safety and quality, evaluating the effectiveness and cost-effectiveness of safety initiatives, pharmacovigilance, and overall availability of medicines and health care resources.

Table 2 *The summary of the objectives introduced in the European level patient and medication safety policy documents that are presented in Table 1. Objectives are presented according to the year they were first mentioned in the policy documents. ME=medication error.*

Year	Objective
2003	• Recognizing medication safety as a priority in health services systems • Need for developing shared definitions for European countries • Development of European-wide standards for medication safety • Establishment of a national focal point for medication safety • Utilization of national ME reporting systems • Promoting medication safety on a multidisciplinary basis • Implementing a proactive focus on risk management • Ensuring medication safety education for health care professionals • Facilitating patient involvement in ensuring safety • Commence national initiatives/projects for safety promotion • Initiating medication safety research
2005	• Establishment of a European-wide patient safety forum • Alliance with WHO • Need for electronic patient records and decision-making support • Assuring patient safety perspective in EU regulation • Patient data protection • Patient access to personal health information • Introduction of risk management • Establishment of national patient safety forums • Ensuring health professionals´ working conditions • Facilitating safe use of medical devices and medical technology • Assisting creation of a safety culture • Commence workplace initiatives/projects for safety promotion

2006	• Strengthen patient safety management and leadership • Recognizing the role of existing patient and medication safety data sources • Establishment of educational programs for health care professionals • Introducing safety indicators • Implementing regular patient safety reports • Need to have insight into medication errors in European hospitals and home-care settings
2007	• Established ME reporting systems • Need to update European legislative framework to minimize MEs (packaging and labeling, dispensation, information for professionals and patients) • Support national centers for safe medication practices • Understanding concordance role in patient safety • Establishment of local multidisciplinary safe medication practices committees • Implementing systematically appropriate methods to detect medication incidents and evaluate the effect of safe medication practices and initiatives • Implementing medication order reviews made by pharmacists • Assuring medicine information and therapeutic guidelines • Ensuring complete and appropriate interpersonal and interdisciplinary communication • Support and enhance scientific advice and risk assessment by promoting the early identification of risks • Promote measures to improve patient safety through high-quality and safe healthcare
2009	• Establishment of national policies and programs on patient safety • Ensuring blame-free reporting and learning systems • Finding ways to classify and measure patient safety at the community and Commission level
2014	• Defining guidelines and tools to promote quality and patient safety • Availability of information to patients on safety and quality • Identify patient safety authorities in charge • Implementing cost-effective evaluation of patient safety programs and policies • Develop voluntary guidelines on how to establish standards and guidelines for patient safety • Shared strategies to ensure patient safety and quality of care between and across all settings of care
2015	• MEs should be considered at all stages of the product life cycle
2021	• Improving the availability, accessibility and affordability of medicinal products and medical devices • Strengthen resilience and resource efficiency in health care

After the commencement of European patient safety work, the following three EU funded patient safety projects, closely related to the policy documents and their objectives, have been carried out to facilitate implementation (Figure 13): Safety Improvement for Patients in Europe (SIMPATIE 2005-2006), European Network for Patient Safety (EuNetPas 2007-2010) and European Union Network for Patient Safety and Quality (PasQ 2012-2016). Medication safety has been integrated to all those projects (Dutch Institute for Healthcare Improvement 2006, EuNetPas 2010, European Union Network for Patient Safety and Quality 2012, Garel 2014). In addition to patient safety projects, EU framework programs have supported patient safety research and innovations (European Commission 2017).

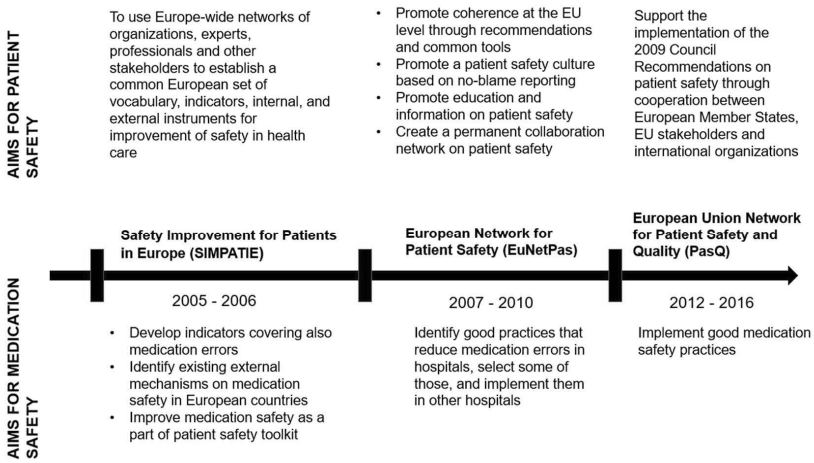

Figure 13 European patient safety programs (according to Dutch Institute for Healthcare Improvement 2006, European Network for Patient Safety 2010, European Union Network for Patient Safety and Quality 2012, Garel 2014).

The latest reports about the implementation state of Council of European Union Recommendation 2009/C 151/01 were released in 2012 and 2014 (European Commission 2012, European Commission Patient Safety and Quality of Care Working Group 2014 a and b). According to the reports, recommendations were implemented in most Member States´ policies and structures, but the level of implementation varied. According to the implementation report, further emphasis should be paid to strengthening patient safety culture, empowering patients, integrating patient safety into health professionals' education and training, and increasing close collaboration between Member States in patient safety. However, there has been no updated information since 2014 about the patient safety initiatives and their implementation in the European Union. As the latest publication on

patient safety, European Commission published a report in 2016 that stated, based on studies, that patient safety programs have the potential to save costs (European Commission 2016).

Overall, it has been noted that no new patient safety regulation has come into effect within the EU in several years (Pilarska et al. 2020). Priorities of the recently published EU Global Health Strategy (European Union 2022) and EU Health Programme 2021-2027 (European Parliament and the Council of Europe 2021, Table 1) relate only indirectly to patient safety. From the perspective of medicines, because of the COVID-19 pandemic and the unstable political situation in Europe, the focus is on access to safe, effective, high-quality, and affordable essential medicines and vaccines (European Parliament and the Council of Europe 2021, European Union 2022). These priorities are also presented in the Pharmaceutical Strategy for Europe (European Commission 2020). This recent development may indicate that patient and medication safety is no longer a specific priority in the European Union.

According to the EU directive 2010/84/EU that came into effect in July 2012, adverse drug reactions may also include medications errors, which should be reported to pharmacovigilance authorities. After the directive was enacted, EU level medication error prevention recommendations were published by European Medicines Agency EMA (2013). This may be one of the reasons why recent European Union level medication safety recommendations focus more on risk management of medication use (i.e., using the specific product) than on system-based medication safety work (European Medicines Agency 2015, European Medicines Agency 2023b). By the EU legislation, medication errors are increasingly reported to the EudraVigilance program and used for risk minimization measures produced by the pharmaceutical industry (Goedecke et al. 2016, Newbould et al. 2017, Hoeve et al. 2020). However, the utilization of this information for European-wide system-based and system-level medication safety development need to be clarified and published. Seeing medication safety more strongly from the pharmacovigilance perspective has also been an international trend outside the EU (International Medication Safety Network 2009, International Society of Pharmacovigilance 2023).

In addition to the work in EMA, the role of the European Directorate for the Quality of Medicines and Healthcare (EDQM) under the Council of Europe is to support the implementation of quality standards for safe medicines and their safe use (European Directorate for the Quality of Medicines and Healthcare 2023). Its recent focus has been on implementation of pharmaceutical care (Council of Europe Committee of Ministers 2020). At the same time, the focal point for European-wide patient safety coordination needs to be clarified as there is no clear leadership role in patient and medication safety work at the European level.

2.3.3 NATIONAL MEDICATION SAFETY STRATEGIES – FINLAND

While the role of WHO is to lead and facilitate patient and medication safety programs globally, the programs and actions must be implemented nationally in different countries to be effective. The systems-based patient and medication safety work was started quite early in Finland because of its active involvement in the preparatory work of the Council of Europe's patient and medication safety recommendations during 2003-2006 (Council of Europe 2006a and b, Airaksinen et al. 2012, Holmström 2017, Schepel 2018). Finland was also actively involved and participated in both EUNetPas and PasQ projects (Figure 13). National preparations for the systematic patient and medication safety work were started by the Ministry of Social Affairs and Health (MSAH) by establishing a patient safety steering group (2006-2009) and the national patient safety network in 2005 (Airaksinen et al. 2012, Holmström 2017, Schepel 2018). The steering group prepared the first national patient safety strategy 2009-2013 (Figure 14).

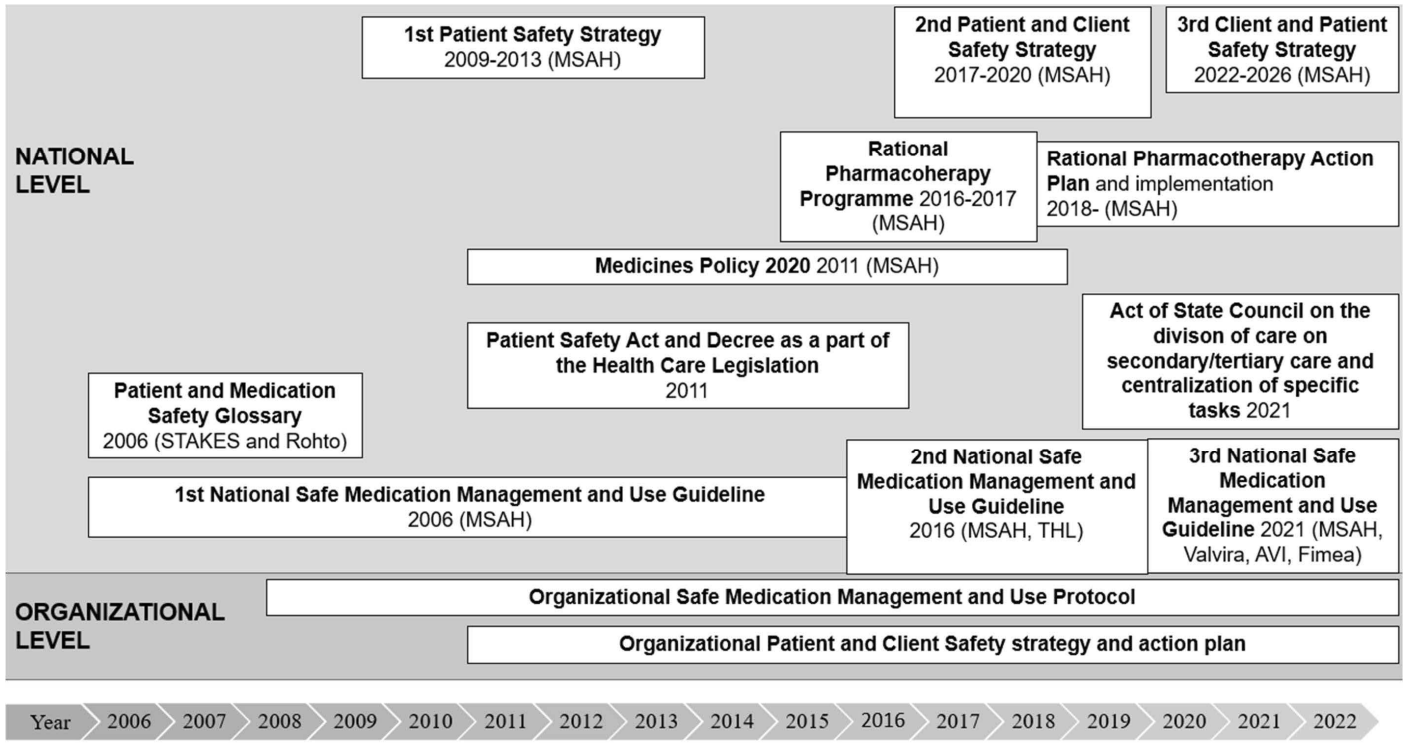

Figure 14 The key patient and medication safety policy documents, legislation, and guidelines requiring social and health care organizations to act in patient and medication safety in Finland.

The national vision of patient safety has progressed during 2009-2026 from anchored structures to the willingness to be a model country in patient safety (Figure 15). The latest Finnish patient and client safety strategy 2022-2026 benchmarks strongly WHO´s global patient safety action plan goals (World Health Organization 2021), as there have not been any recent strategic goals at the European level. The 2022-2026 national client and patient safety strategy is the first one in Finland that includes specific goals for medication safety (Finnish Ministry of Social Affairs and Health 2022a). However, the first initiatives for medication safety (e.g., National Safe Medication Management and Use Guideline 2006) were launched in Finland even before the first national patient safety strategy was published in 2009 (Figure 14). Early-phase attention was also paid to the quality and safety of geriatric care, with special emphasis on the safety of medication use in older adults that were recognized as high-risk patients (Kivelä 2006).

Figure 15 Finnish patient safety strategies and their key visions in 2009–2013, 2017–2021, and 2022-2026.

Concerning medication safety, the strategic choice in Finland from the beginning was to implement medication safety practices in organizations with the help of the National Safe Medication Management and Use (MMU) Guideline that was launched in 2006 and updated in 2016 and 2021 (Figure 14, Finnish Ministry of Social Affairs and Health 2006, Finnish Institute for Health and Welfare 2016, Finnish Ministry of Social Affairs and Health 2021). The Guideline provides instructions for establishing a protocol for safe MMU practices in Finnish social and health care organizations. Since 2011, the protocol for safe MMU practices has been required by law as part of the organizational patient and client safety strategy and action plan (Health Care

Legislation Act 30.12.2010/1326). The self-monitoring plan for ensuring the quality and safety of provided care will become mandatory for organizations providing social and health care services at the beginning of 2024 (Finnish Ministry of Social Affairs and Health 2022b).

Since 2021, national coordination of patient and medication safety work in Finland has been delegated to the Centre for Client and Patient Safety which operates under the Ministry of Social Affairs and Health (the Government Council Act on Division of Work in specialized health care and Centralization of specific tasks 24.8.2017/582, Finnish Centre for Client and Patient Safety 2022, Figure 14). Still, the clear mandate for giving recommendations in patient and medication safety is unclear and the supervision of the safety of health and social services in Finland is divided between multiple national authorities and social and health care organizations themselves (Hakoinen et al. 2017, National Supervisory Authority for Welfare and Health 2023, Figure 16). In addition to those, Safety Investigation Authority (OTKES) has made their own investigations since 2021 to improve the general safety of the health and social care system and services (Safety Investigation Authority 2021). These aspects of divided and unclear responsibilities and mandates should be solved and defined at the national level to provide a strong systems-based authoritative leadership for national patient and medication safety work.

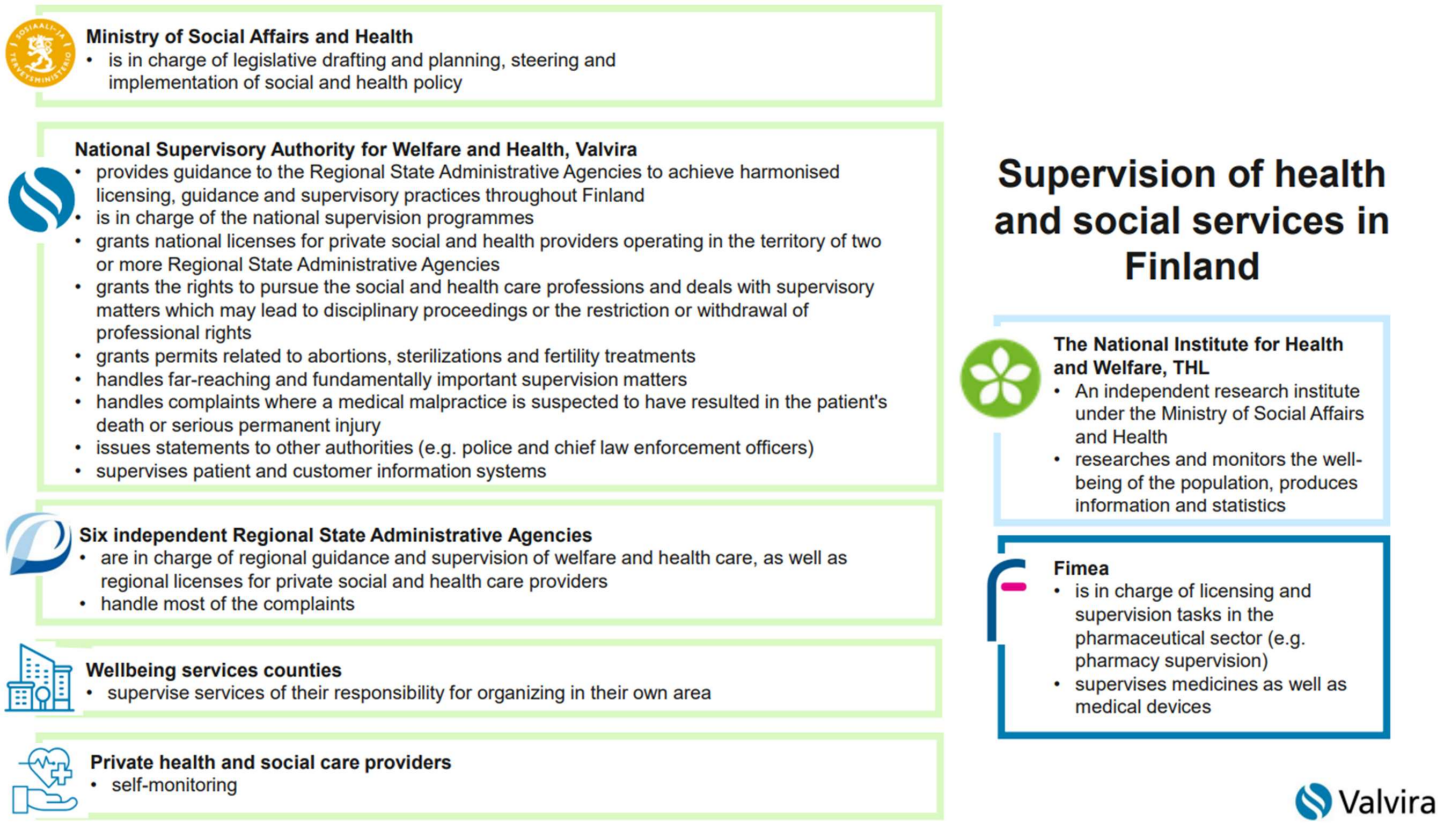

Figure 16 The supervisory role and mandate of social and health care authorities, organizers, and providers in Finland (Source: National Supervisory Authority for Welfare and Health Valvira 2023, published with the permission of Valvira).

2.3.4 ORGANIZATIONAL MEDICATION SAFETY STRATEGIES

A local patient safety strategy is essential for leadership at an organizational level (Botwinick et al. 2006). The steps which should be present in developing and implementing patient safety strategies are described in Figure 17. In an ideal situation, the medication safety strategy is a part of the patient safety strategy, as MEs represent a key risk for patient safety (World Health Organization 2017, Schepel 2018, Panagioti et al. 2019, World Health Organization 2021). The strategic goals related to medication safety should be based on the identified strengths, weaknesses, and opportunities in medication-use process in the organization (internal influence) and national or international goals, standards, and guidance (external influence, Botwinick et al. 2006, Schepel 2018). Managers and leaders are responsible for being committed to the strategy and ensuring that safety is a strategic priority in an organization. Patient and medication safety officers and organization leaders are in a key position to help promote patient and medication safety and achieve strategic goals (Botwinick et al. 2006, American Society of Health-System Pharmacists 2019, World Health Organization 2021). Also, patient involvement for patient and medication safety is essential (Trier et al. 2015, Council for International Organizations of Medical Sciences 2022). However, the strategy must still be effectively implemented in practice.

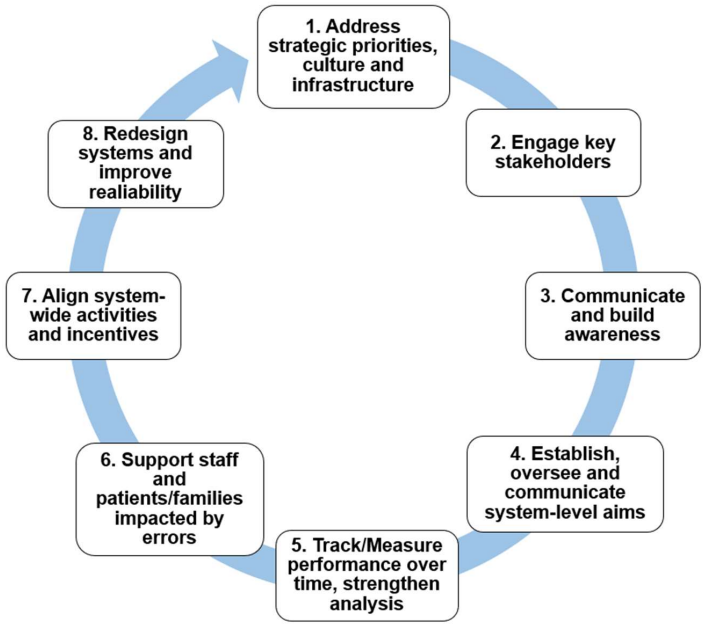

Figure 17 Steps in a patient safety strategy process for achieving patient safety goals (Botwinick et al. 2006).

In Finland, organizational level medication safety strategy usually refers to safe MMU protocol (Figure 14). The National Safe Medication Management and Use Guideline (Finnish Ministry of Social Affairs and Health 2021) is a recommendation that is required to be implemented in social and health care organizations as a minimum medication safety and risk management requirement in their safe MMU protocols. Some organizations have also their own additional medication safety goals as a part of their patient safety strategy (e.g., Helsinki University Hospital 2023).

2.4 MEDICATION ERRORS IN REPORTING SYSTEMS AND REGISTER-BASED DATA

2.4.1 MEDICATION ERROR REPORTING SYSTEMS (MERS)

Medication error reporting systems (MERS) are among the recommended actions to learn from errors and near misses in health care (Council of Europe 2006, Aspden et al. 2007, Council of Europe 2009, Holmström 2017, World Health Organization 2017, World Health Organization 2020). They can be national, local, health facility, or organizational level reporting systems (Holmström 2017, World Health Organization 2020). However, MERS typically produce limited information on MEs, especially if the error reports do not provide any narrative information about the safety incident (Holmström 2017).

It has been noted that the incident data that health care organizations generate in their reporting systems have significant limitations in reflecting the complexity, frequency, nature, and severity of errors occurring (World Health Organization 2020). This is mainly because of underreporting, challenges in reliable classification, quality of data and difficulties in interpreting the error rates; a high error rate could indicate actual problems or positive reporting culture (Crawford et al. 2003, Brady et al. 2009, World Health Organization 2014, Westbrook et al. 2015, Holmström et al. 2019, World Health Organization 2020). There are several studies recognizing multiple factors behind underreporting MEs, such as it is seen too time-consuming, there are fears of repercussions or lack of safety culture (Hartnell et al. 2012, Holmström et al. 2015, Rutledge et al. 2018). Furthermore, these error reporting systems may rarely capture severe, fatal errors (Cheung et al. 2011). Still, MERS are an essential and valuable component in the medication risk management of health care organizations, as they provide signals on unsafe processes that otherwise could go unnoticed (Holmström 2017, World Health Organization 2020). These signals should be used for learning and developing patient and medication safety (Council of Europe 2006, Holmström 2017, World Health Organization 2020 and 2021).

2.4.2 MEDICATION ERRORS IN REGISTER-BASED DATA

As described previously, MERS data has some limitations, especially when evaluating severe MEs. Therefore, MERSs should be complemented with other data sources and methods for medication risk management (Linden-Lahti et al. 2009, Kaboli et al. 2010, World Health Organization 2014, Härkänen et al. 2020). Other register-based medication error data, such as health care authority or patient insurance-based safety incident databases, can serve as valuable national level data sources in this respect, according to previous

studies (Vincet et al. 2006, Jonsson and Ovretveit 2008, Linden-Lahti et al. 2009, van Noord et al. 2010, Bismark et al. 2011, Björksten et al. 2016). Also, pharmacovigilance-based register data can be utilized in medication safety development (World Health Organization 2014, Schepel 2018, Schepel et al. 2021). However, these databases have been underused, despite evidence of their successful use in medication risk management research. At the organizational level, electronic patient record systems provide a register that has the potential for ME identification and screening, adding to error reporting systems (Kaboli et al. 2010, Schiff et al. 2017, Lambert et al. 2019), e.g., by using Global Trigger Tool in which records are reviewed retrospectively using triggers to identify possible errors (Hibbert et al. 2016, Härkänen et al. 2020, Tchijevitch et al. 2021, Institute for Healthcare Improvement 2023). Additionally, error reporting systems, especially at the national level, do not exist in every country (Holmström et al. 2012 and 2015, Holmström 2017, World Health Organization 2020). Instead, national ME data often consists of multiple data sources, e.g., in Finland (Figure 18).

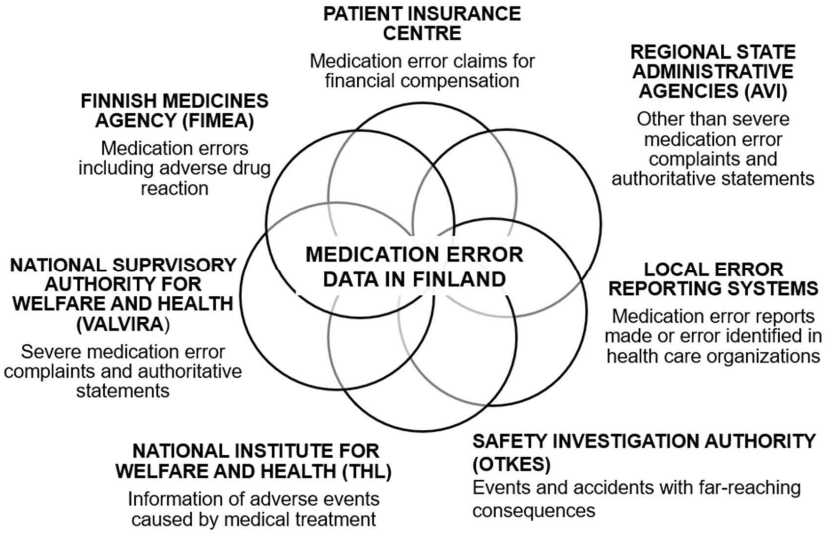

Figure 18 Illustration of various national and local registers maintained by authorities and health care organizations that contain retrospective documentation on adverse drug events and medication errors in Finland.

2.4.3 MEDICATION ERROR CLASSIFICATION SYSTEMS

MERS data has been typically described and analyzed using error classification systems and taxonomies. Theoretical or conceptual frameworks have usually guided the development of classification systems, or the process has been data driven (Dovey et al. 2006). Classification system can be contextual (e.g., the place or the medicine involved), modal (how the error happened, e.g., omission), or psychological (why the error occurred, e.g., skill-based error) (Aronson 2009). Classification systems and taxonomies need to relate to similar events, describe essential clinical and systemic factors, and support analysis purposes (Macrae 2016).

There are various classification systems and taxonomies for medication errors. Among the internationally most used are frameworks developed by WHO and NCCMERP in the United States (National Coordinating Council for Medication Error Reporting and Prevention 1998, World Health Organization 2009). Although there are multiple taxonomies for MEs, they often share the limitation of being in too general level and describing only outcomes, not the causes of the errors (Ferner and Aronson 2006). Taxonomies and classifications used in MERS do not enable optimal aggregation of reports into categories that reliably highlight system weaknesses (World Health Organization 2020).

The challenge in classifying and describing the prevalence of MEs relates closely to the variability of definitions. The studies are variable, especially considering relationship of MEs as a part of ADEs, and do not always differentiate if ADEs are preventable or non-preventable. According to studies, relative frequency of hospitalizations because of all ADEs ranges from 0.03% to 7.3%, and from 9.7 to 383.0/100,000 population, whereas the mortality rate ranges from 0.1 to 7.88/100,000 population (Silva et al. 2022). According to other studies, the pooled prevalence for preventable medication harm is 3% and for overall medication harm 9% (Hokinson et al. 2020), but the overall prevalence of MEs varies greatly according to the definition, context, and research method (Aspden et al. 2007, McLeod et al. 2013, Avery et al. 2018, Alqenae et al. 2020, Laatikainen et al. 2022). Further, it has been noted that most studies measure potential harm rather than actual harm (Young et al. 2022). As the data in medication safety studies are usually based on error reporting or observation in a hospital setting, it may cause bias that medication errors are specific problem only in hospitals. Nevertheless, studies conducted e.g., in care units of older adults have found a high prevalence rate of preventable medication harm (Hodkinson et al. 2020). Also, primary care is a prevalent setting for MEs (Panesar et al. 2015, Elliot et al. 2021, World Health Organization 2021).

By using modal classification system, wrong dose, wrong drug, wrong formulation, wrong patient, or omitted medication are typical medication errors (Pierson et al. 2007, Kunac and Tatley 2011, Huckels-Baumgart and Manser 2014, Ferrah et al. 2017, Alshehri et al. 2017, Alghamdi et al. 2019). In

addition, investigating MEs by the phase of the medication use process, errors in prescribing, administration and monitoring of medication treatment are most typical (Aspden et al. 2007, Pierson et al. 2007, Lewis et al. 2009, Schachter 2009, Kunac and Tatley 2011, Tanti et al. 2013, Huckels-Baumgart and Manser 2014, Panesar et al. 2016, Alshehri et al. 2017, Ferrah et al. 2017, Alghamdi et al. 2019, Hodkinson et al. 2020, Elliot et al. 2021). Additionally, transitions in the medication use process from one professional or unit to the next are special risks for MEs (Dlugacz 2011, Avery et al. 2018, Ferrah et al. 2017, World Health Organization 2019b). Errors in the medication use process can be errors of commission when the action is done incorrectly; or errors of omission when something that should have been done was not done (Reason 1990, Botwinick et al. 2006, World Health Organization 2009).

Most typical medicines included in MEs are anticoagulants, antidiabetics, drugs for the central nervous system, cardiovasculars, hypnotics and sedatives, anti-inflammatory and antirheumatic drugs, antibiotics, and antibacterial drugs (Tanti et al. 2013, Alshehri et al. 2017, Assiri et al. 2018, Alghamdi et al. 2019, Alqenae et al. 2020, Hodkinson et al. 2020, Tyynismaa et al. 2021). However, errors concerning these medicines vary, e.g., according to patient group or care setting. Look-alike and sound-alike (LASA) medicines are also specific risk factors recognized to increase the possibility of MEs (Institute for Safe Medication Practices 2019, Bryan et al. 2021).

2.4.4 SEVERE MEDICATION ERRORS

Harm for the patient is defined as severe when the error had been or had the potential of being life-threatening, required high-level hospitalized care or prolonged hospitalization, or caused major permanent or significant injury with incapacity (Gates et al. 2019). Still, the definitions of severe patient safety incidents vary greatly (Hegarty et al. 2020).

Considering how typical and common intervention medication treatment is in health care and how many patients use medicines daily, severe MEs are relatively rare (Pierson et al. 2007, Linden-Lahti et al. 2009, Kale et al. 2012, Avery et al. 2013, Tanti et al. 2013, Thomas and MacDonald 2016, Alshehri et al. 2017, Ferrah et al. 2017, Montané et al. 2018, Mulac et al. 2021, Elliot et al. 2021, Tchijevitch et al. 2021). However, a meta-analysis on preventable medication harm across health care settings found that of preventable harm, 26% can be considered clinically severe or life-threatening (Hodkinson et al. 2020). Some studies estimate that even 12% of preventable harm would cause permanent disability or patient death, and most of these incidents relate to medicines, therapeutic management, and invasive clinical procedures (Panagioti et al. 2019). In a Norwegian study, 5.2% of all MEs were associated with severe harm, and 0.8% were fatal (Mulac et al. 2021). The total numbers of severe MEs are still unknown, as serious events may not always be reported to error reporting systems (Cheung et al. 2011, Ferraco and Spath 2011,

Tchijevitch et al. 2021) and definitions of severe patient safety incidents vary greatly (Hegarty et al. 2021). However, the burden of MEs contributing to or causing deaths is considerable and justified as a global medication safety challenge (World Health Organization 2017, Montané et al. 2018, Hodkinson et al. 2020, Elliot et al. 2021, France et al. 2023).

According to previous studies and literature, high-risk patients for medication errors are:

- intensive and acute care patients (Hodkinson et al. 2020, Suclupe et al. 2020)
- children (Avery et al. 2013, Mulac et al. 2021, Kuitunen 2022)
- older patients (Phillips et al. 2001, Avery et al. 2013, Assiri et al. 2018, Montané et al. 2018, Mulac et al. 2021)
- polypharmacy patients (Avery et al. 2013, Assiri et al. 2018, Saedder et al. 2015, World Health Organization 2019)
- patients with co-morbidities (Assiri et al. 2018).

Considering severe MEs, especially pediatric patients, patients with comorbidities, polypharmacy, and high age are probably the most vulnerable ones to the severe harm caused by MEs (Buajordet et al. 2001, Phillips et al. 2001, Saedder et al. 2015, Mulac et al. 2021a). These patient groups are also prioritized in WHO global medication safety initiatives (World Health Organization 2019a, 2019c and 2021). Higher risk is connected to physiological and specific features in drug treatment that predispose to harm, but more research is needed to understand all contributing factors with these patients.

Some high-risk medicines have been recognized to be related to severe MEs, e.g., methotrexate, antithrombotics, insulins, and opioids (Cohen et al. 2009, Maaskant et al. 2013, Saedder et al. 2014, Thomas and MacDonald 2016, Institute for Safe Medication Practices 2018, Montané et al. 2018, Institute for Safe Medication Practices 2021a, Institute for Safe Medication Practices 2021b, Tyynismaa et al. 2021). However, a recent study argued that high-alert medication lists might also contain medicines that may not be independent predictors of patient harm (Alves et al. 2021). The medicines may also contribute to deaths (Montené et al. 2018), and the cause-and-effect relationship of MEs is not always easy to assess.

Many high-alert medicines are intravenously administered (Institute for Safe Medication Practices 2018, Schepel 2021, Tyynismaa 2021, Kuitunen 2022). While the intravenous administration route has specific medication safety challenges, such as fast therapeutic effect and difficulties in reversing effects due to erroneous doses (Kuitunen et al. 2021), severe risks are also associated with other administration routes (Tyynismaa et al. 2021). The wrong administration route may be prevalent especially for severe MEs (Phillips et al. 2001). It has been estimated that if we concentrate on developing medication safety especially with high-risk medicines, we could reduce hospitalizations, extended hospitalizations, disability, life-threatening

conditions, and death by almost 50% compared to current situation (Saedder et al. 2014).

The main characteristics of severe MEs, such as most prevalent error types, are similar to those of other MEs (Björksten et al. 2016, Mulac et al. 2021, Bosma et al. 2021). However, severe MEs may have more complex error processes comprising multiple errors and contributing factors (Reason 1990, Reason 2000, Linden-Lahti et al. 2009, Huckels-Baumgart and Manser 2014, Björksten et al. 2016, Thomas and MacDonald 2016). Typical contributing factors to severe MEs are inattention, work conditions, inadequate skills, and communication problems (Huckels-Baumgart and Manser 2014) which are quite general safety factors influencing clinical practice (Vincent et al. 1998). According to previous studies preventability of severe errors seems to be high, which indicates that resources addressed to this type of MEs can be effective (Kaboli et al. 2010, Thomas and MacDonald 2016).

According to care settings, severe MEs are a concern in both social and health care units (Linden-Lahti et al. 2009, Hodges et al. 2018). Hospitals can be seen as one key high-risk setting as they care for high-risk patient groups and use widely high-risk medicines and administration routes (Kuitunen 2022) although less in know about the incidents in outpatient and primary care settings (Panesar et al. 2016). Especially in severe errors, the harm caused to the patient is often devastating. It is also devastating to health care professionals involved in the incident; the error can have a long-lasting impact on them and their ability to work. This is widely called a second victim effect (Wu et al. 2000), although we still lack appropriate official terminology to describe this phenomenon (Tumelty 2021).

Factors that may prevent severe MEs do not differ from general medication safety strategies, although studies including interventions specified to severe MEs are limited. It has been found that nurses´ educational level may influence the occurrence of severe MEs (Chang and Mark 2009). There is also some evidence that temporary staff may be associated more often with harmful MEs than permanent staff (Pham et al. 2011). Moreover, research suggests that especially severe MEs could be reduced e.g., with clinical pharmacy interventions (Kaushal et al. 2008, Breuker et al. 2017). The preventive factors for severe MEs can also be technological solutions, such as computerized physician order entry (CPOE) or barcode systems (Walsh et al. 2008, Nucklos et al. 2014, Hodkinson et al. 2020, Linden-Lahti et al. 2022). Because of the complexity of especially severe MEs, multi-interventions for the medication use process are needed (Marufu et al. 2022).

2.5 LEARNING FROM SEVERE MEDICATION ERRORS – SUMMARY OF RISK ANALYSIS METHODS

2.5.1 RETROSPECTIVE LEARNING FROM SEVERE ERRORS: ROOT CAUSE ANALYSIS (RCA)

The processes in health care are complex; reaching zero errors is an unreachable and paradoxical aim (Reason 2000). Therefore, we should concentrate on reducing errors but also enhancing error detection, learning from errors, and improving error recovery (Patel et al. 2015).

In retrospective learning, we learn from the errors or near misses that already happened. MERSs are typical tool for that (Holmström 2017, World Health Organization 2020). In addition, we need in-depth analysis to comprehensively learn why and how errors happen, especially for complex and severe patient safety events (Parker and Lawton 2006, National Patient Safety Foundation 2015, VHA National Centre for Patient Safety 2021). Root cause analysis (RCA) is one of the most used analyses for severe health care errors and is based on Human Error Theory (Reason 1990, 2000, National Patient Safety Foundation 2015, Wiegmann et al. 2022). Retrospective analysis for severe patient or medication safety events is not mandatory in many countries (e.g., Finland). Still, some international health care accreditation programs require it (e.g., Joint Commission International 2021).

RCA is a retrospective, inter-disciplinary, systematic, iterative process whereby the factors that contribute to an incident are identified by reconstructing the sequence of events and repeatedly asking “why” until the underlying root causes (contributing factors or hazards) have been elucidated (World Health Organization 2009, National Patient Safety Foundation 2015, VHA National Centre for Patient Safety 2021). The RCA analysis aims to find actions that could prevent errors from happening again and how the overall risk associated with the process can be minimized. Because of limited resources, RCAs should be prioritized risk based on errors that produce the most value to prevent severe errors if contributing system factors are recognized and eliminated or controlled. The decision tree can help to evaluate if the event includes system failure and is suitable for RCA (Reason 2003, Meadows et al. 2005, Figure 19).

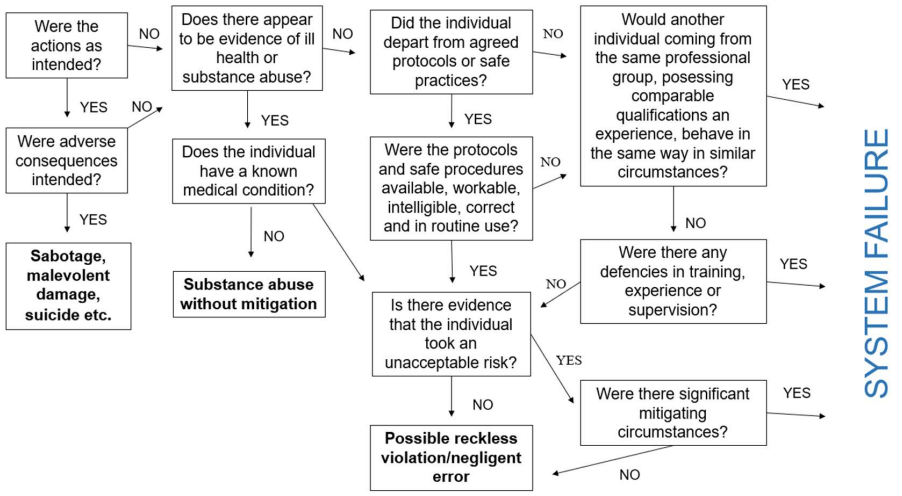

Figure 19 Incident decision tree to helps evaluate if the event includes system failure and is suitable for root cause analysis (RCA) (modified from Reason 2003, Meadows et al. 2005).

RCA is conducted according to a defined process (Croteau 2015, National Patient Safety Foundation 2015, VHA National Centre for Patient Safety 2021, Figure 20). Within the last ten years, there has also been some evolution of the RCA process and definition to emphasize that there typically is more than one root cause and analysis itself is not enough without the actions (Root Cause Analysis and Action, RCA²) (National Patient Safety Foundation 2015, Wiegmann et al. 2021). As the RCA aims to prevent severe errors and the evidence of already happened errors disappear quickly, RCA should be started as soon as possible (recommended within 72 hours of error recognition) and concluded within 45 days. Methodological expertise should be assured in the RCA team.

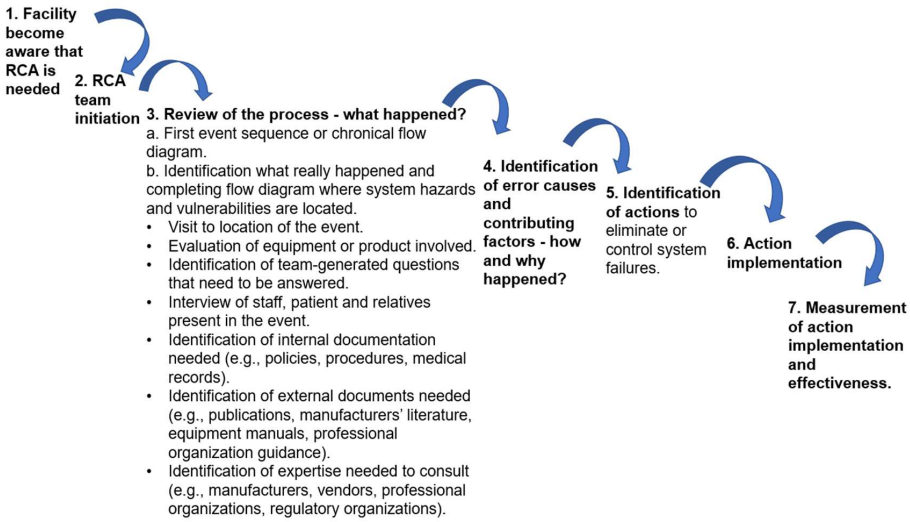

Figure 20 Root cause analysis (RCA) process steps (Croteau 2015, National Patient Safety Foundation 2015, VHA National Centre for Patient Safety 2021).

A non-punitive system approach is essential in the RCA analysis, and the RCA team should not assess individual performance (National Patient Safety Foundation 2015, VHA National Centre for Patient Safety 2021). To be objective and ensure that the analysis is focused on the system failure instead of the one specific patient case, the RCA team should preferably not involve professionals directly involved in the event. While it is easy to know afterwards what should have been done right, the RCA team should avoid this kind of thinking called hindsight bias (World Health Organization 2009). Things that did not happen are often equally important to the analysis (Latino 2011). The challenge of finding root causes is that problems always depend on relationships, causalities, or spaces around them (Conklin 2013). Effective RCA does not look only at specific events but also the entire process and its supporting systems which may be organizational or even institutional with a wide range of causes and contributing factors (Figure 21, Vincent et al. 1998, Croteau and Schyve 2011, Finnish Association of Patient and Client Safety 2013, National Patient Safety Foundation 2015, VHA National Centre for Patient Safety 2021). This is a critical step in RCA because if the team does not find latent root causes in the system, they will remain in the process and cause new errors.

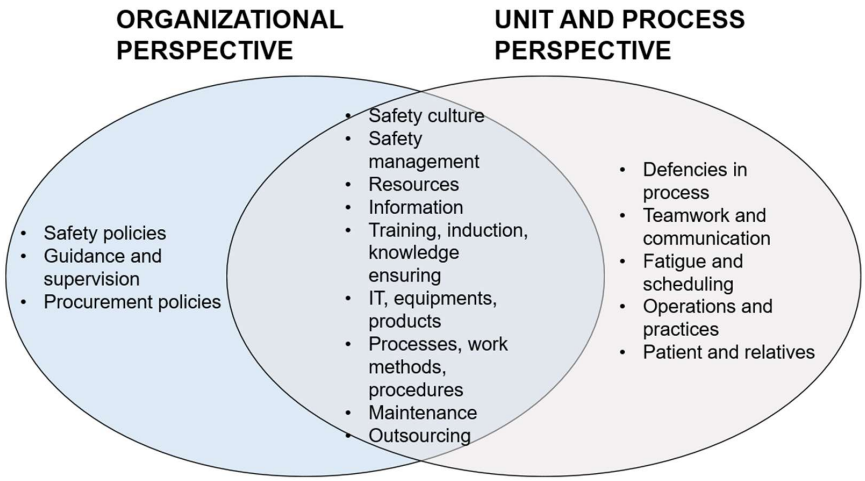

Figure 21 System levels, causes, and contributing factors that should be considered in a root cause analysis (RCA) process (Finnish Association of Patient and Client Safety 2013, National Patient Safety Foundation 2015).

In recent years, there have been arguments that RCA is not an effective analysis method for health care (Kellogg et al. 2017, Tobovich and Shojania 2017, Peerally et al. 2017, Kumar et al. 2020). However, alternative analysis methods are not widely used or validated in health care (Hagley et al. 2019). Studies have found variable results about the impact of RCA on patient safety (Martin-Delgado et al. 2020, Shah et al. 2022). If the organization fails to develop safety with RCA, the reason might be that the analysis or improvement actions were not conducted properly; not in the RCA method itself (Latino 2015, Tobovich and Shojania 2017, Kellogg et al. 2017, Peerally et al. 2017, Kumar et al. 2020, VHA National Centre for Patient Safety 2021). RCA gives a framework and process for analyzing events, but it depends on the analysis team, which causes and contributing factors they identify, and the organization how it takes actions to root causes found (Peerally 2017, Wiegmann et al. 2021).

The effectiveness of various kinds of safety development actions is described with the action hierarchy (Figure 22, Institute for Healthcare Improvement 2019, ISMP 2020, VHA National Center for Patient Safety 2021). In the action hierarchy, actions are seen stronger when they remove the dependence on human performance. Still, in practice the weaker and easier-to-implement actions seem to be the most proposed safety solutions (Card et al. 2012, Huckels-Baumgart and Manser 2014, Kellogg et al. 2017, Hibbert et al. 2018). Weaker actions are needed as they are often necessary to complement actions with higher strength, but as only safety intervention, they leave an opportunity for human errors in system. For safety culture and future error reporting activity, feedback from the RCA findings and actions is

essential for the staff, patients, and relatives (National Patient Safety Foundation 2015, Richter JP et al. 2015, VHA National Center for Patient Safety 2021). RCAs may provide useful data and information for the organization when developing their patient safety strategies (Hooker et al. 2019).

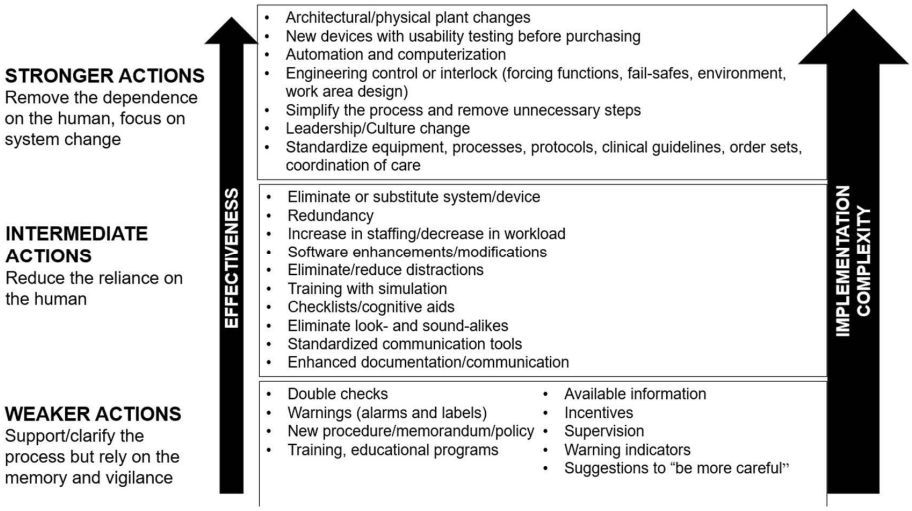

Figure 22 Patient safety hierarchy of improvement actions (modified from Institute for Healthcare Improvement 2019, Institute for Safe Medication Practices 2020, VHA National Center for Patient Safety 2021).

Considerable variation has been found in how RCA processes have been conducted in practice (Wu et al. 2008). Also, some modifications of RCA have been made for health care purposes (e.g., PRISMA-method, Driesen et al. 2022). Some health care organizations use Cause and Effect Diagram (Ishikawa diagram, Ishikawa 1982), which has the same idea as RCA. Still, it is simplified and more formulated to concentrate only on causes from people, materials, methods, environment, and equipment (Institute for Healthcare Improvement 2017). The weakness of diagrams and existing lists of cause and contributing factors is that the cause categories, which are not included in the diagram or the list, can be missed (Latino 2011). Challenges may also emerge if RCA is used as a deductive instead of an inductive analysis method. In the future, implementing machine-learning methods may also assist RCA teams in identifying better safety-related information from the narrative descriptions of patient safety events (Liang et al. 2020).

Another example of retrospective method for analyzing errors in health care has been MTO analysis (Man-Technique-Organization) (Ternov 2011b). It is also derived from systems theory and aims to identify underlying causes like RCA. The difference from RCA is that the error process is described with a map that assists in analyzing contributing factors, latent causes, safety

barriers, and situational factors in every event sequence. It also asks the team to consider what happened before actual error process.

2.5.2 LEARNING FROM SEVERE ERRORS PROSPECTIVELY

Ideally, errors should be prevented proactively before any harm happens to the patient. This is also a criterion for high-reliability organizations and requirement of some health care quality accreditations (Bilys 2016, Joint Commission International 2021). Proactive analysis should be carried out at least for high-risk activities, error-provoking systems, processes, and error-likely conditions (Feldman and Roblin 2011, Conklin 2013). Failure Mode and Effect Analysis (FMEA) and its applications are one of the most used prospective risk analysis methods in health care for patient and medication safety (Feldman and Roblin 2011, Hover et al. 2014, Shaqdan et al. 2014, Latino 2015, Rodriguez-Gonzalez et al. 2015, Liu et al. 2020, Sova et al. 2022). Still, the range of risk analysis methods is wide (Table 3). Also, RCA has be seen to have potential for prospective error analysis as the weaknesses in the process could be analyzed systemically before the error happens (Latino 2015). However, the evidence of this kind of implication of RCA still needs to be improved.

Table 3 *Proactive error analysis methods used in health care settings (DeRosier et al. 2002, Marx and Slonim 2003, Smith et al. 2010, Feldman and Roblin 2011, Ternov 2011b, Latino 2015, Bilys 2016, Institute for Healthcare Improvement 2017, Liu et al. 2020).*

Name of the method	Description of the method
Failure Mode and Effect Analysis (FMEA)	Components that could fail and their probable effect on safety are predicted using a process diagram. The method systematically identifies the parts of the process that most need change. The method finds questions to: • How is care expected to be delivered? • What could go wrong? • Why could failure happen? • What are the consequences? FMEA lists all possible failure modes of a specific product or system. After the FMEA team has recognized all potential failures and the consequences of the failures, critical analysis is performed by considering the risk factors of occurrence (O), severity (S), and detection (D) to prioritize the limited resources to the high-risk vulnerabilities (risk priority number RPN).
Hazard Analysis and Critical Control Point (HACCP)	All stages in the process are described and then every potential hazard is considered. Critical points in the process are identified and control or monitoring mechanisms are established.

Healthcare Failure Mode and Effect Analysis (HFMEA)	Combines methodology of FMEA, HACCP and root cause analysis. HFMEA analysis consists of the following: 1) Defining the topic of the analysis 2) Assembling the multidisciplinary team 3) Describing the process 4) Conducting the hazard analysis 5) Describing the actions and countermeasures
Fault Tree Analysis (FTA)	Anticipatory study of potential hazards. It starts by hypothesizing a specific undesired event. Potential precursors or causal events (that lead to the event) are recognized. The method is recommended especially for complex processes.
Sociotechnical Probabilistic Risk Assessment (ST-PRA)	Process for modeling the combinations of multiple failures leading to a specific undesirable outcome. When it includes the contributions of behaviors or human error as a cause of the adverse outcome, it becomes known as sociotechnical probabilistic risk assessment (ST-PRA). It follows the FTA procedure but also defines whether precursors or causal events must happen together before hazard becomes active. If it is identified that critical hazards can happen if only one precursor or causal event happens, defenses should be implemented in the process.
Hazard and Operability Study (HAZOP)	Processes are reviewed and potential hazards and problems are identified. The consequences of the potential hazards and problems are evaluated. Causes for hazards are identified and actions are proposed.
Deviation-Effect-Barrier (DEB)	Same principle as in retrospective MTO (Man-Technique-Organization) analysis but reversed. The process is mapped, and deviation is hypothesized. Observation, interviews, or incident reports validate hypotheses. The system effect of validated deviation is evaluated. Latent failures and safety barriers are identified, and action plans are made for those.
SWIFT	"What if" technique. A systematic team-oriented technique for hazard identification. Identification is supported by a checklist to help avoid overlooking the hazards.

In FMEA, a specific topic for the analysis is chosen, and a multidisciplinary team proactively anticipates what could go wrong and assess the priority for the development resources needed to manage the risks prospectively (Feldman and Roblin 2011, Institute for Healthcare Improvement 2017, Liu et al. 2020, Table 3). It has been used in health care as a part of implementation plans for devices, systems, and processes or evaluating existing ones (Bilys 2016). FMEA has been applied especially for health care purposes as Healthcare Failure Mode and Effect Analysis (HFMEA, Table 3) (DeRosier et al. 2002, Feldman and Roblin 2011, VHA National Center for Patient Safety 2023). It includes hazard analysis suitable for health care setting, as well as an action plan and countermeasures. As FMEA/HFMEA is resources consuming

method (Habraken et al. 2009, Bilys 2016), it is important to focus the analysis on especially high-risk processes where severe errors may happen. In Finland, the research literature is limited evaluating the stage in prospective patient and medication safety risk assessments and the first published application has been made by Sova et al. (2022).

2.6 SUMMARY OF KEY FINDINGS OF THE LITERATURE

- Variations in the medication safety terminology and medication error definitions have been recognized as key challenges for reliably estimating the overall prevalence rate of MEs and the burden they cause to patients, health care and society. This applies even to severe MEs harming patients. After 2010, when the definition of "adverse reaction" was changed in the European Union to include reactions caused by MEs, the coherent understanding about MEs became even more challenging. Despite the lack of a unified definition for MEs, there is a global understanding that MEs are one of the major challenges to patient safety. Especially MEs in prescribing and administration phase of the medication use process require specific safety interventions for prospective risk management.
- Although severe MEs are relatively rare compared to the prevalence of pharmacotherapy as a medical intervention, they may have great potential to be preventable. Also, the high-risk patient groups and medicines are quite well known. Severe MEs can be prevented with the same medication safety interventions as other MEs. However, in-depth error and risk analysis (retrospective and proactive) and multi-interventions are needed because they may be more complex error processes. As severe MEs are a global challenge in all patient care settings, the emphasis on preventing them should be a priority in medication safety strategy at all stages.
- The patient and medication safety work in Europe was initiated by the Council of Europe vision statements launched in 2003 and was active for over ten years after that. However, it seems that active patient and medication safety work has slowed down within the Europe after the last European Union patient safety project (PasQ 2012-2016), and there are no recent strategic goals considering system-based patient and medication safety. WHO and the European Directorate for the Quality of Medicines and HealthCare, which collaborates with the Council of Europe, seems to be the main organizations providing strategic goals and framework for European medication safety work. Focal point in patient and medication safety work at the European level should be clarified.
- According to the European Parliament and the Council of the European Union directive 2010/84/EU responsibility of EU level ME reporting was transferred to the EMA. However, this data has strengthened and benefitted mainly pharmacovigilance work. As all MEs do not include specific medicinal products (e.g., error in medication reconciliation) or adverse drug reaction, there is now a partly unrecognized medication safety field where EU-wide responsibilities must be defined.

3 AIMS OF THE STUDY

Medication safety is the third global patient safety challenge, which WHO is trying to tackle by coordinating global measures and actions (WHO 2017, WHO 2021). Severe medication errors (MEs) are not very common compared to other medication errors and near misses, but their occurrence can be severely harmful or even fatal. Therefore, we must more comprehensively understand and learn from them by using different kinds of ME data and analysis methods.

The present doctoral dissertation concentrated on investigating severe MEs as a threat to patient safety in the health services systems. The study aimed to facilitate learning from severe errors by analyzing errors in the National Supervisory Authority for Welfare and Health (Valvira, Finland) data and exploring the applicability of cause-based drug-related problem (DRP) classification system in classifying severe MEs. The study also aimed to contribute to preventing errors by evaluating the implementation and transferability of safe medication practices in European hospitals.

The study consists of three studies, two of them focusing on analyzing and developing methods to investigate severe ME data derived from a national authority register (Studies I, II). The third study evaluated the implementation process of selected safe medication practices in hospitals within 11 EU countries, focusing on facilitators and barriers to implementation (Study III). The specific objectives of the study are described in Figure 23.

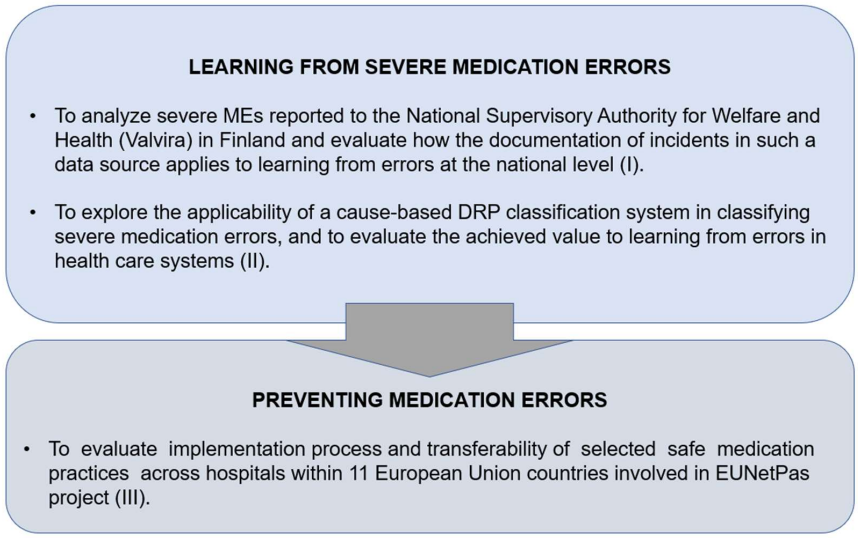

Figure 23 Outline and the objectives of the study.

4 MATERIALS AND METHODS

4.1 STUDY DESIGN

The empirical part of this academic dissertation consists of three original studies. All studies (I-III) were qualitative, and the main research method was retrospective document analysis (Table 4). Studies I and II employed the same data with different study aims and analysis methods. While studies I and II were conducted on authoritative national data to learn from severe MEs in Finland, study III was part of the EUNetPas project at the international level (European Network for Patient Safety 2010). System-based theory on human errors was used as a theoretical framework in all studies (Reason 1990, Reason 2000).

Table 4 *Materials and methods used in Studies I-III.*

STUDY	STUDY AIMS	METHODS	DATA SOURCE	ANALYSIS
I	To analyze severe MEs reported to the National Supervisory Authority for Welfare and Health (Valvira) in Finland and evaluate how the documentation of incidents in such a data source applies to learning from errors at the national level.	Retrospective document analysis	All medication-related 1) complaints that Valvira had investigated and closed, and 2) authoritative statements that Valvira had made for the Police of Finland during 2013-2017 (n=58).	Deductive, qualitative content analysis including patient characteristics, patient harm, care setting, professionals involved, medicines included, stage in the medication process, error preventability and corrective actions.
II	To explore the applicability of a cause-based drug-related problem (DRP) classification system in classifying severe medication errors and evaluate the value to learning from errors in health care systems.	Retrospective document analysis	The same data as in Study I.	Qualitative applicability analysis to pilot-test classifying MEs in Valvira's data using an aggregated DRP classification system developed by Basger et al. (2015).
III	To evaluate the implementation process and transferability of selected safe medication practices across hospitals within 11 European Union countries involved in the EUNetPas project.	Retrospective document analysis	The evaluation reports (n=75) from the hospitals that participated in the implementation (n=55) of the selected practices in the EUNetPas project.	Inductive, qualitative content analysis about the facilitators and barriers to implementing the practices.

4.2 WHAT SEVERE MEDICATION ERRORS REPORTED TO HEALTH CARE SUPERVISORY AUTHORITY TELL ABOUT MEDICATION SAFETY? (I)

4.2.1 STUDY SETTING, MATERIAL AND DATA COLLECTION

This study was a retrospective document analysis (Weinger et al. 2003). The material consisted of 1) medication-related complaints that Valvira had investigated and closed, and 2) medication-related authoritative statements that Valvira had made for the Police of Finland during 2013-2017. In the authoritative statements, Valvira assesses the appropriateness of the provided care in cases under inspection by the Police to assist in determining whether criminal proceedings should take place.

The medication-related complaints and statements fulfilling the following inclusion criteria were included in the study: the primary cause was classified as "pharmacotherapy" by Valvira; the case was closed; and Valvira assessed the case to include inappropriate patient care (Figure 24). The data search was done first in Valvira's electronic database using the automated search tool and then finalized manually. The cases were not included or excluded based on the severity of the outcome to the patient; instead, cases with actual harm or near miss (the error was noticed and corrected before it reached the patient) were included in the study material. The documentation of the complaints and statements included in most of the cases: 1) a copy of the patient records and other documents needed for incident evaluation; 2) responses from the professionals involved and/or managers of the health care organization; 3) an external expert (physicians or other specialists) opinion; and 4) the incident report written by the Valvira's Senior Medical or Legal Officer. This incident documentation was qualitative narrative data in nature, and it described the incident and its circumstances, as well as the conclusion of the case. The total material per case varied between 20-150 pages.

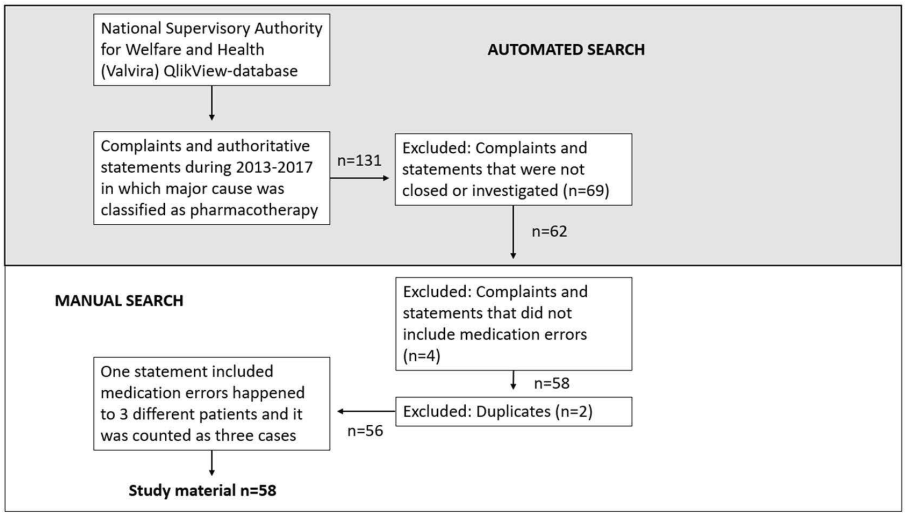

Figure 24 Data inclusion and collection protocol for medication errors investigated by the National Supervisory Authority for Welfare and Health (Valvira) in Finland in 2013-2017.

For collecting the data, a structured data collection form was developed by the research group based on previous study (Linden-Lahti et al. 2009). The data collection form was anonymous and included no information on the patients, professionals, or organizations involved in the error cases. The data collection form recorded the following information: 1) patient background information (age, gender); 2) medicines involved in the error; 3) step(s) of the medication process where the error happened; 4) setting (e.g., hospital) where the error happened; 5) professional group(s) involved; 6) harm to the patient; 7) researcher´s assessment of preventability of the error. Data from the complaints and statements were collected by one researcher using the data collection form.

4.2.2 DATA ANALYSIS

Harm for the patient in the cases was assessed with four categories: death, severe harm, non-severe harm, and no harm. Harm for the patient was defined as severe when the error had been life-threatening, led to hospitalization or prolonged hospitalization, or caused permanent or significant injury with incapacity (Gates et al. 2019). Medicines were regarded as high-alert medicines if they were present in the lists of the Institute for Safe Medication Practices (ISMP 2018, 2021a, and 2021b). The preventability of the errors in this study was defined according to the systems approach to human error (Reason 1990) and by modifying the definitions used in previous studies (Hallas et al. 1990, Linden-Lahti et al. 2009, Table 5). Those MEs that could

potentially cause harm to the patients, but were noticed before reaching the patient, were categorized as prevented.

Table 5 *Definition of the medication error preventability used in the study (modified according to Hallas et al. 1990 and Linden-Lahti et al. 2007).*

Medication error preventability	Description
Prevented	The error was prevented before it reached the patient.
Likely preventable	There was an existing procedure, operating model, or a guideline, and the error would have been prevented when acting according to it; but it was not followed.
Potentially preventable	There was no existing procedure, operating model, or guideline, but the error could have potentially been prevented from re-occurring with some medication safety development actions.
Unlikely preventable	Error or adverse drug event that was unlikely to be anticipated and would be difficult to prevent to re-occur even with new systemic defenses or other prospective medication risk management actions.

While the qualitative data documented in the incident reports were carefully read case by case, the information of interest was recorded in structured data collection form. In cases with difficulties categorizing the data, discrepancies were solved as the consensus of two researchers. The quantified, structured, and categorized data were analyzed using descriptive statistics (frequencies and percentages, Microsoft Excel).

Cases that included information on the organizations' actions to prevent the re-occurrence of such MEs and improve medication safety were further analyzed. Those medication safety actions were identified, analyzed, and categorized using the Institute for Healthcare Improvement (IHI) Action Hierarchy Template (IHI 2019). According to the action hierarchy, the stronger the preventive action is, the less it is based on human performance (Institute for Healthcare Improvement 2019, VHA National Center for Patient Safety 2021).

4.3 APPLICABILITY OF DRUG-RELATED PROBLEM (DRP) CLASSIFICATION SYSTEM FOR CLASSIFYING SEVERE MEDICATION ERRORS (II)

4.3.1 SELECTION OF DRP CLASSIFICATION SYSTEM

A drug-related problem (DRP) is an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes (Pharmaceutical Care Network Europe 2020). One major cause for DRPs are MEs (e.g., failures associated with the medication use process) (Pharmaceutical Care Network Europe 2020). As MEs can cause DRPs (e.g., error in prescribing, Figure 4), this connection supports piloting existing DRP classification systems for classifying MEs.

Several DRP classification systems have been established over time (Basger et al. 2014). One important feature of the DRP classification systems is that they should be able to differentiate DRPs and their causes (Basger et al. 2015). The present study applied the newest comprehensive DRP classification system, which was aggregated by Basger et al. based on a systematic inventory of existing DRP classification systems (Basger et al. 2014 and 2015). Their classification system is comprehensive, easy to use, and separates DRPs and their causes. It forms a hierarchical classification system consisting of nine cause-of-DRP categories, including 33 subcategories and 58 sub-subcategories (Table 10). Basger et al.'s (2015) aggregated classification system was adopted as such for the present study.

4.3.2 STUDY SETTING, MATERIAL AND DATA COLLECTION

The study setting, material and data collection were the same as in Study I and are described in the previous section of this dissertation (4.2.1.). Data inclusion and collection protocol are described in Figure 24.

4.3.3 DATA ANALYSIS

MEs were identified and classified from Valvira's data by one of the researchers. First, the qualitative and partly narrative data in Valvira's documentation was carefully read case by case. Identified ME process and contributing factors were summarized as a brief anonymized case description for each case. MEs were categorized from these brief case descriptions using Basger et al.'s. aggregated DRP classification system (Basger et al. 2015). Where difficulties were encountered in the categorization, another researcher was consulted, and the consensus of the two researchers decided the final

classification. In cases where no suitable category was found for the ME, the error was classified to the "Other" category (a cause that cannot be classified into any other categories, Category 9 in Table 10). One of the researchers made notes of those MEs for detecting possible missing categories in the aggregated DRP classification system. Because severe MEs are often complex processes, including several errors (Reason 1990 and 2000, Huckels-Baumgart an Manser 2014, Linden-Lahti et al. 2021), all identified MEs were categorized from the description of each case.

Error setting and harm to the patient were identified and documented for the data analysis similarly with Study I to explain the essential characteristics of the MEs in the data. The data categorized in this study were quantitatively analyzed in Microsoft Excel for descriptive statistics (frequencies and percentages).

4.4 FACILITATORS AND BARRIERS IN IMPLEMENTING MEDICATION SAFETY PRACTICES ACROSS HOSPITALS WITHIN 11 EUROPEAN UNION COUNTRIES (III)

4.4.1 SELECTION OF MEDICATION SAFETY PRACTICES (MSP) FOR THE IMPLEMENTATION IN THE EUNETPAS PROJECT

The expert group responsible for the medication safety project (WP4) within EUNetPas project conducted in 2007-2010 (European Network for Patient Safety 2010) made the selection process of MSPs. The expert group invited Member States and European stakeholders to participate in collecting MSPs applied in their hospitals. The expert group disseminated a call for proposals through national contact persons. These contact persons used their national networks to collect the proposals and sent them to WP4 expert group that made the selection. The selection criteria were that the practices must 1) consider the systems approach in the medication management process in the hospital (including prescribing, communication, and medicine administration), 2) include actors' (e.g., physicians, nurses, pharmacists, and patients) involvement, and 3) be transferable to other hospitals. The selected practices were expected to be implemented in the given time frame (9 months) and to be easy and inexpensive to implement.

The expert group received 63 MSPs from 16 Member States via national contact persons and their networks during 2008. Of these practices, the expert group selected the following seven for the implementation exercise: medicine bed dispensation (two versions); safety vest; discharge medication list for patients; medication reconciliation at discharge; medication reconciliation at admission and discharge; and sleep card. The selected practices are described in Appendix 1. as presented to the participating organizations in the EUNetPas project.

4.4.2 STUDY SETTING, MATERIAL AND DATA COLLECTION

Hospitals for implementing one or more of the seven practices were recruited with the help of the expert group (WP4) members and partners in 11 EU Member States that volunteered to participate (Austria, Belgium, Denmark, Finland, France, Greece, Ireland, Italy, Lithuania, the Netherlands, and Portugal). The hospitals were able to choose the practice(s) for implementation independently. Starting from April 2009, a nine-month time frame was given for the practice implementation and submission of the evaluation report. The hospitals were provided with a description of the selected practices (Appendix 1) and a standard evaluation form. However, they could independently plan the way and scope of implementation to adopt the

practice into their medication management processes. There was no standardized implementation process introduced for the hospitals.

The material for this study was based on the written evaluation reports from the hospitals that participated in implementing the selected practices. The reports were requested to be written in English. The reports were collected by EUNetPas expert group and delivered to the researcher for data analysis. The evaluation form (Appendix 2) consisted of 19 open-ended questions. The core topics covered in the evaluation form were the hospital's baseline situation in medication safety before the implementation of the practice; a description of the implementation process; an assessment of the implementation experience, and outcomes of implementation on medication safety. If the hospital implemented more than one practice, they reported their implementation process separately.

4.4.3 DATA ANALYSIS

All evaluation reports were analyzed using inductive content analysis (Hsieh and Shannon 2005). Inductive content analysis was chosen as analysis method because it enabled recognizing all the factors that were mentioned to effect on implementation. One researcher conducted the analysis, and the analysis strategy was decided with other researchers before starting the analysis and regularly discussed during the analysis process. MS Word software was applied to the analysis.

The main researcher rated the success of the implementation process at nine months based on the narrative description in each report and estimate of the success by the reporter on the evaluation report (rating: failed, ongoing or succeeded).

The facilitators and barriers for implementation of the practices were identified by categorizing themes arising from the data. The facilitators and barriers identified from narratives open questions in evaluation reports were compiled into three separate analyses: 1) identifying all facilitators (i.e., general facilitators, not depending on the practice), 2) identifying all barriers (i.e., general barriers, not depending on the practice) and 3) identifying facilitators and barriers that were practice specific. As all facilitators and barriers were identified and listed, they were clustered into themes. Practice-specific facilitators and barriers were collected under each practice but were not clustered. Also, actors (i.e., health care providers) involved in the implementation process were identified as part of the content analysis.

4.5 RESEARCH ETHICS

All the studies I-III were conducted in accordance with good scientific practice guidelines (All European Academies 2017, Finnish National Board on Research Integrity 2021). Good research practice and data protection guidelines were followed throughout the research process. Patients or the public were not involved in the study planning or designing.

According to Finnish Act on Secondary Use of Social and Health Information (552/2019), Valvira can give permission to use data including authoritative statements in research purposes that fulfils the legislative requirements. The studies I and II were granted a study approval from the Valvira. Because of the nature of register-based data collected to supervisory purposes and the use of data according to Finnish Act on Secondary Use of Social and Health Information (552/2019), consent from patients or professional for publication was not applicable. Valvira´s study approval included a statement that the results of the study are allowed to be presented in a way that specific patients, professionals, or organizations are not recognized. Data was pseudonymized by one researcher for the purposes of study analysis made in study group and reporting. No patients, professionals or organizations included are recognizable.

Study I and II were retrospective register-based document analysis from authority data collected for supervisory purposes. According to Finnish National Board on Research Integrity, ethical approval is not needed for retrospective register-based study unless there is a special risk for information security in merging data or it is a medical study (Finnish National Board on Research Integrity 2021). Studies I and II were not medical studies that intervened to patient's physical or mental integrity according to definition of Finnish Act on Medical Study (1999/488).

The Study III was part of EUNetPas project evaluation and conducted in cooperation with the project. The evaluation forms did not include any confidential information and specific hospitals or units involved in MSP implementation are not recognizable in the results of the study.

5 RESULTS

5.1 WHAT SEVERE MEDICATION ERRORS REPORTED TO HEALTH CARE SUPERVISORY AUTHORITY TELL ABOUT MEDICATION SAFETY? (I)

5.1.1 MEDICATION ERRORS IN THE DATA OF VALVIRA

A 5-year study period found 58 cases with MEs in Valvira's database. In the medication process, errors were fatal in 21 cases (36%) and caused severe harm in 9 cases (16%). Non-severe harm resulted from an error in 19 cases (33%). In 3 cases (5%), the error was detected before it reached the patient, and in 6 cases (10%), the researcher could not assess the harm level because of the lack of information in the case reports.

Of the patients who had suffered from ME, 59% (n=34) were female, and 41% (n=24) were male (Table 6). The average age of the patients was 74 years, with a range of 25-99 years. The majority (83%, n=48) of the patients were >60 years old. According to this data, the ME victim was most likely a female over 80 years (n=25, 43%). In total, 91% (n=53) of the errors were assessed as likely or potentially preventable, while 2 cases (3%) resulting in patient death were assessed to be unlikely preventable.

Table 6 *Characteristics of medication errors (n=58) investigated by Valvira during 2013-2017.*

Characteristic	N	%
PATIENT GENDER	**58**	
Female	34	59
Male	24	41
PATIENT AGE (years)	**58**	
0 – 19	0	0
20 – 39	4	7
40 – 59	6	10
60 – 79	15	26
80 – 99	33	57
SEVERITY OF HARM	**58**	
Death	21	36
Severe harm	9	16
Non-severe harm	19	33
No harm	3	5
Not able to assess	6	10

PREVENTABILITY	**58**	
Likely preventable	39	67
Possible preventable	14	24
Unlikely preventable	2	4
Prevented	3	5
ERROR SETTING*	**64**	
Assisted living facility	16	25
University Hospital	10	16
Primary care ward outside the hospital	10	16
Central hospital	10	16
Primary care hospitals	9	14
Public health center	4	6
Home care	3	5
Pharmacy	1	2
Private medical center	1	2
HEALTH CARE PROFESSIONAL(S) INVOLVED*	**74**	
Physician	37	50
Practical nurse	17	23
Nurse	13	18
Student	5	7
Pharmacist	2	3
MEDICATION PROCESS PHASE*	**81**	
Prescribing	38	47
Administration	15	19
Monitoring	14	17
Dispensing	6	7
Documentation	5	6
Use of medicine by the patient	1	1
Distribution from pharmacy	1	1
Ordering medication from the pharmacy	1	1

*One error process can include several settings, professionals involved, or failures.

A typical care setting for a ME was a hospital (in secondary care n=20, in primary care n=9, total n=29; 45%), but also settings where older people are mostly cared for (e.g., primary care wards outside the hospital, assisted living facilities, home care), were highly represented (n=29; 45%). In 6 cases (10%), two different organizations were involved in the ME process, while most cases (n=52; 90%) were associated with one organization.

Physicians (n=37; 50%) were the health care professionals most involved in the investigated ME incidents, followed by practical nurses (n=17; 23%) and nurses (n=13, 18%). In 28% (n=16) of the cases, more than one health care professional was involved in the ME process. In 7 cases (12%), Valvira had concluded that the ME was caused by process deficiencies in the organization, not by individual health care professionals' inappropriate performance. Most

errors occurred in prescribing (n=38; 47%), administration (n=15, 19%), and monitoring (n=14, 17%) phases of the medication process. In 41% (n=24) of the cases, the same ME was observed in several phases of the medication use process.

5.1.2 MEDICINES INVOLVED IN THE ERRORS

The total number of medicines involved in all error cases (n=58) was 131, representing 77 different active substances (Table 7). In these cases, specific active substances were identified for 126 medicines, while for five medicines, only the therapeutic ATC group (level 2-3 code) was known (Fimea 2023). Nearly half of the cases (n=26; 45%) included more than one active substance. The top 5 therapeutic groups (ATC levels 2-3) most frequently involved in the errors (n=58) were antithrombotic agents (n=17; 13%), opioids (n=10, 8%), antipsychotics (n=10, 8%), drugs used in diabetes (n=8; 6%), and drugs for cardiac therapy (n=8; 6%). Oxycodone and enoxaparin were the most common specific active substances associated with the MEs. Both medicines were reported in 7/58 cases (Table 7). Errors with enoxaparin were associated with prescribing too high doses, insufficient therapeutic monitoring, or treatment duration. Problems with oxycodone were typically exceeding the prescribed dose when using the oral suspension, giving medicine to the wrong patient, using the wrong administration route, or failing to adjust the dose according to changes in the patient's condition.

Table 7 *Medicines (n=131) involved in all error cases (n=58) according to level 2-3 ATC codes (Finnish Medicines Agency 2023). Only medicines mentioned in >1 error cases are presented according to specific active substances.*

ATC GROUP	N (%)	SPECIFIC ACTIVE SUBSTANCE MENTIONED IN >1 ERROR CASES (N OF THE CASES)
B01 ANTITHROMBOTIC AGENTS	17 (13.0)	enoxaparin (7), warfarin (4), acetylsalicylic acid (3)
N02A OPIOIDS	10 (7.6)	oxycodone (7), fentanyl (2)
N05A ANTIPSYCHOTICS	10 (7.6)	quetiapine (4), haloperidol (3)
A10 DRUGS USED IN DIABETES	8 (6.1)	metformin (3)
C01 CARDIAC THERAPY	8 (6.1)	isosorbide mononitrate (2), isosorbide dinitrate (2), digoxin (2)
N05C HYPNOTICS AND SEDATIVES	7 (5.3)	temazepam (4)
N05B ANXIOLYTICS	6 (4.6)	diazepam (3), lorazepam (2)
C03 DIURETICS	5 (3.8)	furosemide (5)
C07 BETA BLOCKING AGENTS	5 (3.8)	metoprolol (3), bisoprolol (2)
N03 ANTIEPILEPTICS	5 (3.8)	-
A12AX CALCIUM, COMBINATIONS	4 (3.1)	calcium and vitamin D combination (4)
J01 ANTIBACTERIALS FOR SYSTEMIC USE	4 (3.1)	-
R03 DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	4 (3.1)	-
H03 THYROID THERAPY	3 (2.3)	levothyroxine (3)
A06 DRUGS FOR CONSTIPATION	3 (2.3)	-
N01 ANESTHETICS	3 (2.3)	-
N06D ANTI-DEMENTIA DRUGS	3 (2.3)	-
V03 ALL OTHER THERAPEUTIC SUBGROUPS	3 (2.3)	naloxone (3)
A02 DRUGS FOR ACID RELATED DISORDERS	2 (1.5)	-
A07 ANTIDIARRHEALS, INTESTINAL ANTI-INFLAMMATORY/ANTI-INFECTIVE AGENTS	2 (1.5)	-
H02 CORTICOSTEROIDS FOR SYSTEMIC USE	2 (1.5)	-
N02B OTHER ANALGESICS AND ANTIPYRETICS	2 (1.5)	paracetamol (2)
N06A ANTIDEPRESSANTS	2 (1.5)	-
S01 OPHTHALMOLOGICALS	2 (1.5)	-
OTHER	11 (8.4)	-
TOTAL	**131**	

In total, 36% (n=47) of the active substances in MEs were identified as high-alert medicines (Institute for Safe Medication Practices 2018, Institute for Safe Medication Practices 2021a, Institute for Safe Medication Practices 2021b). Active substances involved in the MEs resulting in severe harm or death of a patient (n=30) are described in Table 8. Many high-alert medicines are at the top of the severe ME list (enoxaparin, oxycodone, warfarin). Still, also other medicines were associated with severe harm or death of the patient.

Table 8 *Active substances (n=78) involved in MEs that caused severe harm or death of a patient (n=30). Only active substances mentioned in >1 errors are presented with a name.*

MEDICINE (n=78)	N (%)
Enoxaparin*	5 (6.4)
Furosemide	4 (5.1)
Oxycodone*	4 (5.1)
Warfarin*	3 (3.8)
Naloxone	3 (3.8)
Quetiapine	3 (3.8)
Metoprolol	3 (3.8)
Bisoprolol	2 (2.6)
Isosorbide mononitrate	2 (2.6)
Metformin*	2 (2.6)
Digoxin*	2 (2.6)
Diazepam	2 (2.6)
Other	43 (55.1)
Total	**78**

*Included in the Institute for Safe Medication Practices (ISMP) list of high-alert medicines at the time of research

The administration route for 130 medicines involved in all errors (n=58) was identified. The medicines were administered typically orally, intravenously, or subcutaneously (Table 9). Most medicines in severe MEs were administered perorally (72%).

Table 9 *Administration routes of the medicines involved in all MEs (n=58) and MEs that caused severe harm or death of a patient (n=30).*

ADMINISTRATION ROUTE OF THE MEDICINE	MEDICINES IN ALL MES (N=130) N (%)	MEDICINES IN MES CAUSING SEVERE HARM OR DEATH (N=81) N (%)
PER ORAL	89 (69)	58 (72)
INTRAVENOUS	15 (12)	7 (9)
SUBCUTAN	13 (10)	10 (12)
EPIDURAL	4 (3)	4 (5)
INHALATION	4 (3)	-
INTRAMUSCULAR	2 (2)	2 (3)
OCULAR	2 (2)	-
TRANSDERMAL	1 (1)	-

5.1.3 ACTIONS TAKEN IN THE ORGANIZATIONS AFTER THE MEDICATION ERROR HAD OCCURRED

In 60% (n=35) of the cases (n=58), the documents available in Valvira described the organization's changes to their medication use processes to prevent the re-occurrence of the errors. Reported organizational changes and/or actions to improve medication safety were multiple, ranging from staff training to introducing technology-based systemic defenses to the processes. A summary of different actions and their level of strength based on the IHI Action Hierarchy (Institute for Healthcare Improvement 2019) is presented in Figure 25.

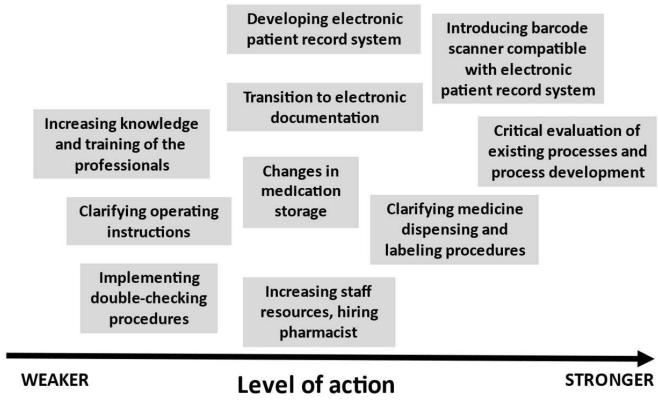

Figure 25 Reported actions taken by health care organizations to improve medication safety after the ME had occurred. The strength of the actions classified according to the IHI Action Hierarchy (Institute for Healthcare Improvement 2019).

5.2 APPLICABILITY OF DRUG-RELATED PROBLEM (DRP) CLASSIFICATION SYSTEM FOR CLASSIFYING SEVERE MEDICATION ERRORS (II)

5.2.1 APPLICABILITY OF DRP CLASSIFICATION SYSTEM

Characteristics of medication errors (n=58) investigated by Valvira during 2013-2017 are described in Table 6 as they were the same as in study I.

It was possible to classify all MEs according to Basger et al. (2015). In total, 100 MEs were identified from the cases (n=58) (Table 10). In 53% (n=31) of the cases, more than one ME was identified (mean number of DRPs, 1.7 per case). A small proportion (8%, n=8) of the MEs identified from the reports were classified in the "Other" category (a cause that cannot be classified into one of Basger et al.'s eight categories, Category 9, Table 9). The"Other" category included the following MEs (n=8):

1) dispensing errors in a community pharmacy (n=1)
2) documenting errors related to medication administration (e.g., no information available had the medication been administered or in which dose, n=5)
3) prescribing errors in which cessation of the medication was conducted inappropriately (n=1)
4) dispensing error in the care unit detected before reaching the patient (near miss, n=1).

The identified MEs (n=100) fell into all nine main categories of Basger's classification, 21/33 (64%) of the subcategories and 21/58 (36%) of the sub-subcategories (Table 8). Most of the MEs (n=89, 89%) were categorized into these six main categories: "Drug selection" (n=22, 22%), "Drug use process" (n=18, 18%), "Monitoring" (n=14, 14%), "Dose selection" (n=13, 13%), "Treatment duration" (n=11, 11%) and "Logistics" (n=11, 11%). Subcategory and sub-subcategories were used for all MEs if there were such defined in Basger et al.´s classification system.

Table 10 *Aggregated Classification System for Causes of DRPs created by Basger et al. (2015). MEs found in Valvira's data (n=100) are presented as bolded.*

Aggregated System Category	Aggregated System Subcategory	Aggregated System Sub-subcategory
1. Drug selection (n=22)	**1.1 Inappropriate drug due to contraindication, ineffectiveness, regimen (regular rather than "when required") or safer alternative available (n=7)**	**1.1.1 Precaution with the use of this drug (n=1)** **1.1.2. Drug (absolutely) contraindicated (n=5)** 1.1.3. An unnecessary drug is taken because of the use of another drug **1.1.4. Drug is not the most safe/effective treatment for the patient's medical condition according to guidelines (n=1)** 1.1.5. Drug is not effective for the indication being treated 1.1.6. Medical condition is refractory to drug
	1.2 No indication for drug (n=4)	**1.2.1. No (documented) indication apparent (n=4)** 1.2.2. No indication due to duplication 1.2.3. Indication does not warrant drug treatment
	1.3 Inappropriate combination of drugs, or drugs and food, or drugs and alcohol (n=4)	**1.3.1. A drug interaction may cause/causes an undesirable reaction by increasing the therapeutic effect of one or both drugs (n=3)** **1.3.2. A drug interaction may cause/causes an undesirable reaction by decreasing the therapeutic effect of one or both drugs (n=1)** 1.3.3. A drug interaction may cause/causes a hypersensitivity reaction
	1.4 Indication not treated/missing therapy	(no sub-subcategory)
	1.5 More cost-effective drug available	(no sub-subcategory)

	1.6 Synergistic/preventive drug required and not given (n=7)	**1.6.1. Preventive drug therapy is required to reduce the risk of developing a new condition (n=2)** **1.6.2. A medical condition requires additional pharmacotherapy to attain synergistic or additive effects (n=5)**
2. Drug form (n=1)	**2.1 Inappropriate or suboptimal drug form (n=1)**	(no sub-subcategory)
3. Dose selection (n=13)	**3.1 Drug dose too low (n=1)**	(no sub-subcategory)
	3.2 Drug dose too high (n=8)	(no sub-subcategory)
	3.3 Dosage regimen not frequent enough	(no sub-subcategory)
	3.4 Dosage regimen too frequent	(no sub-subcategory)
	3.5 Deterioration/improvement of disease state requiring dosage adjustment (n=3)	**3.5.1. Deterioration of disease state requiring dosage adjustment (n=3)** 3.5.2. Improvement of disease state requiring dosage adjustment
	3.6 Dosage instructions unclear, incomplete, or not understood by patient/carer (n=1)	(no sub-subcategory)
4. Treatment duration (n=11)	**4.1 Duration of treatment too short (n=7)**	(no sub-subcategory)
	4.2 Duration of treatment too long (n=4)	(no sub-subcategory)
5. Drug use process (n=18)	**5.1 Inappropriate timing of administration and/or dosing intervals by patient/carer/nurse (n=5)**	(no sub-subcategory)

5.2 Drug underused/underadministered (n=4)	5.2.1. The patient chose to take the wrong dose, which was lower than prescribed 5.2.2. The patient chose to take a drug on a "when required" basis rather than on a regular basis 5.2.3. The patient misunderstood the directions 5.2.4. The patient felt better or worse 5.2.5. The patient had a fear of adverse effects 5.2.6. The patient did not believe the drug was effective/believed the drug was toxic 5.2.7. The patient occasionally forgot to take the drug **5.2.8. The drug was underadministered by the health care professional/carer (n=4)**
5.3 Drug overused/overadministered (n=3)	5.3.1. The patient chose to take the wrong dose, which was higher than prescribed 5.3.2. The patient misunderstood the directions 5.3.3. The patient forgot they had already taken the drug **5.3.4. The drug was overadministered by carer or health care professional (n=3)**
5.4 Drug not taken/administered at all	5.4.1. The patient chose to discontinue a drug by choice or for an illogical or irrational reason 5.4.2. Patient forgot to take the drug (no sub-subcategory)
5.5 Wrong drug selected, taken, or administered	(no sub-subcategory)
5.6 Drug abused	
5.7 Patient, carer, or nurse unable to use/does not use drug/form as directed (n=1)	5.7.1. Patient uses drug incorrectly through difficulty or ignorance **5.7.2. Patient barriers are present (n=1)**

	5.8 Adequate information not provided or not understood or misunderstood or not followed (n=5)	**5.8.1. Adequate information about drug not provided (n=3)** 5.8.2. Incorrect information about drug provided **5.8.3. Adequate information about disease state management not provided or not understood or not followed (n=2)** 5.8.4. Incorrect information provided about disease state
	5.9 Patient uses or stores drug inappropriately	5.9.1. Inappropriate use/storage 5.9.2. Stockpiling
6. Logistics (n=11)	**6.1 Prescribed drug not available (n=1)**	6.1.1. The patient/carer had difficulties obtaining the drug **6.1.2. A drug has been discontinued, is not on formulary, or is out-of-stock (n=1)** 6.1.3. A drug order does not meet legislative requirements
	6.2 Drug order incorrect, incomplete, poorly legible/illegible or discrepant (also known as transferring error) (n=2)	6.2.1. A drug order is incorrect or incomplete **6.2.2. Drug order/transition of care discrepancy (n=2)** 6.2.3. The way in which information/directions were written caused the patient/carer to misuse the drug
	6.3 Error in drug selection (n=8)	6.3.1. Doctor chooses the wrong drug 6.3.2. Pharmacist selects the wrong/expired drug from dispensary shelf 6.3.3. Nurse administers drug from the wrong patient's drug chart **6.3.4. Patient takes someone else's drug (n=8)**
7. Monitoring (n=14)	7.1 Monitoring too frequent	7.1.1. Monitoring of disease state too frequent 7.1.2. Therapeutic drug monitoring too frequent 7.1.3. Monitoring for the effect/adverse effect of drug too frequent
	7.2 No or too infrequent monitoring (n=14)	**7.2.1. Monitoring of disease state absent or too infrequent (n=4)** **7.2.2. Therapeutic drug monitoring absent or too infrequent (n=5)** **7.2.3. Monitoring for the effect/adverse effect of drug absent or too infrequent (n=5)** 7.2.4. Monitoring may have occurred but is unavailable or not documented

	7.3 Inappropriate test ordered	(no sub-subcategory)
	7.4 Patient unable to attend/pay for monitoring	(no sub-subcategory)
8. Unexpected or adverse drug reaction or no obvious cause of DRP (n=2)	**8.1 An adverse drug reaction occurred (n=2)**	8.1.1. A drug causes an undesirable reaction that is not dose related **8.1.2. A drug causes an undesirable reaction at normal therapeutic dose (n=2)** 8.1.3. Allergic drug reaction
	8.2 No obvious cause of treatment failure	(no sub-subcategory)
9. Other: A cause that cannot be classified into one of the 8 categories (n=8)		

5.3 FACILITATORS AND BARRIERS IN IMPLEMENTING MEDICATION SAFETY PRACTICES ACROSS HOSPITALS WITHIN 11 EUROPEAN UNION COUNTRIES (III)

5.3.1 IMPLEMENTATION OF MEDICATION SAFETY PRACTICES

At the initiation stage of the implementation project, the participating hospitals (n=79) from 11 EU countries committed to implementing a total of 113 practices, but 75 evaluation reports were returned from 55 hospitals in 11 EU member states (Table 11). According to the returned reports, 59% (n=67) of the planned practice implementations (n=113) were actually started in the hospitals and reported to the EUNetPas. Eight reports were returned unfilled, as the implementation had not started as planned.

Of those hospitals that started the implementation, 78% (n=52) reported implementing the practice as described or modified. The implementation was rated as successful in these cases. The implementation was reported as partly successful (some units or professionals involved had adopted the practice), or the implementation was still ongoing in 11 (16%) cases at the end of the given time frame. Implementation was rated failed (n=4, 6%) when the practice was not implemented, although implementation efforts were made.

Table 11 *Participation of the 11 European Union member states in implementing seven selected medication safety practices in the EUNetPas project.*

Practice	**Hospitals that planned to participate in the implementation process** (n)	**Countries involved in the implementation and submitting the evaluation report** (n of reports provided for countries submitting ≥1 reports)	**Hospitals that started the implementation process** n (%)	Implementation failed[a] n (%)	Implementation partly succeeded or was on-going[a] n (%)	Implementation succeeded[a] n (%)
Bed dispensation (A)	10	Portugal (3), Austria, Ireland	5 (50)	0	0	5 (100)
Bed dispensation (B)	10	Greece (3), Ireland (2), Italy (2), Lithuania	8 (80)	0	1 (13)	7 (87)
Safety vest	28	Ireland (6), Finland (4), Portugal (4), Italy (2), Lithuania (2), France	16 (57)	3 (19)	4 (25)	9 (56)
Medication reconciliation at admission and discharge	17	Portugal (5), France (3), Ireland (2), Belgium, Italy	12 (71)	1 (8)	2 (17)	9 (75)
Discharge medication list for patients	21	Portugal (4), Ireland (2), Italy (2), Finland, France	8 (38)	0	1 (13)	7 (87)
Medication reconciliation at discharge	23	Denmark (5), Portugal (4), Italy (3), The Netherlands (2), Austria, Ireland, Lithuania	16 (70)	0	3 (19)	13 (81)
Sleep card	4	Ireland (2), Austria, Italy	2 (50)	0	0	2 (100)
Total	**113**	**75 (66%)**	**67**	**4 (6)**	**11 (16)**	**52 (78)**

[a] According to the evaluation reports submitted by the participating hospitals at the end of the nine-month implementation period.

At least in a quarter (24%, n=16) of the cases the hospitals needed to modify the practice locally. Especially medication reconciliation practices needed local modification, and they often were more like discharge medication list practices. In the given implementation and evaluation time frame, it was not possible to assess whether the implementation was sustainable.

5.3.2 FACILITATORS AND BARRIERS TO MSP IMPLEMENTATION

Most participating hospitals described problems they encountered during the practice implementation, but many facilitators were also identified (Figures 26 and 27). The facilitators were identified to include elements in working environment, interprofessional cooperation, planning process, feedback systems, existing resources, and external support for implementation (Figure 26). Especially safety culture and national patient safety programs were seen effective general facilitators for the implementation. The practice was more likely to be implemented if the planning was done with due care, health care professionals valued inter-professional cooperation, the working environment, and tools (e.g., information technology) enabled practice implementation, and the workers got updated feedback about the practice. A medication process that already included a safety practice was in some hospitals identified as a good basis implementing new safety practices (e.g., when a medication list was implemented in an already existing medication reconciliation process). Practice specific facilitators and barriers are described more precisely in the original publication.

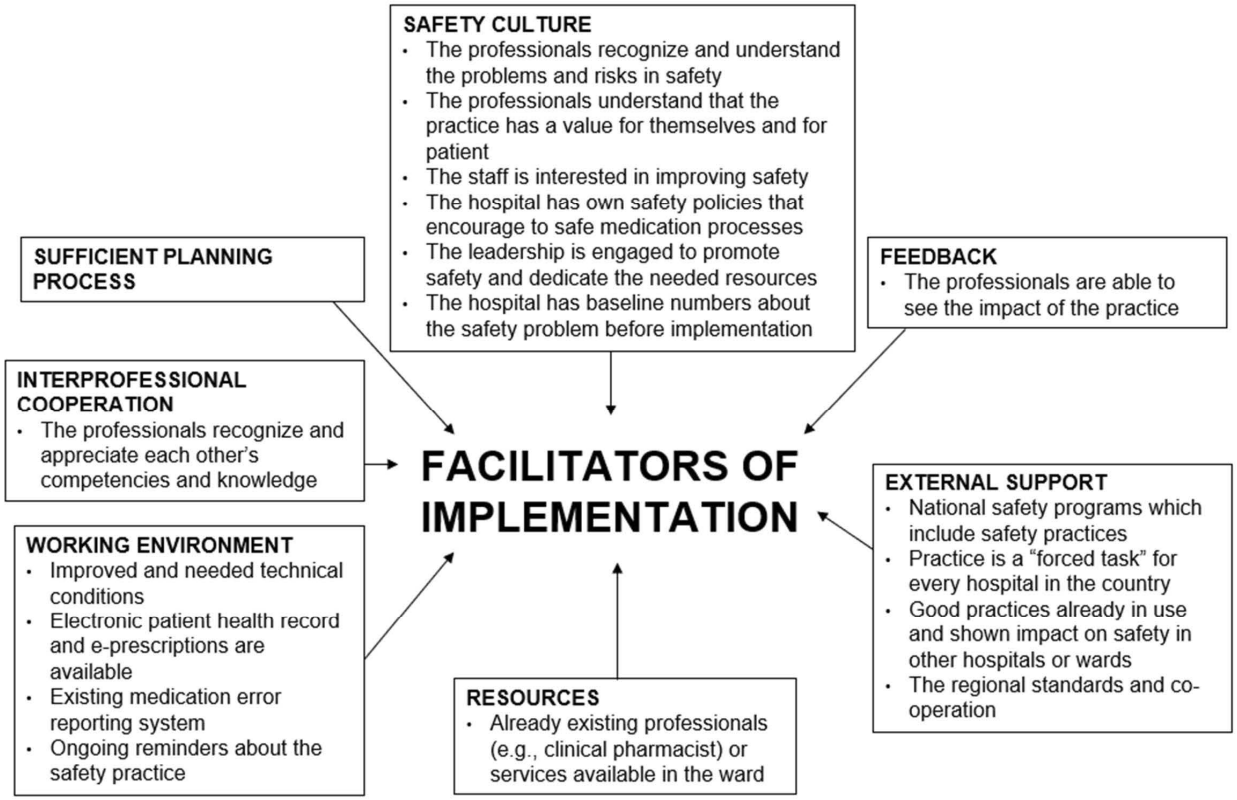

Figure 26 General facilitators reported by hospitals (n=67) in implementing new medication safety practices.

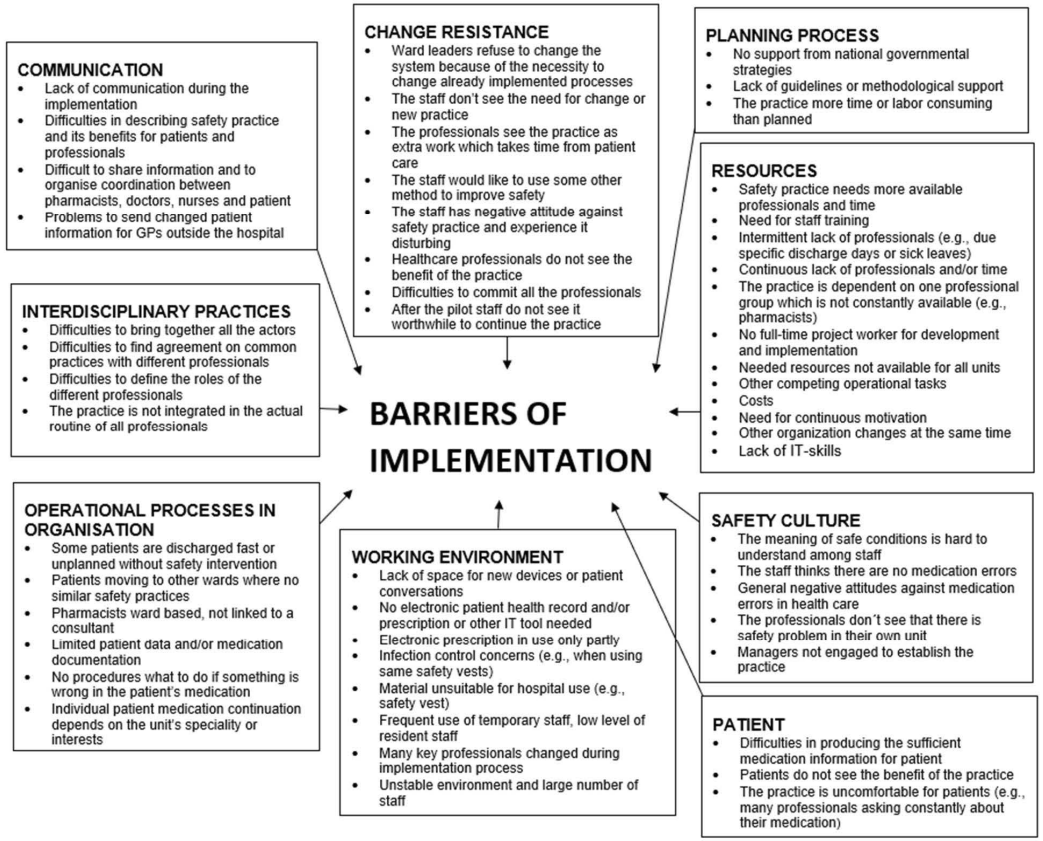

Figure 27 General barriers reported by hospitals (n=67) in implementing new medication safety practices.

Barriers of the implementation related on communication, interdisciplinary cooperation, processes, working environment, patients, safety culture, planning the implementation, change resistance, and resources (Figure 27). Lack of time for practice implementation was the most mentioned barrier reported in 34% (n=23) of the evaluation forms. It was related to all seven practices. The relatively short nine-month time allocated for practice implementation in the study appeared as a major barrier, especially for the medication reconciliation practice. The evaluation phase of the practice was still ongoing in many hospitals when the project ended. The barriers were often associated with the lack of resources and non-compliance of the unit's staff for MSP implementation. Especially physicians, as a professional group, were seen unwilling to develop shared practices and commit to them. Many hospitals reported problems in implementing the practice in the existing processes of the unit or a lack of tools supporting implementation (e.g., no electronic patient records available). The lack of safety culture and operational processes that did not promote implementation (e.g., managers' engagement) were mentioned in several reports. The practice was also seen as uncomfortable for patients in some reports (e.g., their medication history was asked several times and by many professionals during the medication reconciliation process). There was also a need for more external expert support in planning the implementation process.

Implementing a safety practice in all hospital wards simultaneously encouraged the implementation of the practice more on those wards having acute safety problems (e.g., safety vests in wards with medication room vs. wards without the room). In the project's initial stages, many hospitals planned to implement more than one medication safety practice. However, other concurrent projects were often barriers to the actual implementation of multiple practices.

6 DISCUSSION

6.1 MAIN FINDINGS (STUDIES I-III)

This doctoral dissertation provides an overview of evolution of patient and medication safety terminology, strategies, and initiatives over time internationally and in Finland. The empirical studies included in this dissertation have their roots in the early phase European level initiatives to get systems-based patient safety work started within Council of Europe and European Union member states as part of the emerging global patient safety movement. These studies, as well as many of the recommendations launched in Europe at that time, are still valid today, but also new challenges can be seen at current patient and medication safety field.

This study focused on severe MEs as a challenge to safe care in all social and health care settings where medicines are used. In addition, this study presents that severe MEs occur, even though we are still lacking the overall understanding this challenge in Finland. This study did not focus on their incidence but showed that the evaluation methods to learn from severe MEs need further development. The findings in this study support that the theoretical framework of human error and Systems Engineering Initiative for Patient Safety (SEIPS) (Reason 1990, Reason 2000, Carayon et al. 2006, Holden et al. 2013, Carayon et al. 2014) are useful for investigating and understanding severe MEs. This is because severe MEs are often a result of complex processes, including many errors, professionals and organizations failing to prevent the error before it causes harm to the patient.

Based on this study, the health care authority data proved to be a rich and multi-dimensional source of medication safety information. A primary reason for its uniqueness is that it provides information on severe errors that are rare (Pierson et al. 2007, Kale et al. 2012, Avery et al. 2013, Tanti et al. 2013, Thomas and MacDonald 2016, Alshehri et al. 2017, Ferrah et al. 2017, Mulac et al. 2021, Elliot et al. 2021, Tchijevitch et al. 2021) and may not be reported to other MER systems (Cheung et al. 2011, Holmström et al. 2019). As the authority documentation is descriptive and qualitative, it provides a detailed picture of "what went wrong and why" and in which phases of the medication process, causing a severe incident. According to the previous study, Valvira´s data is potential also for simplified root cause analysis (Linden et al. 2009). Therefore, findings in this study complement the previous studies that recommend using the authority documentation as an essential source of medication safety information (Jonsson and Ovretveit 2008, Linden-Lahti et al. 2009, Björksten et al. 2016). In countries with well-established MERS providing structured national information, authority documentation could be a supplementary data source on severe MEs. A shared environment to learn, especially about medication-related preventable deaths, is needed in national

level (France et al. 2023). The national supervisory authorities' central role as a provider of medication safety information should also be recognized and established in national and international patient safety improvement policies. This has been a recommendation of Council of Europe already in 2006 but the implementation of this recommendation is still in progress.

The present study also suggests that the aggregated DRP classification system by Basger et al. (2015) has potential to be applied to categorizing severe MEs in national supervisory authority data and producing new insights into the causes of the MEs. Because of its authoritative nature, Valvira's data had comprehensive documentation on ME cases that enabled us to identify reliably multiple MEs and their causes in each case. To our knowledge, this was the first international study to pilot-test the applicability of a DRP classification system for this purpose.

Even though the aggregated DRP classification system helped to describe MEs and their causes in more detail, we still need tools to describe complex medication errors. As described earlier, severe errors often include multiple chained errors (Reason 1990, Reason 2000, Huckels-Baumgart and Manser 2014, Thomas and MacDonald 2016). Making these error chains visible using only structured classification is challenging, although some successful examples exist (Huckels-Baumgart and Manser 2014). But in terms of learning in-depth from severe MEs and complex error cases, qualitative analysis (e.g., root cause analysis or causal tree analysis) can still be seen as more informative because these tools enable the description of multiple error chains and the contributing factors in the medication use process (Smith et al. 2009, VHA National Center for Patient Safety 2020). As the existing in-depth ME analyses are resource-consuming, future innovations in classification systems are needed.

In addition to theoretical understanding and learning from severe MEs, practical development of medication safety in social and health care organizations is essential. The current study indicates that implementing MSPs into the daily practice of hospitals is challenging and often requires local adaptation of the procedures. As previous research is scarce, our study provides unique information on general and practice specific facilitators and barriers to MSP implementation in European hospitals. Our study also indicates that implementation of MSP is challenging and time-consuming, especially when the practice requires changing existing work processes. An interesting finding was that practices presumed to be easy and inexpensive to implement still failed to implement. Consequently, hospitals need to be provided with enough support and guidance to implement and evaluate new MSPs, as noted also previously (Groene et al. 2009).

As learned from the EUNetPas project, implementing MSPs across hospitals and countries by only introducing general descriptions of the given practices may not be the most efficient way of successful practice implementation. Instead, the hospitals need to participate more actively in identifying their own priority medication safety problems to improve the

safety of their medication processes. Following this, the hospitals would need to identify the best practice for a particular safety problem, e.g., a safety vest does not eliminate the primary cause for interruptions in dispensing if the phone is still ringing. Also, previous studies have found that the lack of safety practice effectiveness may merely reflect an implementation failure rather than the actual ineffectiveness of the practice (Graig et al. 2008).

In the EUNetPas project, the expert group used the inventory method instead of the purely evidence-based for selecting MSPs because system-based patient and medication safety work was still in its infancy phase in globally and in Europe. Evidence on the effectiveness of practices intended to reduce medication errors in hospitals was scarce. Today the selection of MSPs would likely be more evidence-based. Many interventions and practices for medication safety have been described in the literature, but there is a need for more research on their effectiveness and implementation (Dückers et al. 2009, Berdot et al. 2016, Khalil et al. 2017, Rapport et al. 2018, Marufu et al. 2022). However, practices included in the EUNetPas exercise are still valid and widely used in European hospitals. For example, medication reconciliation is one globally recommended MSP (World Health Organization 2019b), although the evidence of its impact is still limited (Redmond et al. 2018, Ciapponi et al. 2021, Killin et al. 2021). In many countries, implementing electronic patient record systems, electronic prescribing, and medication management systems has remarkably changed within the last ten years, solving some medication safety challenges, and introducing new ones (Linden-Lahti et al. 2022). The emphasis of recent new medication safety practices has been on utilizing electronic health record systems and technology to prevent MEs, e.g., Automated Dispensing Cabinets (ADC), Barcode Assisted Medication Administration (BCMA), closed-loop Electronic Medication Management Systems (EMMS) and smart infusion pumps (Melton et al. 2019, Ahtiainen et al. 2020, Zheng et al. 2021, Linden-Lahti et al. 2022, Kuitunen 2022). Of those, especially computerized physician order entry (CPOE) and barcoding systems seem to impact reducing MEs and ADEs (Ciapponi et al. 2021). Although introducing innovative technology has the potential to make the medication process safer, it may also produce new risks for MEs and requires adaptation in medication work processes (Mulac et al. 2021b, Zheng et al. 2021, Linden-Lahti et al. 2022).

The PaSQ project followed the EUNetPas and it had a specific focus in implementing medication reconciliation practices in EU countries (European Union Network for Patient Safety and Quality 2012). Hospitals also from Finland participated in PaSQ and the project had national impact e.g., in Päijät-Häme for developing their medication reconciliation practices (Riukka et al. 2019). Overall, the projects have enabled sharing MSPs across Europe (Agra-Varela et al. 2015), even though multinational projects are challenging. There still is a need for established European-wide patient and medication safety work to ensure the coordination and collaboration with the WHO Europe, the EU, the Council of Europe, authorities and institutions, health

care organizations, professionals, and patients. Currently, the focal point of patient and medication safety seems to be missing in European level which may be one reason for the PaSQ being the last project for ten years.

6.1.1 WHAT CAN WE LEARN ABOUT SEVERE MEDICATION ERRORS IN VALVIRA'S DATA?

This study was one of the first studies on severe MEs in Finland. Our study revealed that older people, particularly those >80 years were the most vulnerable to severe MEs investigated by Valvira. Previous studies have reported similar findings, indicating that the effects of MEs are likely to be more harmful to older adults with reduced physiological and cognitive functions (Linden-Lahti et al. 2009, Buajordet et al. 2011, Phillips et al. 2001, Saedder et al. 2015, Salmasi et al. 2018). Although older adults have been recognized as a patient group with higher risk for MEs, there is limited understanding of this phenomenon in Finland. Because older people were prevalent in Valvira´s data, the medicines involved in the errors represent medicines typically and commonly used in the care of this age group. However, many of those medicines are also categorized as potentially inappropriate medications for older adults and thus, to be prescribed and used with caution in geriatric care (American Geriatrics Society 2023).

Many of the top ten medicines associated with severe errors in this study, such as antithrombotic agents and opioids, have been reported as high-alert medications by the previous studies and the ISMP (Buajordet et al. 2001, Saedder et al. 2014, Institute for Safe Medication Practices 2018, Yardley et al. 2018, Schepel et al. 2021, Institute for Safe Medication Practices 2021a and 2021b). This finding strengthens the need to adopt effective, evidence-based error safeguarding interventions for various stages of these medicines' medication process. However, severe errors also occurred with medicines not regarded as high-alert medications. This finding may indicate that the severity of the error may be caused by the medication itself but also by the health status, multi-morbidities, age of the patient, and other systemic contributing factors (Buajordet et al. 2001, WHO 2019c). There were also cases where multiple medication was administered in ME case and they all weren´t the primary cause for severe outcome. While many studies have emphasized, e.g., intravenous administration as a high-risk administration route (Kuitunen et al. 2021), our study also highlights the risk associated with oral treatment.

Our study revealed that assisted living facilities, primary care wards outside the hospitals, and home care were equally prone to severe MEs than hospitals. Those settings are often environments where the frailest older adults with complex medical problems are treated even though these units may lack well-established medication use processes and personnel having sufficient competence in geriatric care and pharmacotherapy (Hakoinen et al. 2017, Mononen et al. 2020).

This study indicates that preventive medication safety risk management actions in caring for older people, and other high-risk populations such as children, should be a high priority in social and health care settings. In Finland, patient safety challenges in assisted living facilities have been a national crisis reflecting deficiencies in several key areas of safe medication care, such as lack of staff competencies and recourses allocated to elderly care (Uusitalo 2023). The first sights of problems in assisted living facilities were seen in Valvira 2016-2017 and this might be seen also in our study results. The recent challenges in the availability of social and health care professionals can be a risk that the crisis to be repeated.

This study is in line with the previous studies demonstrating that most MEs take place in prescribing and administration stages of the medication process (Lewis et al. 2009, Phillips et al. 2011, Panesar et al. 2015, Salmasi et al. 2018, Mulac et al. 2020). According to our study supported by similar findings by Panesar et al. (2016), monitoring medication use and adverse effects (e.g., with laboratory tests or state of patient condition) represents a phase of the medication process that defensive actions should be strengthen. The severe incidents in this study also typically included more than one ME, many organizations or health care professionals and several medicines which reminds us of the complexity of severe errors and the importance of medication safety risk management also in transition of care.

As suggested by previous studies, most of the severe MEs in this study were assessed as likely or potentially preventable, providing the health care organizations an opportunity to reduce the re-occurrence of these errors by systems-based prospective risk management actions and intervention, i.e., systemic defenses (Gurwitz et al. 2000, Linden-Lahti et al. 2009, Mulac et al. 2020). According to Study I, more than half of the errors had already led to the development of systemic defenses, processes, resources, and competencies. It is an encouraging finding that the current severe ME prevention measures seem to base on systems thinking, understanding human errors, and applying medication safety interventions with varying levels of strength, such as adding pharmacist resources or technical solutions (IHI 2019, VHA National Center for Patient Safety 2021). When developing medication safety, it is important to develop medication processes with varying actions and always, when possible, select the strongest possible defenses. Thus, there is also a need to have more evaluation data which of the medication safety practices are effective in practice.

6.1.2 APPLICABILITY OF DRP CLASSIFICATION SYSTEM ON SEVERE MEDICATION ERRORS

As Valvira's data included severe and non-severe MEs in different social and health care settings, our study indicated that the DRP classification might be applied to MEs with various levels of harm occurring in different care settings.

Still, there were also some challenges in using aggregated DRP classification system for all MEs included in our data. This concerns especially the potential limitation of not being able to categorize all MEs prevented before they reached the patient (near misses). With severe MEs in Valvira's documentation, this situation was not usually an issue as the errors investigated had typically reached the patient and caused problems or harm to the patient. However, this limitation of DRP classification can become a major challenge when classifying other ME data, especially potential MEs. As there was only one near miss case in our study material, there is a need for further research with more extensive data acquired from other ME sources, such as ME reporting systems commonly used in health care organizations.

With Basger et al.'s aggregated DRP classification system, we were able to categorize the problem (ME) and its cause. Subgroups and sub-subgroups of causes were seen useful in categorizing the causes in a way that provides detailed information about the incident for medication error prevention and risk management purposes from the systems approach, although further research is needed on ME categorization. Already existing ME classification systems could be further developed to include similar subgroups of error causes as Basger et al.'s aggregated DRP classification system has. Still, the strength of Basger et al.'s aggregated DRP classification system is that it is readily available and specifically designed for risk management in the medication use process. There is a need to optimize ME classification further to provide enough information about error causes and contributing factors.

Having as much information as possible is beneficial when developing medication safety based on reported errors, especially severe ones (Mulac et al. 2021). For example, prescribing error (as an outcome) can mean anything from the wrong drug or dose selection to the duration of the medication treatment (Ashcroft et al. 2015). In study I, with the same Valvira data as used in study II, we identified the most common ME types but were using an outcome-based ME taxonomy. By analyzing the same data using Basger et al.'s aggregated DRP classification system, we described and understood the MEs and causes contributing to the incidents in more detail. Another strength of using Basger et al.'s aggregated DRP classification system is that it indicates whether health care professionals or patients were causally related to the ME. Even though we found Basger et al.'s aggregated DRP classification system potential for categorizing severe and non-severe MEs, it could be further optimized for classifying MEs and DRPs by e.g., adding or re-naming classification categories. The original study II presents more spesific descriptions of the optimization suggestions.

There are many DRP classification systems available (Basger et al. 2014). In this study classification system of Basger et al. was chosen as it was the most recently developed system and aggregated wide range of different classification systems. Other cause-based DRP classification systems could also be potential for ME classification system but for the integrity of future

classification systems and research, only one global classification framework would be ideal.

It became evident that we could not describe all contributing factors identified that caused the error by using the aggregated DRP classification system. This result indicates that Basger et al.'s aggregated DRP classification system in its current form does not alone meet the need for comprehensively categorizing a wide range of factors contributing to severe MEs. Therefore, it is important to recognize the limitations of the DRP classification system and use other methods to supplement the understanding of the multiple causes and factors contributing to MEs.

6.1.3 FACILITATORS AND BARRIERS TO MSP IMPLEMENTATION

This study, among other studies, indicated that when considering the implementation of an MSP in hospitals, the primary focus should be on safety culture (Halligan and Zecevic 2011, Taylor et al. 2011, Holmström et al. 2015). In supporting system-based organizational culture, the health care professionals are more likely to understand the medication safety risks at their own hospital, commit themselves to MSP implementation, and value the implementation. In addition to safety culture, the role of hospital leadership was identified as important. Leadership, resources, and commitment to quality and safety are key enabling factors in patient safety improvement work (Burnett et al. 2010, Halligan and Zecevic 2011, Taylor et al. 2011). Study findings also indicated that active interprofessional cooperation is essential for successfully implementing practices. This study also supports previous findings that if many new practices were implemented at the same time, there is a high possibility that the resources are not sufficient for implementing all of them (Burnett et al. 2019). According to our findings, national guidelines and safety projects seem to serve as good facilitators for practice implementation in hospitals.

One major barrier to implementing the new MSPs was found to be in changing work processes because of implementation of the new practices. It is not easy to change health care processes as the changes typically has impact also to other steps of the complex process and professionals. Usually there is a need to impact on attitudes, design new workflows and commit the multidisciplinary team to change (Reed et al. 2016). Safety culture, national guidelines and projects, expert support, sufficient resources, electronic patient records, interprofessional cooperation, and clinical pharmacy services best facilitated the successful practice implementation. These fundamental issues still today play a role in the safety of health systems in the EU and globally, influencing medication safety (Bauer et al. 2015, Rapport et al. 2018, WHO 2021).

This study showed general facilitators and barriers for MSP implementation, but each MSP has practice-specific factors influencing the

implementation that we need to understand better. According to the findings, electronic patient records facilitate implementation, especially in bed dispensation, medication lists and medication reconciliation practices. Established clinical pharmacy services were one key facilitator in implementing medication reconciliation and medication list practices. Although pharmacists would be an ideal part of the medication safety practice implementation team, our study indicated that their work resources were limited, hindering their participation in the implementation activities. Our findings also showed that patient involvement might be crucial for compliance with MSP, as noted also in recent medication safety guidelines (Council for International Organizations of Medical Sciences 2022).

6.2 RELIABILITY AND VALIDITY OF THE RESEARCH METHODS (STUDIES I-III)

6.2.1 SEVERE MEDICATION ERRORS REPORTED TO HEALTH CARE SUPERVISORY AUTHORITY (I)

In retrospective document analysis, the researchers could not contact the professionals or organizations involved in the errors. Therefore, misinterpreting the free-text data was possible and all the information to determine comprehensively why the errors happened was not available. The preventability of the errors was especially challenging to evaluate and prone to hindsight bias. Furthermore, only one researcher made the evaluation of the preventability, which can be seen a limitation. Reliability of the classification was ensured with exact criteria for preventability and in unclear cases the classification was made as a consensus of two researchers.

The information on the conducted safety development actions in the organizations was in some cases missing or incomplete. Also, determining whether one specific ME caused the harm or death of a fragile patient with comorbidity was not always a clear cause-effect relationship.

6.2.2 APPLICABILITY OF DRUG-RELATED PROBLEM (DRP) CLASSIFICATION SYSTEM FOR CLASSIFYING SEVERE MEDICATION ERRORS (II)

Basger et al.'s aggregated DRP classification system proved potential for classifying the severe MEs in our study. Still, more studies are needed using other ME incident data from other reporting systems to confirm our findings. Although our data included all ME cases investigated by Valvira within five years, the data had quite a limited number of cases. This problem particularly concerns the number of severe MEs, which were the special focus of this study.

A larger number of severe ME cases in our data may have allowed us to generate more specific information about the applicability of the DRP classification system. The available data set was large enough to conclude whether DRP classification is even potential for classifying MEs.

Our data was rich and extensive, and narrative in nature. Thus, it was suitable for qualitative analysis, even though primarily collected for authoritative purposes. The data enabled us to identify many MEs and their causes. Our rich data may also be considered a limitation when comparing our results with other studies that may have used data with less information about the ME incidents.

In our study, one researcher made the classification and only in cases where difficulties were encountered in the categorization, another researcher was consulted, and final classification decided as consensus. More research is needed to evaluate the applicability and utilization of DRP classification systems for classifying and analyzing ME data of different types and levels of harm, particularly data for understanding severe MEs and their contributing factors.

6.2.3 FACILITATORS AND BARRIERS TO IMPLEMENTING MEDICATION SAFETY PRACTICES (III)

Most of the study participants were not from native English-speaking countries, while the free-text evaluation reports needed to be written in English, affecting the quality and contents of the reports. Especially challenging was to estimate the actual phase of the implementation process.

Only a few reports were received from hospitals that still need to start the implementation process, causing a loss of information about barriers affecting the start of the implementation. In addition to these hospitals, many did not send a report, most likely because they did not start the implementation.

The barriers to planning and implementing the practices were more common in the returned evaluation reports in comparison to the facilitators. However, several key facilitators were identified, essentially informing hospitals planning to implement the described safety practices or improving their existing ones.

The MSPs were seldom implemented completely according to the EUNetPas practice examples as the practices needed to be adapted to units, working cultures, and processes. This could have influenced the experienced facilitators and barriers. As this was a retrospective document analysis focusing on identifying general and practice-specific facilitators and barriers for MSP implementation, the real-life conditions and environments affecting the implementation of each practice were not investigated. This may be seen as influencing the external validity of the study.

6.3 PRACTICAL AND POLICY IMPLICATIONS (STUDIES I-III)

6.3.1 SEVERE MEDICATION ERRORS REPORTED TO HEALTH CARE SUPERVISORY AUTHORITY (I)

The information on MEs in Finland is dispersed in multiple data sources and there is a need to have a more coordinated and comprehensive picture of national medication safety. At least the supervisory authorities (Valvira, Regional State Administrative Agencies and Fimea) should have some shared information and overall view on MEs reported to them. In addition to need of shared information on MEs in Finland, it should be more clearly appointed which authority or organization (e.g., Finnish Centre for Client and Patient Safety) has the mandate and liability to guide and develop national medication safety improvement actions.

Especially the data of Valvira gives valuable national insight into severe MEs in Finland, and the content of this data is described in Study I. The data of Valvira is an essential part of national ME data and it should be utilized and shared nationally regular-based, not only as research data. The fear of litigation can prevent individual social and health care organizations to publish severe MEs. Thus, Valvira could have stronger role in national patient safety development with sharing the lessons learned in severe errors and publishing recommendations based on them as Finnish Safety Investigation Authority does. This would also be in concordance with the expectations of the patients and relatives that the same kind of error would not happen to any other patients.

This and a previous study (Linden-Lahti et al. 2009) reveal that geriatric patients are the most vulnerable patient group for severe harm caused by MEs. Severe MEs happen in all patient care settings, especially those taking care of geriatric patients, requiring safety interventions extensively in units, organizations, and national level. The complexity of especially severe MEs requires the approach of multi-interventions. As a recognized national medication safety challenge, preventing severe MEs, especially in geriatric care settings, should be one priority when defining future strategic goals for medication safety. As the national Safe Medication Management and Use Guideline will be updated in near future, the results of this study are available to be utilized in that work. From the international perspective, study revealed that the global medication safety challenges are present also in Finland (World Health Organization 2017).

According to this study, there has been many initiatives taken in organizations after severe ME. However, conducting sufficient RCAs and selecting effective medication safety practices according to those requires competence in organizational level. These competence and actions could be

promoted with e.g., Medication Safety Officers (American Society of Health-System Pharmacists 2019).

6.3.2 APPLICABILITY OF DRUG-RELATED PROBLEM (DRP) CLASSIFICATION SYSTEM FOR CLASSIFYING SEVERE MEDICATION ERRORS (II)

This study presented a novel classification system approach for especially severe MEs in terms of having more information on their causes. The aggregated DRP classification system developed by Basger et al. (2015) gives one more potential ME classification system to supplement existing ones. However, more applicability research is needed with different data for evaluation. Still, according to our study the DRP classification system could be utilized in further medication safety research that is aiming to describe error causes. In addition to analysis purposes, caused-based classification system could be beneficial to those authorities who investigate severe MEs (e.g., in Finland Valvira and OTKES) and organizations conducting root cause analysis. It gives a framework to widely identify potential causes for MEs and produce more information when medication safety development actions are defined.

DRP and ME classification systems are developed and updated as separate systems by different institutions. This study suggests that there is a need for international assessment if these classification systems could and should be congruent. If so, it could affect the taxonomies used in existing MERS and further recognizing error causes and preventing them.

6.3.3 FACILITATORS AND BARRIERS TO IMPLEMENTING MEDICATION SAFETY PRACTICES (III)

In the study, we recognized facilitators and barriers to implementing MSPs, and the results give valuable information for all units and organizations planning to implement MSP, especially those included in EUNetPas-project (European Network for Patient Safety 2010). The barriers identified in the study should be considered and prevented, if possible, in implementation projects. The facilitators are those components that should assist successful MSP implementation process. As the study revealed, MSPs can be benchmarked and transferred to other hospitals and even countries, but usually there is a need for practice adaptation to local systems and processes. Especially when implementing and retaining practices that requires considerable changes in work processes and flows, in which nine-month time frame may be tight.

If the MSP does not have the expected outcome on medication safety, one reason can be its unoptimized implementation process. According to this

study, before implementing the MSP, the following aspects should be considered:

- Has the real cause of the medication safety problem been recognized and proper MSP for the specific problem been chosen?
- Does the professionals and patient involved understand and commit on the need for the MSP?
- Is it recognized how the MSP would change the medication and other processes connected, and does it require any workflow or environmental changes, (IT-)systems or materials?
- Are there enough time and sufficient resources for planning, implementing, and conducting the practice?
- Is there a feedback system in place to support practice implementation?

This study gives valuable information about how the MSP should be chosen, implemented, and evaluated for future European-wide patient and medication safety projects.

6.4 FUTURE RESEARCH

Severe MEs, even not so common, are untenable burdens from the individual (patient and professional), public health and economic perspectives. Although severe MEs are seen as a priority in medication safety development internationally (World Health Organization 2017), the research on severe MEs is still limited. The literature for understanding typical medicines involved, most vulnerable patient groups, care settings and error types in severe MEs is most studied. Still, even after this study we need more research on how to learn from and prevent them. In Finland, Valvira has the national level data for this, and it should be utilized with other MERS and register-based data more intensively for ME research purposes.

Severe MEs are often complex error processes involving multiple contributing factors, professionals, and organizations. There is a need to understand these complex processes and the interactions of their components in more detail and discover which causes and contributing factors are the most critical ones to be targeted with interventions. A better understanding of these processes could also assist future research to take a more proactive approach to severe MEs. Furthermore, the utilization of AI has been piloted in analyzing patient safety incident reports (Härkänen et al. 2021) and further research employing these modern technologies could also help to analyze, describe, and understand complex severe MEs in different data. As introduced in the SEIPS model and in our study (I and II), severe errors often include multiple organizations and professionals (Carayon et al. 2020, see Chapter 2.2.1.3). There is a need for further studies on medication safety in the entire patient journey. Further research is also needed on the organizational development

actions after severe MEs to widen the learning opportunities nationally and internationally.

The present ME classification systems represent a target for further study and development. At least the most frequently used ME classification taxonomies (e.g., WHO and NCC MERP) seem to lack the ability to describe the causes and contributing factors at the level they are needed in preventing severe MEs (National Coordinating Council for Medication Error Reporting and Prevention 1998, World Health Organization 2020). There is a need to develop classification systems that produce enough information and enable describing complex errors as a process in the patient journey. In our study (II), we successfully piloted a caused-based DRP classification system on severe MEs and produced a more in-depth understanding of the causes in Valvira's data. As severe MEs are rare, the data used was also limited in number, and there is a need for more research with other data to confirm our findings. More research is needed on how DRP classification systems could be utilized in ME classification and analysis.

As stated previously, there is no updated understanding of the state of patient or medication safety in Europe. This kind of thorough evaluation should be done shortly. Compared to the US, where global awareness of medication and patient safety deficiencies have been initiated, the national coordination of the improvement work has been allocated to the non-profit organization ISMP. In Europe, the same mandate has, at least to some extent, been given to EMA, and there is a need to evaluate how successful strategy this has been, and which are the key improvements that would be needed in system-based medication safety work internationally. The need for updated information about the European stage in medication safety also relates to investigating if the medication safety practices in EUNetPas and PasQ-projects (especially medication reconciliation) are still implemented or even become a part of national medication safety guidelines. As there is more research on different kinds of medication safety interventions, many of which are in use in individual European countries, there is need to review the current state. There is also a need to have more overall research on the effectiveness and successful implementation of medication safety practices.

7 CONCLUSIONS

- MEs reported to a national health care supervisory authority are valuable and unique information sources of severe errors, and this data should be regarded as a part of national incident reporting and learning systems.

- High age remains a key risk factor for severe MEs. This may also be associated with a wide range of medications, including those not typically perceived as high-alert medications or having high-risk administration routes. Ensuring comprehensive medication safety of older and frail patients should be a primary focus of all care settings, emphasizing primary care and long-term care facilities.

- The aggregated DRP classification system with some modifications has potential for analyzing and describing MEs and their causes, especially severe MEs. This finding aligns with the definition framework used in this study, which defines that DRPs can be caused by MEs. Using a cause-based DRP classification system produces additional information essential for understanding why MEs happen and how to prevent such MEs in the future.

- Despite of being complex processes, the severe MEs have a potential to lead to the development of health care organizations' systems, processes, resources, and competencies. Additional methods to analyze and learn from the severe incidents are still needed.

- Medication safety practices are transferable across different organizations and countries. However, implementing medication safety practices in short-term international project is challenging, especially when changes in work processes are required. The key to successfully implementing an MSP is to select the right practice for the right medication safety risk in the right setting and with sufficient resources. The successful implementation requires a presence of a safety culture, including committed leadership and interdisciplinary cooperation. External support and involving pharmacists may facilitate the implementation of MSPs.

- When planning future European-wide patient safety projects like the former EUNetPas, focus should be on evidence-based MSPs with clear implementation and evaluation strategy.

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APPENDICES

Appendix 1. Medication safety practices selected for implementation in EuNetPaS project 2007-2010 (European Network for Patient Safety 2010). Descriptions are based on the information given by the country of origin, and they are in format that was used in project.

Practice and country of origin	Description of the practice
Practice 1: Bed dispensation (A) (Austria)	**Aim**: Reduces the risk of confusion: patients receiving wrong medication or dose; or possible intake by wrong patient. The right patient gets the right medication at the right time. **Description**: The healthcare professional preparing the medication is also administering it. Medications are administered per dose directly at the patient's bed. Mobile carts are used to bring a laptop and a box with the prescribed medications (in original packing) to the patients' rooms. The implementation of reference times for medication administration was a requirement. The physicians decided about the reference times per ward. **Evaluation:** An evaluation is done quarterly (per dose, per day) assess patients their medication at the right time and do they take them?
Practice 2: Bed dispensation (B) (Austria)	**Aim:** Reduces the risk of confusion: patients receiving wrong medication or dose; or possible intake by wrong patient. The right patient gets the right medication at the right time. **Description**: The same nurse, using a mobile cart, is responsible for the preparation, checking "right patient, right medicine," the administration, the supervision of the administration and then the documentation of the medication. This is done directly in the patient's location (in patient's room, or directly in front of the door of the room). The medications are taken out of the original packaging and put into the medicine cups. The medication is administered immediately and the documentation of the administration step follows shortly afterwards. Each administered medicine is signed off by the nurse, and then put into the patient register with the date, time, and name of the acting healthcare professional. Definite administration times have been set: in the morning, at noon, at dinnertime and at night. When these times are not kept, this results in a medication error entry.

Practice 3: Safety vest (Denmark)	**Aim:** To avoid difficulties experienced during the dosing of a medicine in wards because of disruptions (e.g., due to the location where dosing takes place and the circulation in the ward). **Description:** Disruptions are very stressful and increase the risk of medication errors. Errors are often not a reflection of the nurse's qualifications, but of the environment and working conditions. Consequently, the solution is to create more awareness of the need to be undisturbed while dosing medications. To minimize the noise level and the disturbance for the staff when dosing medicine, a (yellow) Safety Vest with "Do Not Disturb" written on the back is worn by the nurse dosing medications in the ward.
Practice 4: Medication reconciliation at admission and discharge (Denmark)	**Description:** A pharmacist, nurses and a physician in an acute care ward work together in a team to reconcile patients' medications at the patient admission and discharge. The team members look at the medication with different perspectives. They learn from each other and experience where the errors occur. A pharmacist visits the ward every day. The pharmacist reviews medical records at the time of admission and discharge to identify possible medication discrepancies. The physician is responsible for the possible medication changes based on the review. New nurses and physicians are offered information and education every month about medication reconciliation by the pharmacist and a nurse who is a specialist in medical records. **Evaluation:** A sample of medical records is audited each month. The results of the audit is presented to the physicians and the nurses during a monthly ward meeting.
Practice 5: Discharge medication list for patients (Sweden)	**Aim:** To reduce medication safety risks related to limited patient knowledge on their medication, indication of the medication and on time. **Description:** The doctor writes a discharge medication list for the patient, in accordance with the patient's medical record. The medication discharge list comprises information on the date of issue, what medication the patient is taking, indication and at which time the medicine should be taken. At the patient discharge, the health professional goes through orally the discharge medication list with the patient. To be sure that this was followed through, a tick box secures that the patient really got the information. The patient should be reminded to show healthcare professionals this list when visiting any healthcare setting after the hospital discharge.
Practice 6: Medication reconciliation at discharge (Sweden)	**Description:** Written discharge information including a Discharge Medication Report is mandatory to be given to a patient at hospital discharge. The information in the report is structured and easy to understand. A copy of the report is sent with the patient's consent to the general practitioner, community pharmacists or other healthcare professionals participating the medication treatment of the patient on the day of the discharge. The sent information contains the medication report, a summary of relevant medication changes (due to allergies, resistances etc.) actively performed during the hospital stay (what and why). The Medication Report is the result of the reconciliation process between healthcare professionals.

Practice 7: Sleep card (Sweden)	**Aim**: Reducing medication safety risks due to unnecessary treatment of patients by sleeping pills. **Description:** A team consisting of representatives from the unit and the pharmacist has designed a small plastic "leaflet" (the "sleep card"). On the "sleep card", different tips are given on measures to help the patient sleep better. The care also includes information on treatment options (medical and non-medical) and which sleeping medication is appropriate for elderly patients. The "sleep card" is carried around by healthcare professionals.

Appendix 2. Evaluation form questions that were slightly adapted for implementation of each medication safety practice.

Before the implementation

- Can you describe the situation or problem in medication safety you wanted to address by implementing the good practice you have chosen?
- Could you give some indications on the baseline situation in medication s afety in your unit?

During the implementation

- Which procedure was followed to identify/select where good practice will take place?
- Who (role and position in the organisation) and/or which committee has been in charge at all steps of implementation?
- Was the time appropriate, i.e., was there enough time to put the practice into place?
- Have you used the example given by the good practice?
- Have you used any existing elements in the hospital?
- Have you created your own initiative? If yes, why? What was needed to adapt?
- What is the process and who were the professionals involved?
- What have been the specific actions to reach each target group? (e.g.: intranet, newsletter, staff meetings)
- Involved persons in this meetings
- Which activities and by whom have been taken to implement the good practice?
- How did you organise it to implement it into the daily routine?

After the implementation

- Can you describe the outcome situation after the implementation period?
- On the basis of your experience do you consider that this good practice would be transferable in other units in the hospital? In other hospitals in your country?
- Have you been using evaluation tools already available in the hospital to evaluate the impact (even subjective) of the initiative?
    - If yes, have you noticed any impact?
- Have you been using evaluation tools already available in the hospital to evaluate the impact even subjective) of the initiative?
- In case the initiative was done only in one (some) unit(s), will the hospital expand the initiative to other units?

* Ireland had modified the evaluation form to include a question: “Did you encounter any issues/difficulties/challenges while piloting this good practice. If yes, describe these”.