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Learning from medication errors and developing a national knowledge source for chemotherapy regimens

Fyhr, Ann-Sofie

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ANNSOFIE FYHR
DEPARTMENT OF DESIGN SCIENCES | FACULTY OF ENGINEERING | LUND UNIVERSITY 2022

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Abstract

The basics in cancer treatment are surgery, radiation therapy, and treatment with cancer drugs, often combined. Chemotherapy regimens that define the drugs used, the dosage, the frequency and duration of drug administration, have been developed and used for different cancer diagnoses. Several healthcare professionals are involved in the treatment: the physician prescribing the drugs, the pharmacist preparing or dispensing the drugs, and finally, the nurse or the patient administering the drugs. Chemotherapy errors that can occur during the treatment represent potential risks for severe patient harm. The aims of this PhD thesis were to increase knowledge about serious medication errors (MEs) in chemotherapy and to develop, implement, and evaluate a national knowledge source for chemotherapy regimens (an e-library) that can support healthcare professionals and mitigate patient safety risks.

The characteristics of MEs with parenteral cytotoxic drugs were identified in a retrospective qualitative analysis of 60 cases reported to the Swedish national incident reporting systems 1996-2008. The drugs most involved were fluorouracil, carboplatin, and cytarabine. The largest ME categories included too high doses originating from prescribing, and the wrong drug used during preparation or prescription. Twenty-five of the 60 MEs occurred when physicians were prescribing. Another 25 occurred within the pharmacies. The remaining 10 MEs occurred when the nurses prepared or administered the drug. All the drugs with MEs that occurred during prescription were delivered to the patients. The consequences were especially severe in these cases, including death and harm to the patients. The general failure types (GFTs) and active failures were identified in the 60 cases to better understand why these errors happened. The most frequently encountered GFTs were in *Defences* (e.g., missed double checking of the patient's or the drug's identity) and *Procedures* (e.g., routines that were lacking or insufficient). Working conditions were a common denominator, often underlying the MEs. Examples were high workloads, and low staffing.

A national e-library for chemotherapy regimens with standardised nomenclature and content was developed in close co-operation with healthcare professionals in an iterative process within the Swedish Regional Cancer Centres. The national e-library is a knowledge source containing updated regimens and other supportive information based on the latest evidence, available at: https://kunskapsbanken.cancercentrum.se. To ensure that the design and content complied with the users' needs, the usage and usability of the national e-library were evaluated using mixed methods. Statistics from the website show an average of just over 2,500 visits and 870 unique visitors per month. The web survey, with 292 answers, showed that the visitors were mainly physicians and nurses. Almost 80% searched for regimens, and 90% found what they were looking for and were satisfied with their visit. An expert evaluation showed that the e-library follows many existing design principles. Qualitative interviews with 4 nurses, 3 physicians, and 3 pharmacists revealed various ways to use the information in the regimens. Users have different needs depending on their profession and their workplace, and the e-library can support these different needs. The national e-library was used in the intended way, and the users were able to interact without any problems.

The research in this thesis shows that it is of utmost importance to minimise the potential for errors in the prescribing stage and that a common denominator behind the errors often was working conditions. Today's Swedish national e-library for chemotherapy regimens contains information based on the latest evidence, is embedded in a national quality system, and contributes to organisational and national learning, ultimately supporting healthcare professionals in managing chemotherapy risks.

Key words Chemotherapy, chemotherapy regimens, medication errors, patient safety, e-library, standardisation, user evaluation, usability

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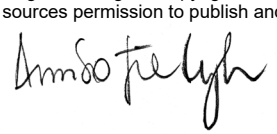
Signature  Date 2022-03-16

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Safety is a continuing journey, not a final destination
Lucian Leape

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Abstract

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Svensk sammanfattning

Grunderna i cancerbehandling är kirurgi, strålterapi och behandling med cancerläkemedel, ofta i kombination med varandra. Regimer med cancerläkemedel som definierar det eller de läkemedel som används, deras doser, hur ofta och hur länge de ska ges, har utvecklats och används för olika cancerdiagnoser. Flera professioner inom sjukvården är involverade i behandlingen: läkaren som ordinerar läkemedlen, farmaceuten som bereder eller delar ut läkemedlen och slutligen sjuksköterskan eller patienten som administrerar läkemedlen. Fel som kan uppstå vid behandling med cancerläkemedel utgör en potentiell risk för allvarliga patientskador. Syftet med denna doktorsavhandling har varit att öka kunskapen om allvarliga medicineringsfel med cancerläkemedel och att utveckla, implementera och utvärdera en nationell kunskapskälla för läkemedelsregimer (ett regimbibliotek) som kan stödja sjukvårdspersonalen och mildra patientsäkerhetsriskerna.

Egenskaperna hos medicineringsfel med parenterala cytotoxiska läkemedel identifierades i en retrospektiv kvalitativ analys av 60 fall som rapporterats till de svenska nationella rapporteringssystemen för allvarliga felhändelser under 1996–2008. De läkemedel som förekom oftast var fluorouracil, karboplatin och cytarabin. De vanligaste typerna av medicineringsfel var för höga doser som ordinerats och fel läkemedel som användes vid beredning eller ordination. Tjugofem av de 60 medicineringsfelen inträffade vid läkarens ordination. Ytterligare 25 av de 60 inträffade vid beredning på apoteken, och de återstående 10 inträffade när sjuksköterskorna beredde eller administrerade läkemedel. Alla medicineringsfelen som skedde vid ordination nådde fram till patienterna och konsekvenserna blev där särskilt allvarliga, inklusive dödsfall och skador. De bakomliggande orsakerna och de aktiva felen identifierades i de 60 fallen för att bättre förstå varför dessa medicineringsfel inträffade. De vanligast förekommande bakomliggande orsakerna gällde *Barriärer* (t. ex. missades att dubbelkontrollera patientens eller läkemedlets identitet) och *Procedurer* (t. ex. rutiner som saknades eller var otillräckliga). Arbetsförhållandena var en gemensam nämnare som ofta låg till grund för de bakomliggande orsakerna. Exempel på detta var hög arbetsbelastning och låg bemanning.

Ett Nationellt regimbibliotek för cancerläkemedel med standardiserad nomenklatur och innehåll har utvecklats inom de Regionala Cancercentrumen i samverkan. Utvecklingen har skett i nära samarbete med professionerna inom sjukvården i en iterativ process. Det Nationella regimbiblioteket är en kunskapskälla som innehåller

uppdaterade regimer och annan stödjande information baserat på senaste evidens och finns tillgängligt via https://kunskapsbanken.cancercentrum.se. För att säkerställa att utformningen och innehållet överensstämmer med användarnas behov utvärderades användningen och användbarheten av det Nationella regimbiblioteket med hjälp av olika metoder. Statistik från webbplatsen visade att den i genomsnitt har drygt 2 500 besök och 870 unika besökare per månad. En webbenkät med 292 svar visade att besökarna främst var läkare och sjuksköterskor. Nästan 80 % sökte efter regimer, och 90 % hittade vad de sökte och var nöjda med sitt besök. En expertutvärdering visade att regimbiblioteket följer många befintliga designprinciper. Kvalitativa intervjuer med 4 sjuksköterskor, 3 läkare och 3 farmaceuter visade att informationen i regimerna används på olika sätt. Användarna har olika behov beroende på profession och arbetsplats och regimbiblioteket kan stödja deras olika behov. Det Nationella regimbiblioteket används på det avsedda sättet och användarna kan interagera utan problem.

Forskningen i denna avhandling visar att det är av yttersta vikt att minimera risken för fel vid ordination av cancerläkemedel och att en gemensam nämnare bakom felen ofta var arbetsförhållandena. Dagens Nationella regimbibliotek för cancerläkemedel innehåller information som är baserad på senaste evidens, ingår i ett nationellt kvalitetssystem och bidrar till organisatoriskt och nationellt lärande, för att kunna stödja sjukvårdspersonalen att hantera patientsäkerhetsrisker vid behandling med cancerläkemedel.

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Appended papers

This thesis is based on the following papers, referred to as Papers I-IV:

I. AnnSofie Fyhr & Roland Akselsson (2012). **Characteristics of medication errors with parenteral cytotoxic drugs**. *European Journal of Cancer Care. 2012 Sep;21(5):606-13. DOI: 10.1111/j.1365-2354.2012.01331.x.*
Fyhr formulated the objectives of the study. The study was conceived and designed by both authors. Fyhr performed the data collection, as well as most of the data analysis. Both authors took part in reflecting on the results and writing the paper, however Fyhr did the main writing.

II. AnnSofie Fyhr, Sven Ternov & Åsa Ek (2017). **From a reactive to a proactive safety approach. Analysis of medication errors in chemotherapy using general failure types**. *European Journal of Cancer Care. 2017 Jan;26(1):e12348. doi: 10.1111/ecc.12348.*
Generally the study was conceived by all authors. However, Fyhr formulated the objectives of the study. The idea to analysis general failure types came from Ternov. Fyhr performed the data collection, and together with Ternov most of the data analysis. All authors took part in reflecting on the results and writing the paper, however Fyhr did the main writing.

III. AnnSofie Fyhr, Jonas Borell, Mats Jerkeman & Åsa Ek (2020). **National e-library for standardized chemotherapy regimens**. *Acta Oncologica. 2020 Sep;59(9):1079-1083. doi: 10.1080/0284186X.2020.1764097.*
The development of a national e-library for chemotherapy regimens was performed within the Swedish Regional Cancer Centres with Fyhr as the project leader. Fyhr formulated the objectives of the study and identified the parts of the project documentation that were relevant to the paper and discussed this with the other authors. The paper was conceived and designed by all authors. All took part in writing the paper, however Fyhr did the main writing.

IV. AnnSofie Fyhr, Johanna Persson & Åsa Ek. **Usage and usability of a national e-library for chemotherapy regimens: a mixed method study**. *JMIR Human Factors*, *2022 Feb 17;9(1):e33651. doi: 10.2196/33651.*
Fyhr formulated the objectives of the study. The study was conceived and designed by all authors. Fyhr performed the data collection, as well as most of the data analysis. All took part in reflecting on results and writing the paper, however Fyhr did the main writing.

Other selected publications by the author

Johanna Persson, AnnSofie Fyhr & Åsa Ek. 2021. User evaluation of a national e-library for standardized chemotherapy regimens. *Proceedings of the 21st Congress of the International Ergonomics Association (IEA 2021):* Volume IV: Healthcare and Healthy Work. Black, N. L., Neumann, P. & Noy, I. (eds.). Springer, Vol. IV. p. 175-181 (Lecture Notes in Networks and Systems; vol. 222).

AnnSofie Fyhr & Anne Hiselius. 2013. Risky medicines management in healthcare. *In*: Synnöve Ödegård (ed.) *Patient safety: theory and practice*.: Liber. [In Swedish.]

AnnSofie Fyhr & Roland Akselsson. 2011. Incidents involving concentrated potassium and sodium solutions. Analysis and lessons learned from reported cases. *Läkartidningen*, 108(16-17):923-7. [In Swedish.]

AnnSofie Fyhr & Anne Hiselius. 2007. Risky medicines management in healthcare. *In*: Synnöve Ödegård (ed.) *In the name of justice. Responsibility, liability and safety in healthcare*.: Liber. [In Swedish.]

AnnSofie Fyhr & Eva Sjökvist Saers. 2007. Young woman died from vincristine administered spinal. Vinca alkaloids should only be given as intravenous infusion via minibag. *Läkartidningen*, 104(36):2529. [In Swedish.]

AnnSofie Fyhr, Mats Jerkeman & Ylva Nilsson. 2006. Pegaspargase near given intrathecally by mistake. Procedures are changed to prevent a recurrence. *Läkartidningen*,103(4):219. [In Swedish.]

AnnSofie Fyhr. 2005. Lessons learned from others' experiences of failure in peroral methotrexate therapy. *Läkartidningen,* 102(14):1052. [In Swedish.]

Nomenclature

The literature and studies in the thesis cover a long time period over which the definitions and meanings of some words have changed. Some of the terms that are used may need to be explained. This table presents a list of such terms and expressions used in the thesis with their definitions or explanations.

Anatomical Therapeutic Chemical code (ATC code)	A unique code assigned to a medicine according to the organ or system it works on and how it works. The classification system is maintained by the World Health Organisation (WHO).
Cancer drugs	Cytotoxic drugs, chemotherapeutic agents.
Chemotherapy	Treatment that uses drugs to stop the growth of cancer cells. Today, there are also other drugs that are used to treat cancer in different ways, including targeted therapy, hormone therapy, and immunotherapy.
Chemotherapy regimen	The drug or drugs to be used, the dosage, the frequency, and the duration of drug administration for the treatment of a given cancer diagnosis are defined.
Computerised physician order entry (CPOE)	A process by which a medical professional enters and sends medication orders and treatment instructions electronically via a computer application instead of on paper charts. The P can also stand for “provider” or “practitioner”.
Double-checking	An independent check by two practitioners of a procedure, for example, the calculation of the drug volume to be used.
Drug	Medicine or medication.
Error	Failure, mistake. An error is an action which is inaccurate or incorrect.
Incident	Any deviation from usual medical care that causes an injury to the patient or poses a risk of harm.
Incident report	Case report. Healthcare staff report near misses and adverse events in an incident reporting system.
Intrathecal	Describes the fluid-filled space between the thin layers of tissue that cover the brain and spinal cord, containing cerebrospinal fluid. Cancer drugs can be injected into the fluid, or a sample of the fluid can be removed for testing.
Lex Maria Act	Legislation on injuries in healthcare. The name Lex Maria comes from an incident in 1936 when four patients at Maria Hospital in Stockholm died as a result of malpractice when they were injected with disinfectant instead of anaesthetic.
Medical error	A preventable adverse effect of medical care.
Narrow therapeutic index	Drugs with little difference between toxic and therapeutic doses.
Parenteral administration	Ways to administer drugs without passing the intestine, examples are infusions, injection, and ointment.
Physician	Medical doctor.
Regions	County councils. Swedish administrative level responsible for healthcare.
Summary of Product Characteristics (SPC)	Explains how to use and prescribe a drug. The information is written by pharmaceutical companies based on their research.

Abbreviations

AE	Adverse event
ADE	Adverse drug event
ADR	Adverse drug reaction
ATC code	Anatomical Therapeutic Chemical code
BSA	Body surface area
CPOE	Computerised physician order entry
DRP	Drug related problem
EMA	European Medicines Agency
FDA	Food and Drug Administration, USA
FMEA	Failure modes and effect analysis
FTA	Fault tree analysis
GFT	General failure types
HAZOP	Hazard and operability
HIT	Health information technology
HSAN	Swedish Medical Responsibility Board (Hälso- och sjukvårdens ansvarsnämnd)
IOM	Institute of Medicine, USA
ISMP	Institute for Safe Medication Practices, USA
LASA	Look-alike, sound-alike
ME	Medication error
NAT	Normal Accident Theory
NCCC Guideline	National Clinical Cancer Care Guideline
NCC MERP	The USA National Coordinating Council for Medication Error Reporting and Prevention
PDSA	Plan-Do-Study-Act
RCCs	Regional Cancer Centres
SPC	Summary of Product Characteristics
STAMP	System theoretic accident model and processes
XML	Extensible Markup Language

Thesis background

For a better understanding of this thesis, a short historical background, of medication errors in chemotherapy together with a brief description of myself, the author, will be given.

The Betsy Lehman case from 1994 has been described as a turning point for medication errors in chemotherapy because of the unprecedented publicity (Cohen et al., 1996). She was a healthcare reporter in the USA who died of a drug overdose (cyclophosphamide) during treatment of breast cancer. The total dose for four days was misinterpreted as daily doses, which meant daily doses that were four times too high. Medication errors (MEs) in chemotherapy also received media attention in Sweden in the mid-1990s. Examples are a child's death due to the unintended administration of vincristine intrathecally. Another child's death was due to the use of the total doses for 3-4 days as doses per day instead (the same type of error as in the Betsy Lehman case) and two women who received a too high dose of carboplatin due to a calculation error.

I have a Master of Science in Pharmacy from Uppsala University and am a registered pharmacist. From the beginning of the 1990s until 2010, I was the manager of and responsible for the quality of the chemotherapy preparation at the hospital pharmacy in Lund, Sweden. In the 1990s, all documentation was handwritten and calculations of the doses by the physicians were done by hand. Facts about the regimens and drugs were collected in a textbook, the *Chemotherapy Manual* also called *The Silver Bible* (Cavallin-Ståhl and Seiving, 1993), used by physicians, nurses, and pharmacists. The hospital pharmacists could see ambiguous or incorrect prescriptions by the physicians. The physician was then contacted, and the dose was corrected. Errors were also made by us pharmacists during preparation, often discovered by the nurses administrating the drugs. Double-checking was used by the pharmacy but sometimes the errors were not detected anyway. Among us pharmacists the reoccurring question all the time was, "Why do all these errors occur and what can be done to stop them?"

The *Disturbance Effect Barrier Analysis* (DEB analysis), a proactive risk analysis, of the process of treating patients with chemotherapy (Ternov, Doctoral thesis, 2011) started to be carried out after a tragic event due to a MEs in chemotherapy at the University Hospital in Lund, Sweden. The conclusion of the analysis was that: "'Treatment of patients with cytotoxic drugs', is a process which involves great risks

and tiny margins for error mitigation. Overall, the safety barriers on the ward are weak or non-existent." (Ternov, Doctoral thesis, 2011)[1].

Taking part in the risk analysis was my first contact with Reason's model of organisational accidents and with the Department of Design Sciences, Faculty of Engineering LTH, Lund University. A new world of knowledge had been opened and I wanted to learn more. With my new knowledge on human factors, theories about how errors occur and what can be done to reduce them, I have lectured, written book chapters and debate articles, and above all, tried to apply the knowledge in daily work. At the same time, I have carried out research, which has now resulted in this thesis work.

[1] Quote from Paper IV in Ternov's thesis.

Introduction

In Sweden, with its 10 million inhabitants, nearly 66 000 were diagnosed with a malignant tumour in 2019 (Khan et al., 2020). The most common form of cancer among women is breast cancer and among men prostate cancer. Survival is increasing for several cancers because research has progressed. 72% of women and 74% of men are expected to live 10 years after being diagnosed with cancer (Cancerfonden, 2021). The basics in cancer treatment are surgery, radiation therapy, and treatment with cancer drugs, often in combination with each other. In recent years, many new cancer drugs have been approved by the European Medicines Agency (EMA) and they have led to great success in cancer treatment (European Medicines Agency, 2020). In the last decade, the number of cancer drugs (Anatomical Therapeutic Chemical code [ATC code L01]) has increased from about 50 to more than 150. About two-thirds of these new drugs are tablets and intended to be taken by the patient at home. Many of the treatments have been moved from inpatient care to either outpatient care or home treatment for the past 20 years.

To handle drug treatments chemotherapy regimens have been developed and used for different cancer diagnoses. A chemotherapy regimen defines the drug or drugs to be used, the dosage, and the frequency and duration of drug administration. For successful and safe treatment, it is also necessary to know the following: how to administer the drugs, what supportive drugs are needed, what precautions to take, and the checks required. There is also a need for relevant pharmaceutical (e.g., how to prepare, shelf-life after preparation) and medical (e.g., adverse drug reactions) information. In Sweden about 700 different regimens are in use, one of them is presented in Figure 1. Several healthcare professionals are involved in the chemotherapy process: the physician prescribing the drugs, the pharmacists preparing or dispensing the drugs, and finally the nurse or the patient administering the drugs.

A number of crucial events in relation to chemotherapy have occurred both internationally and nationally following the 1994 Betsy Lehman case. The timeline in Figure 2 shows the events in relation to the chemotherapy process as well as this thesis. One of the first events relate to the Institute of Medicine (IOM)[2], USA, which was established in 1970 by the National Academy of Sciences to provide the nation with unbiased, evidence-based, and authoritative information and advice concerning

[2] The IOM's name was changed to the National Academy of Medicine (NAM) in 2015.

health. In 2000 the IOM published their report, *To Err is Human* (Institute of Medicine. Committee on Quality of Health Care in America, 2000). The report highlighted the high numbers of deaths due to preventable medical mistakes and MEs. It suggested that the focus must shift from blaming individuals for past errors to preventing future errors by designing and building safety into the healthcare system. With inspiration from other high-risk industries such as aviation, recommendations were given. Among them were identifying and learning from errors through an immediate and mandatory reporting system. To be able to understand what countermeasures are needed to avoid errors, we need to know where, how, and why in the process the errors occur. Thus, organisational learning is needed. Other measures recommended in the report were to use well-known design principles, for example, standardisation and simplification. Examples in the report of standardisation are the use of protocols for chemotherapy and simplification by reducing the number of dose strengths of a drug. Cohen states in his book, *Medication errors* (2007) that the response to the IOM report made medical errors a leading public health issue and laid the groundwork for improvements in patient safety in the USA. The report also received a great deal of international attention and the first national patient safety conference in Sweden was held in 2003 (Figure 2).

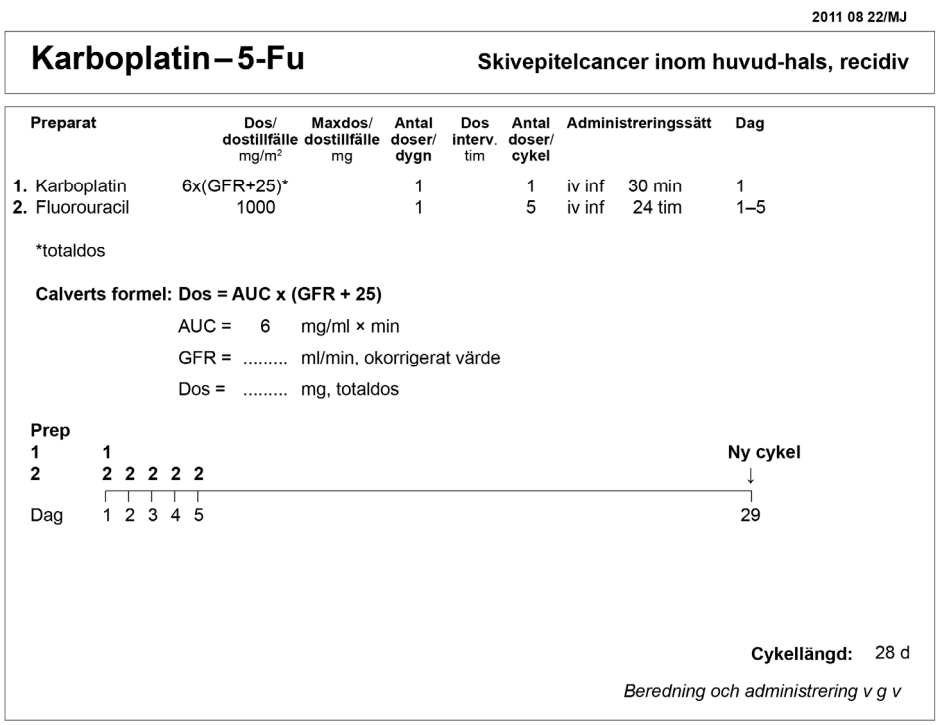

Figure 1. Example of the Karboplatin-5-FU regimen (incomplete) in the *Chemotherapy Manual* (in Swedish). The figure shows which drugs to use, their doses, how often and for what days, and when to give a new course of treatment (a new cycle). It also shows how the drugs should be administered and at what time.

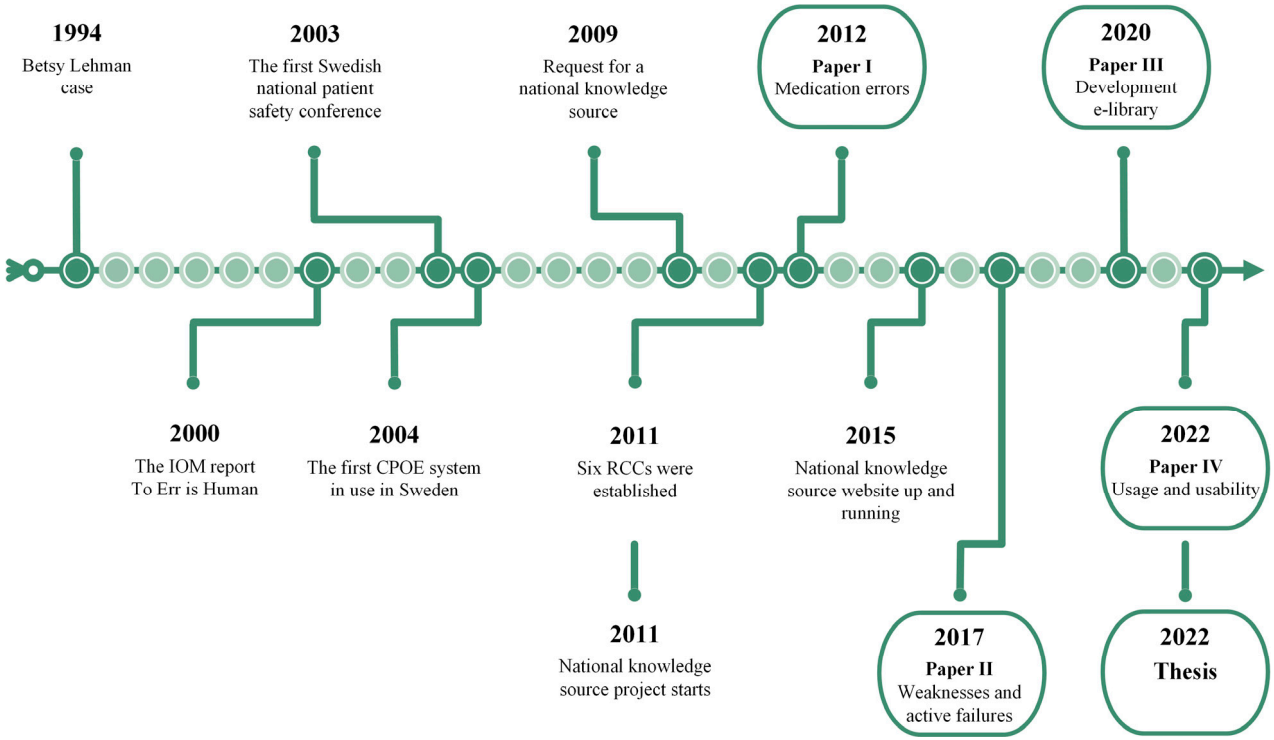

Figure 2. A timeline showing important events related to the chemotherapy process and this thesis. The boxes show when the papers included in the thesis were published.

Chemotherapy is highly beneficial for the patient, but MEs with these drugs represent a potentially serious risk of patient harm (Weingart et al., 2018, Schwappach and Wernli, 2010). A review study (Weingart et al., 2018) found a rate of chemotherapy errors of about one to four per 1000 orders, affecting 1-3% of adult and paediatric oncology patients, occurring at all stages of the medication use process. Oral chemotherapy use is a particular area of growing risk (Schwappach and Wernli, 2010, Weingart et al., 2018). Many regimens are toxic, with narrow therapeutic indices (little difference between toxic and therapeutic doses); regimens might include novel drugs or combinations and require multiple dose adjustments and monitoring of laboratory parameters. Finally, care is delivered over a long time by teams of healthcare professionals that may work in different clinical settings (Schwappach and Wernli, 2010, Weingart et al., 2018). Cancer drugs, given as tablets, injections, or infusions, are included in the list of *High Alert Medications* presented by the Institute for Safe Medication Practices (ISMP), USA (2018). High-alert medications are drugs that bear a heightened risk of causing significant patient harm when they are used in error (Institute for Safe Medication Practice (ISMP), 2018). The highlighted risk for patient harm emphasises the need for better knowledge about these serious MEs, such as how and why they occur. We need to learn from them so that we can reduce or prevent future occurrences.

The prescribing stage appears to be associated with more adverse outcomes. Therefore, the use of computerised physician order entry (CPOE) is recommended (Kullberg et al., 2013, Rahimi et al., 2019). Since 2004, different CPOE systems for chemotherapy have been introduced in Sweden (Figure 2). Today, there are three different commercial CPOE systems in use in Sweden, but there are still some clinics that use handwritten orders and documentation. The introduction of CPOE systems has reduced the number of prescribing errors (Voeffray et al., 2006, Meisenberg et al., 2014, Bubalo et al., 2014), but there is a need for further improvements in this stage of the medication use process. There needs to be a source of common knowledge that supports organisations using a CPOE system with updated information on the regimens.

There are many autonomous oncology clinics in Sweden. This has resulted in the same chemotherapy treatments occurring under different names and with different dosages and ways to administer the treatment, causing uncertainty and risks for mix-ups. This could be a risk, for example, when patients are treated at different hospitals. There is a need for strategies to overcome these uncertainties and risks, as well as a need for tools that support healthcare staff in performing their work efficiently and safely. One such tool, a national knowledge source for chemotherapy regimens, was requested by the heads of oncology clinics in 2009 (like the *Chemotherapy Manual* but a national, continuously updated, and web-based tool instead) (Figure 2).

The Swedish government initiated an investigation of a national cancer strategy that was presented in 2009: *A National Cancer Strategy for the Future* (Wigzell et al., 2009). Among the proposals in the report was the development of Regional Cancer Centres (RCCs). In 2011, six RCCs covering the whole country were established with an overall goal to contribute to more equal, accessible, and patient-focused cancer care. Among the development areas described in the national cancer strategy, were to work with knowledge-based healthcare, cohesive and efficient care processes, prevention and early detection, and rehabilitation. Knowledge-based healthcare comprises work with the National Clinical Cancer Care Guidelines (NCCC Guidelines), National Quality Registers, and locally with the improvement and development of care processes at hospitals to ensure the best and safest care for patients (Confederation of Regional Cancer Centres in Sweden, 2020). One of the early projects started by the RCCs in 2011 was to develop a national knowledge source for regimens (a national e-library) (Figure 2). The purpose was to standardise nomenclature and content in chemotherapy regimens, to facilitate the exchange of information between hospitals, CPOE systems, and patients, and to provide a support for healthcare professionals in their work related to chemotherapy regimens. The thesis author was the project leader and the driving force in the development of the national e-library. Along the way, research work was conducted to support the development process (Figure 2).

The introduction and use of technology is a general and often successful way to prevent errors and improve work processes. But all technology can introduce new errors, even when its sole purpose is to prevent errors (Institute of Medicine. Committee on Quality of Health Care in America, 2000). The few studies that examined the impact of health information technology (HIT) on clinical outcomes in oncology have shown mixed results (Weingart et al., 2018). They give examples of reduced error rates but also of newly introduced errors (Weingart et al., 2018). To produce a useful and easy-to-use HIT, some fundamental principles are recommended. They include an explicit understanding of the users and tasks, the involvement of the users throughout design and development, an iterative design process, and user evaluation (Gould and Lewis, 1985, Giacomin, 2014). To gain the benefits of HIT there are several key principles of implementation and continued development that must be considered, such as engagement of interprofessional stakeholders, optimisation of the workflow before implementation, standardisation, stepwise implementation, and commitment to ongoing quality improvement (Chung et al., 2018, Shulman et al., 2008, Hoffman et al., 2011, Gaguski and Nguyen, 2016, Goldspiel et al., 2015). All these principles have served as inspiration during the development process of the national knowledge source and are important for the evaluation of success, usage and usability investigated through the research process.

Aim of the thesis

The chemotherapy process is inherently complex with people from several professions working together in treating patients. Chemotherapy errors that can occur in the process represent potential risks for severe patient harm. The research presented in this thesis wants to contribute to and support the continuous improvement of chemotherapy processes. The general aims of this thesis research were to learn from MEs in the chemotherapy process, and to develop a national knowledge source for chemotherapy regimens (an e-library) that can support healthcare professionals and mitigate these types of patient safety risks in a Swedish context.

Research aims

The aims of the research presented in this thesis were:

I. To increase knowledge about serious medication errors in the chemotherapy process.

A better understanding of the characteristics of these errors enables a better understanding of the causes contributing to the errors, such as organisational weaknesses. It also enables proposals for improvements to prevent such errors in the future. This knowledge can also guide the development of the content in an e-library for reducing some types of MEs.

II. To develop, implement, and evaluate a national knowledge source for chemotherapy regimens for proactive risk reduction in the chemotherapy process.

In a practical chemotherapy context, such a tool can support the professionals involved in the process when performing their work. It is vital to gain knowledge of the practical characteristics of the tool, and if the professionals can utilise it as intended. In a national knowledge source for chemotherapy regimens, information about regimens can be continuously updated and contribute to organisational learning.

Objectives

The more specific objectives were:

To identify the characteristics of serious medication errors involving parenteral cytotoxic drugs. This involves characteristics such as the drugs involved, the types of errors made, where in the medication use process errors take place, how errors were discovered, and what the consequences were for the patients (Paper I).

To investigate organisational weaknesses and active failures underlying medication errors. Do this by applying a tool to identify general failure types (GFTs) modified to fit the process of managing cytotoxic drugs in healthcare (Paper II).

To describe the development process of a national standardised knowledge source for chemotherapy regimens: an e-library. Describe the development process and present an overview of the e-library's content, as well as its embeddedness in the national quality system of cancer care (Paper III).

To evaluate the usage and usability of the national e-library. Do this by applying a mixed qualitative and quantitative methodology (Paper IV).

The chemotherapy process

Chemotherapy is administered in a wide variety of cancer therapies, both for curative and palliative care, and is used in the treatment of small children on up to elderly people. Cancer drugs can be given as tablets, injections, or infusions. They can be given as a single drug every day or at other intervals. Combinations of drugs are also used in complex regimens over several consecutive days repeated after 2 to 3 weeks or at other intervals. For most of the drugs, the dose is based on body surface area or other patient-specific factors (e.g., weight or renal function) or as standard doses. Some cancer drugs have a narrow therapeutic index (little difference between toxic and therapeutic doses), for instance, paclitaxel and vincristine. At the same time, for some of these drugs such as cytarabine, dosages vary widely depending on the condition being treated, how the drug is used, and the use of supportive therapy.

Based on the patient's diagnosis and various examinations, the physician decides which chemotherapy regimen to use. If the clinic uses a CPOE system, all the relevant regimens are available there. The system supports prescription, administration, and monitoring. Dispensing/preparation is most often done by pharmacists, either at a community pharmacy (for tablets) or a hospital pharmacy (for infusions). They have separate support systems. The medication use process for chemotherapy can be outlined as in Figure 3.

Medications are of considerable help if healthcare providers can administer them to patients safely and appropriately. Yet, healthcare providers are humans and as such, fallible. Drug treatment is a process involving a team of professionals: physicians, nurses, pharmacists, along with the patient. There needs to be good communication, both written and verbal, about the medications in the team and between the team and the patient. The process contains many subprocesses and in every step, there is a possibility for error: drugs can be mixed-up, doses can be miscalculated, the wrong strengths of drugs can be chosen, preparations can be erroneous, and patients can be mixed-up (Institute of Medicine. Committee on Quality of Health Care in America, 2000). A commonly used expression to get this process right is: "the "five rights" of medication use: the right patient, drug, time, dose, route" (Institute for Safe Medication Practice (ISMP), 1999). But as what was pointed out eight years later, "The five rights are not a behavioural model for achieving medication safety, but goals for which organizations must accept responsibility and design failsafe ways that they can be achieved" (Institute for Safe Medication Practices (ISMP), 2007).

In chemotherapy, with all its different regimens, there needs to be a national knowledge source supporting organisations using CPOE systems, providing updated information on the regimens. No such regimens on the national level had previously been developed in Sweden. This led to the need for a national e-library that has since been developed and is presented in this thesis. Not many e-libraries exist for chemotherapy regimens. Other e-libraries, such as the Health Service Executive of Ireland (Health Service Executive Ireland), the Comprehensive Cancer Network® in the USA (National Comprehensive Cancer Network USA), and a haematology oncology Wiki (HemOnc.org, Warner et al., 2015), similarly describe the regimens.

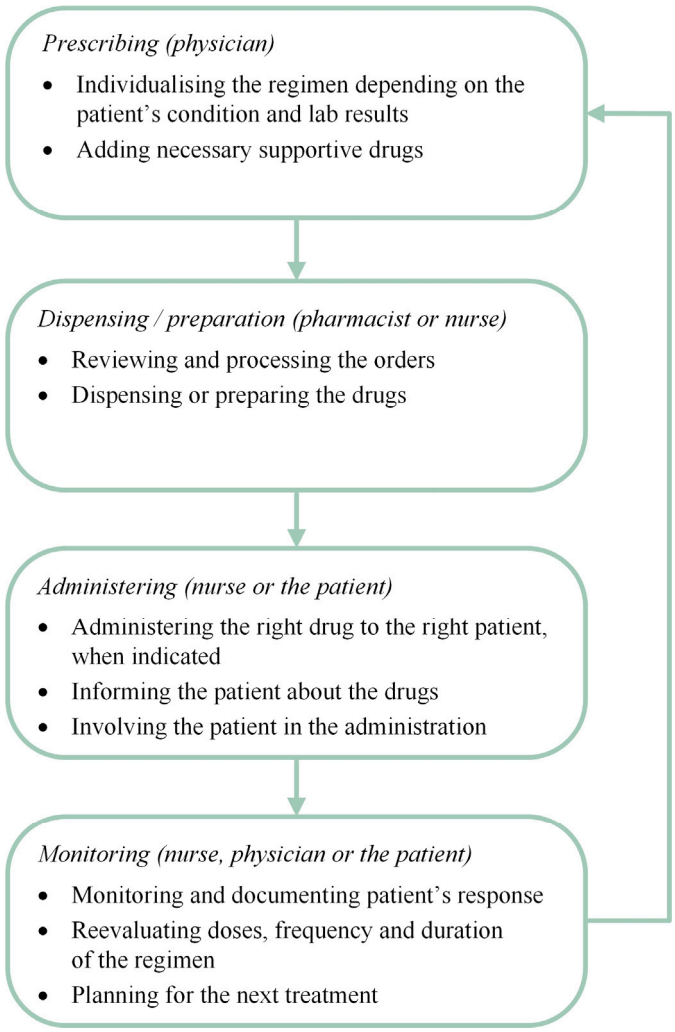

Figure 3. The chemotherapy medication use process. The process is iterative, and the patient returns for the next treatment according to the regimen protocol.

Theoretical framework

This chapter presents the theoretical contexts that has served as a basis for the thesis research. It will start by reviewing the terminology and definitions of MEs and related terms such as adverse events and adverse drug reactions as they are inconsistent. There are many theories in the safety science research literature describing the origin of incidents and accidents. This thesis will shortly describe the theories of Charles Perrow and James Reason, which are well established and have been used in the studies performed. Risk management in healthcare involves several organisational levels where decision-making takes place, and some levels are discussed here related to the development process of the e-library. Risks and safety problems can sometimes be related to a mismatch between how everyday work is accomplished and how work is presumed to happen. In the chemotherapy process, no such gap should exist or should at least be as minimal as possible. But people are flexible and adaptive, adjusting their work to match the conditions; therefore, resilience engineering will shortly be described. After this, different ways to minimise the risks for MEs will be addressed, including redesigning the work process and standardisation. Incident reporting is mandatory and fundamental in patient safety. But the reports themselves are not enough; there need to be learning from them by which the organisation can perform safer. Finally, principles related to developing HIT will be forwarded.

Medication errors and related terms

The terminology and definitions vary when reading the literature about MEs and the medication use process. In a review study of terms used in patient safety related to drugs, Pintor-Mármol, et al. found 147 articles with 60 terms using 189 different definitions (2012). The terms that were utilised most frequently were ME, adverse drug event (ADE), adverse drug reaction (ADR), drug related problem (DRP), and adverse event (AE). Definitions of the most common terms found in (Pintor-Mármol et al., 2012) are presented in Table 1.

A review study of different definitions of MEs included 45 studies in which Lisby, et al. found 26 different wordings and concluded that there was inconsistency in defining MEs (2010). The interconnections between different terms also vary,

making it difficult for the reader to fully comprehend (Yu et al., 2005, Nebeker et al., 2004, Falconer et al., 2019, Ferner, 2012). The relationship between AEs, ADRs, and MEs is discussed by Aronson (2009). The definitions have changed over time, especially for ADR. For an update, see Nydert (Doctoral thesis, 2020). In this research the definition of a MEs was (Ferner and Aronson, 2006): "A medication error is a failure in the treatment process that leads to, or has the potential to lead to, harm to the patient. "

Table 1. Definitions of MEs and other terms used in patient safety related to a drug.

Term (Reference)	Definition
Error (Reason, 1990)	"The failure of a planned action to be completed as intended (i.e., error of execution) or the use of a wrong plan to achieve an aim (i.e., error of planning)."
Medication errors (National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP), 2021)	"Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer. Such events may be related to professional practice, healthcare products, procedures, and systems, including prescribing, order communication, product labeling, packaging, and nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use."
Adverse event (AE) (Institute of Medicine. Committee on Quality of Health Care in America, 2000)	"An injury caused by medical management rather than the underlying condition of the patient."
Adverse drug event (ADE) (Institute of Medicine. Committee on Quality of Health Care in America, 2000)	"An injury resulting from medical intervention related to a drug."
Adverse drug reaction (ADR) (European Medicines Agency, 2022)	"A noxious and unintended response to a medicine."
Drug related problem (DRP) (Pharmaceutical Care Network Europe Foundation (PCNE), 2006)	"An event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes."

Accident models used in healthcare

The theories of Charles Perrow and James Reason were an important basis of the IOM report, *To err is human* (2000). Perrow developed the Normal Accident Theory (NAT), a framework for analysing failure potential within and between systems (1999). He argues that errors in systems occur often and are indeed expected as part of normal operations. Systems are categorised based on how these errors propagate and interact within the larger system. If failures propagate and interact predictably, the system is considered linear. If failures behave unpredictably, the system is considered interactively complex. Systems that are slow and with opportunities for detection and response to failures are loosely coupled. Systems that are fast with fewer opportunities for detection and response are tightly coupled. An interactively complex system with tight coupling has a particular propensity for catastrophic failure. A change in the structure – such as reducing coupling or reducing interactive complexity – can reduce the probability of a catastrophic event.

Clinical oncology can be considered as a relatively complex system (Chera et al., 2015) where MEs can lead to severe consequences for the patient.

Reason's work provides a good general understanding of errors. He differentiates between slips or lapses and mistakes (1990). Slips and lapses represent execution failures (e.g., picking the wrong drug from the shelf). A mistake is a planning failure (e.g., misjudgement of a patient's condition). In considering how humans contribute to errors, it is important to distinguish between active failures and latent conditions (Reason, 1990). Active failures occur at the level of the frontline operator, and their effects are felt almost immediately. It can be the nurse administering a drug or the surgeon holding the scalpel. This can be called the "sharp end" (Cook et al., 1998). Latent conditions tend to be removed from the direct control of the operator and include aspects such as poor design, faulty maintenance, or poorly structured organisations. This can be called the "blunt end". Latent conditions pose the greatest threat to safety in complex systems because they are often unrecognised and can result in active failures or in combination with active failures result in accidents (Reason, 1990). In processes, several layers of defence are built-in as safety barriers to prevent accidents from happening. Safety barriers can be written procedures, double-checking, or some forcing function. Latent conditions combined with weak or missing barriers create organisational weaknesses. The necessary condition for an organisational accident is the rare conjunction of a set of holes in the successive defences. These "windows of opportunity" are rare because of the multiplicity of defences and the mobility of the holes – the metaphor is the Swiss cheese model (Reason, 1997).

Levels of decision-making in healthcare

Risk management in healthcare, as well as in other sectors, involves many nested levels of decision-making. There are several hierarchical levels in healthcare: staff working close to the patient (sharp end), the administration of a hospital, regions, and the regulators such as the National Board of Health and Welfare (blunt end). The various levels dynamically have different roles and responsibilities. The focus in an accident investigation should include both *what* causal factors can be identified and *where* they are in the organisational hierarchy (Rasmussen and Svedung, 2000). Three hierarchical levels – macro-meso-micro – have been used to gain a better understanding of learning from accidents, both from the railway (Cedergren and Petersen, 2011) and healthcare (Wrigstad et al., 2014, Wrigstad et al., 2015) sectors. It is clear from these studies that a majority of the direct causes of the accidents are at the micro-level. All of these causes can be found close to the accident scene (i.e., close to the sharp end). Conditions at the macro-level (blunt end) are generally more difficult to pinpoint. However, we know through research that decisions made at the blunt end can generate conditions at, or close to the sharp end that can increase the

risk for errors (Reason, 1997). The three hierarchical levels adapted to healthcare from (Cedergren and Petersen, 2011) are presented in Table 2.

Table 2. Three hierarchical levels in healthcare, adapted from Cedergren and Petersen (2011).

Hierarchical level	Description
Macro	Regulators, government, and associations. For example, the Ministry of Health and Social Affairs, the National Board of Health and Welfare, the European Medicines Agency, pharmaceutical companies.
Meso	Management at hospitals and regions.
Micro	Patient and the healthcare team.

Top-down and bottom-up approaches can be used to describe different implementations. Top-down is a planned approach instigated and sustained by formal leaders. Bottom-up is an incremental change approach that represents an emergent process cultivated and upheld by senior members of an organisation and frontline workers. Both approaches, as well as combinations thereof, are adopted in practice (Shanley, 2007, Riley et al., 2010). In a patient safety initiative study, a combination of top-down and bottom-up processes best facilitated the implementation. It was the combination of top-down behaviours, such as vision creation and resource support, with bottom-up actions that developed a sense of localised autonomy and engagement (Stewart et al., 2015). A combination of both approaches was also used in the development of the e-library (Paper III). The heads of Swedish oncology clinics requested a national source for chemotherapy regimens that was driven top-down within the RCCs. The bottom-up input from the stakeholders was also necessary in the development process.

Work-as-imagined versus work-as-done and resilience

Assumptions about how work is carried out often differ considerably from how work is carried out in reality. There is a difference between *work-as-imagined* and *work-as-done*, where the former is an idealised view describing what should happen under normal working conditions. An example is a written protocol for how to perform an activity, such as the administration of a drug. *Work-as-done*, on the other hand, describes what actually happens, how work unfolds over time in complex contexts (Hollnagel et al., 2015). There can be a mismatch between how everyday work is accomplished, *work-as-done,* and how work is presumed to have happened, *work-as-imagined.* This can sometimes lead to safety problems. Thus, the gap between the two should be as little as possible (Hollnagel et al., 2006). For example, the gap when dispensing medication in the community pharmacy setting has been examined (Ashour et al., 2021). Deviations from standardised protocols were found for various reasons, including efficiency (omitting and changing sub-tasks),

availability of resources (not only staff but also access to accurate and comprehensive patient data), thoroughness (adding sub-tasks to ensure a safe supply of medicines), and delegating safeguards (other individuals' sub-tasks would render their own checks unnecessary) (Ashour et al., 2021). The use of the *Chemotherapy Manual* with a collection of chemotherapy regimens for the southern part of Sweden was a way to reduce the differences in *work-as-imagined* between different clinics. Standardisation of the regimens across clinics reduces the variance. The same applies to the use of a national e-library for regimens.

However, systems can behave reliably because people are flexible and adaptive; they adjust their work so that it matches the conditions. Resilience engineering focuses on a system's capacity to cope with complexity and variable conditions (Hollnagel et al., 2006). "The essence of resilience is therefore the intrinsic ability of an organisation (system) to maintain or regain a dynamically stable state, which allows it to continue operations after a major mishap and/or in the presence of a continuous stress" (Hollnagel et al., 2006, p. 16). In a group interview study, Göras, et al. explored how complexity was managed and how the professionals adapted to create safe care in the operating room. They concluded that abilities described in the theory of resilience were used by the staff as a strategy to manage complexity in the operating room (Göras et al., 2020).

Redesigning the work process

One way to reduce MEs is to analyse previous incidents and figure out how they can be prevented. It is often useful to redesigning the system to make it difficult, and sometimes impossible to make mistakes. One such example is switching from syringe to infusion for intrathecal vincristine. More than 100 cases have been reported worldwide of vincristine inadvertently being given intrathecally, rather than by the intravenous route, often with a fatal outcome (Gilbar et al., 2015). The World Health Organisation (WHO) issued an alert in 2007 stating that vincristine (and other vinca alkaloids) should only be given intravenously via a mini bag (2007). This information was disseminated in Sweden and implemented via hospital pharmacies into the health care system (Fyhr and Sjökvist Saers, 2007). The recommendation from WHO has been followed by many institutions but not all (Gilbar et al., 2015). In the development of the national e-library this principle is implemented (Paper III). Another example is to move from handwritten chemotherapy orders to CPOE systems (Kullberg et al., 2013).

Standardisation as a preventive safety barrier function

Standardisation is defined by Leotsakos et al. (Leotsakos et al., 2014) as: ". . . the process of developing, agreeing upon and implementing uniform technical specifications, criteria, methods, processes, designs or practices that can increase compatibility, interoperability, safety, repeatability and, quality." The standardisation of workflow processes, prescribing, preparation, dispensing, and administration, is recommended as safeguards to prevent MEs (Goldspiel et al., 2015, Huertas-Fernández et al., 2017). Standardised order sets (Classen et al., 2010), standardised design and architecture (Kukreti et al., 2014), and standardised protocol and dosing (Dabliz et al., 2021) are beneficial when implementing CPOE systems. A final recommendation is to standardise nomenclature for chemotherapy regimens (Rubinstein et al., 2020, Terkola et al., 2021). Standardisation of nomenclature and content has been a guiding principle in the development of the national e-library (Paper III).

Organisational learning

Learning from incident reporting is fundamental to improving patient safety (Institute of Medicine. Committee on Quality of Health Care in America, 2000, World Health Organization (WHO), 2005). The healthcare staff in Sweden are governed by the Patient Safety Act (Ministry of Health and Social Affairs, 2010) and are obliged to report risks of adverse events and near misses. Learning from incidents or more serious events like MEs means gathering information from the individual(s) involved in an incident/event and from the incident/event itself and converting it to general knowledge for the entire organisation, or at least for those people for whom the knowledge is important (Jacobsson et al., 2011). Classical terms used to describe the actual learning process are *single-loop* and *double-loop* learning and come from Argyris and Schön (Argyris and Schön, 1996). Double-loop learning occurs when an error is detected and corrected in ways that involve the modification of an organisation's underlying norms, policies, and objectives (Argyris and Schön, 1978). Organisational learning can be any type of learning by which the organisation increases its ability to perform its activities better. In this context it means performing them safely or at least safer (Jacobsson et al., 2011). Another definition used in the healthcare context is: ". . . an organisation that facilitates learning of all of its members and continuously transforms itself" (Nikula, 1999).

Studies identifying MEs, their characteristics and underlying causes, report that we can learn and use them as a source for organisational learning and improved patient safety (Papers I and II).

User-centred and iterative design process

User-centred design is a general term for a philosophy and methods that focus on designing for and involving users in the design and evaluation of computerised systems (Abras et al., 2004). This way of working, with an early focus and an explicit understanding of the users' needs when developing HIT is stressed in the literature (Gould and Lewis, 1985, Giacomin, 2014). The national e-library presented in this thesis was developed according to this approach. It was iterative in the sense that it followed the Plan-Do-Check-Act (PDCA) cycle (Riley et al., 2010), which was applied in the development of the e-library (Paper III). It was user-centred in the sense that representatives from all stakeholders were part of the design/development process.

Different professionals must work together as a team in the chemotherapy process (Goldspiel et al., 2015, Gaguski and Nguyen, 2016). Physicians, nurses, hospital pharmacists, therapists, dieticians, and patients should be included (Leape, 2009). The patients and their families should also be involved in the care. They have been identified as what is referred to as *vigilant partners* in ensuring safe cancer care (Schwappach and Wernli, 2010). The patients' intentions to participate in error prevention were associated with self-efficacy, preventability of incidents, and perceived effectiveness of actions (Schwappach, 2010). It is also clear from the Paper I results that patients and their relatives can take an active part in error prevention. Multidisciplinary teams, also including software engineers, were involved in the development, implementation, and evaluation of the e-library (Papers III and IV). Representatives for patients were involved in the development of the patient information sheets.

Methods and materials

This chapter presents the research design and methods used in the various studies. The research presented in this thesis focuses on serious MEs with parenteral cytotoxic drugs (cancer drugs) in Sweden and what we can learn by analysing them. Another focus is on developing, implementing, and evaluating a national knowledge source in the form of a national e-library for chemotherapy regimens. An overview of the papers is found in Table 3.

Research and development processes

The research extends over a long period, more than two decades, and several changes have taken place. There has been an interaction between the research process and the development process, where the knowledge and results from the research process were translated into a practical, usable knowledge tool. At the time of the first studies (Papers I and II), Sweden had 9 million inhabitants, 42,000 of whom were diagnosed with cancer for the first time (2008). In the last studies (Papers III and IV), Sweden had 10 million inhabitants, and nearly 66,000 were diagnosed with cancer for the first time (2019). During the same period, the number of cancer drugs increased from about 50 to more than 150. The treatment options have thus increased sharply, which also means an even greater need for a national e-library for chemotherapy regimens.

The research process started at a chemotherapy preparation unit in a Swedish university hospital where a need was seen in practice. From the literature and from adverse event reports in the media, it was clear that MEs posed a risk for the patients. But we needed more knowledge about these serious MEs – the characteristics of these errors, and the contributing causes – in order to find ways to prevent them in the future. From the results of Papers I and II, it was clear that errors made by physicians in prescribing the cancer drugs had the most severe consequences for the patients. The successive introduction of CPOE systems into the chemotherapy process was one way to improve and make the process safer for the patients. The RCCs, with a focus on knowledge-based healthcare, initiated a project to develop a national source for regimens – an e-library – with the goals of standardising nomenclature and content in chemotherapy regimens, and of facilitating the

exchange of information between hospitals, CPOE systems, and patients. The research on the development, implementation, and evaluation of the national e-library for chemotherapy, are presented in Papers III and IV.

The research presented has used different methods for data collection, data analysis, design methods and evaluation. In addition to what is listed below, there have been numerous informal talks and meetings with practitioners, representatives from the CPOE systems, the pharmaceutical industries, and authorities. This has also contributed relevant knowledge.

The following section outlines the research methods behind the analyses of incident reports and the development, implementation, and evaluation of the e-library, and connects the methods and procedures used to their respective, contextual aims. Some of the details included here are not included in the papers that report the studies.

Table 3. An overview of the four included papers.

	Aims	Methods	Results	Conclusions
I 2012	To identify the characteristics of the MEs involving parenteral cytotoxic drugs in Sweden in order to answer the following questions: Which drugs were involved? What types of errors were made? Where in the medication use process did the errors take place? How were these errors discovered? What were the consequences for the patients?	Retrospective qualitative analysis of 60 cases reported to a national incident reporting system 1996-2008.	The most involved cytotoxic drugs were fluorouracil, carboplatin, cytarabine and doxorubicin. The most common error type was too high doses, followed by wrong drug. 25 of the MEs occurred during prescribing. Another 25 occurred during preparation by pharmacies. 5 occurred preparation by nurses, and 5 during administration. 14 of the MEs were intercepted by pharmacists, nurses or patient/relative.	The most severe MEs occurred during prescribing by physicians. It is of utmost importance to minimise the potential for errors in the prescribing stage.
II 2017	To present the development of a proactive tool for identifying general failure types (GFTs) that fit the process of managing cytotoxic drugs in healthcare; present the results from applying the tool to 60 reported MEs and thereby identify GFTs and active failures and propose a proactive application of the tool by healthcare providers.	A GFT tool was modified to fit the chemotherapy process. This was applied to the serious MEs presented in Paper I. The general failure types and active failures could be identified.	The most frequently encountered GFTs were defences, procedures, organisation, and design. Working conditions were often the common denominator underlying the MEs. Among the active failures identified, a majority were classified as slips, one-third as mistakes, and for a few no active failure or error could be determined.	The GFT tool facilitated the qualitative understanding of how the organisational weaknesses and local characteristics influence the risks. A tool was proposed to be further developed into a proactive self-evaluation tool as a complement to incident reporting and event and risk analyses.
III 2020	To develop a national e-library – with standardised nomenclature and content in chemotherapy regimens.	The development was done in participation with professionals related to chemotherapy. An iterative improvement process was applied, following the PDSA Cycle.	The main result was the national e-library itself and placing it in its national and local contexts.	The overriding aim of developing the national e-library was to mitigate patient safety risks by using standardised chemotherapy regimens and to support staff in performing their work.
IV 2022	To evaluate the usage and usability of the national e-library for chemotherapy regimens that had been developed to reduce MEs and increase patient safety.	A mixed method was used, including the compilation of subjective views of the users (web survey, spontaneous user feed-back, and qualitative interviews), analysis of statistics from the website, and an expert evaluation of the usability of the web page.	According to the web survey, most visitors were physicians and nurses. 80% looked for regimens. 90% found what they looked for and were satisfied with their visit. The expert evaluation concluded that many existing design principles were followed, giving useful improvement suggestions. The interviews revealed that most hospital use a CPOE system and that they use the national e-library in various ways: to import XML files, transfer information, or as a reference.	The user evaluation indicates that the national e-library is used in the intended way and that the users can interact without problems. Users have different needs depending on their profession and their workplace and these can be supported.

Analysis of incident reports for increased knowledge about serious medication errors

Investigating characteristics of medication errors

In Paper I, the methodology consisted of a retrospective qualitative analysis of cases reported to the national incident reporting systems. The inclusion criteria were: A ME reported according to the Lex Maria Act or to the Swedish Medical Responsibility Board (HSAN) between 1996 and 2008 involving a cytotoxic drug (ATC classification L01) and administered parenterally at a hospital. A total of 60 reports were included. In 50 (83%) of the MEs, the patient was an adult and in 10 (17%) of the events a child.

The incident reports were read and tables were compiled based on: 1) cytotoxic drugs involved; 2) type of error: wrong dose (too high, too low), wrong drug, wrong patients, wrong ambulatory pump, other; 3) where the error occurred in the medication use process (i.e., in prescribing and transcribing, preparation or administration); 4) the error detection mechanisms (i.e., how and by whom the error was discovered); 5) the consequences for the patient according to the NCC MERP Index for Categorising Medication Errors, (the USA National Coordinating Council for Medication Error Reporting and Prevention 2011). This index was used for classification of the severity of the outcome: *Category B-D Error, No harm; Category E-H Error, Harm;* and *Category I Error, Death* (i.e., an error that may have contributed to or resulted in the patient's death). *Category A is No error* and thus was not included. The various characteristics were chosen to provide facts about the errors that were as complete as possible. The thesis author did the compilation and the second author (in Paper I) checked that the facts from the incident reports had been transferred correctly.

Investigating organisational weaknesses and active failure

A tool based on 11 general failure types (GFTs) was developed to investigate organisational weaknesses underlying the reported MEs (Paper II). The proactive approach to enhanced safety management called Tripod Delta was originally presented by Reason as a diagnostic evaluation tool for accident prevention on oil rigs (Hudson et al., 1994). The underlying philosophy of Tripod Delta is to know what is controllable and what is not and to assess GFTs (Reason, 1997). These are organisational factors found through accident investigations to be latent conditions.

Modifications had to be made to the original GFTs to fit the chemotherapy process. The modified tool used in the study contained the following 11 GFTs: 1) *Hardware/Software*, 2) *Design*, 3) *Maintenance management/Follow-up (monitoring of patient),* 4) *Procedures,* 5) *Error enforcing conditions,* 6) *Housekeeping,* 7) *Incompatible goals,* 8) *Communication,* 9) *Organisation,* 10) *Training*, and 11) *Defences.*

The modifications were performed by the thesis author and the second author of Paper II. The second author is a licensed physician with experience from the Swedish National Board of Health and Welfare who worked with investigations of serious medical events. During the tool development process, Reason's original GFTs were slightly modified by omitting some items not relevant to healthcare, such as quality of stock system, age of equipment and compliance to specifications in the *Hardware* GFT; maintenance work or an associated stoppage causing a hazard in the *Maintenance management* GFT; management of contractor safety in the *Organisation* GFT; and personal protection, escape and rescue in the *Defence*s GFT. Four major additions were made to the original GFTs to fit the healthcare setting. These additions were based on the authors' expertise in the field. Software was added to the *Hardware* GFT heading, Follow-up (Monitoring the patient) was added to the *Maintenance management* GFT heading, situational factors were included in the exemplifications of the *Error enforcing conditions* GFT, and the absent or insufficient safety barriers item was included in *Defences* GFT. Exemplifications from healthcare of each GFT were added from a set of 30 incidents reported according to the Lex Maria Act or to the Swedish Medical Responsibility Board (HSAN) *on oral* cytotoxic drugs.

The final assessments of the reported 60 MEs in Paper I were carried out using the modified GFT tool. The information in the incident reports varied in precision and richness of details. The analysts aimed at using as many GFTs as possible to explain the event. However, in order to "compensate" the reports with limited information, and make the results more comparable, it was decided to limit the number GFTs to four. The thesis author and the second author, respectively, analysed the report descriptions and identified GFTs. The two sets of results were then compared. In reports where judgements differed, the GFT tool was supplemented with relevant explanatory notes. The reports were judged again on two additional occasions before there was an agreement on the judgements. In addition, for each incident report, the active failures were identified and compiled in a table. The active failures according to Reason's classifications (1995) were divided into different categories: slips (mix-up of drugs, pumps, patients, transcription error); mistakes (misinterpreted information, knowledge about treatment, follow-up of patient, calculation error); or not possible to categorise. The table also included the responsible professional (physician, pharmacist, or nurse) and the consequences for the patients (death, harm, or no harm according to NCC MERP).

Development, implementation and evaluation of a national e-library for proactive risk reduction

User-centered and iterative development

The development started after a request from the heads of Swedish oncology clinics and was driven within the RCCs. The primary users of the chemotherapy regimens are physicians, nurses, and hospital pharmacists. Their expert knowledge, expertise and experience were used to develop the e-library, in an iterative development process involving users from the start (Abras et al., 2004, Carayon and Hoonakker, 2019). Regimens developed locally and regionally were used as inspiration for how the comprehensive information in them could be displayed. The knowledge from the analysis of the incident reports with serious MEs (Papers I and II) and from the literature was also used in the design process. One example is that dose limitations (maximum doses and maximum cumulative doses) are always included in the regimens for that specific drug. Standardisation of the nomenclature and the content was another guiding principle. Using the same name for a regimen in all clinics reduces the risk of error when patients are treated at more than one hospital. Finding important information about the prescription and which premedication is necessary under the same heading makes it easier for the physician and reduces the risk of it being missed.

The development process involved the following steps which included iterative approaches:

Project formation, reference, and task-specific groups.

The project group, consisting of 5-6 members, involved hospital pharmacists, physicians, oncology nurses, and software engineers. The reference group of about 35 participants involved physicians and nurses representing oncological clinics, representatives for the CPOE systems, and hospital pharmacists. Task-specific teams were formed, with some members from the reference group and the project group, and used for special issues. The project group generated ideas that were suggested to the reference group, such as how to present regimen information. In meetings with the reference group, the ideas were tested, discussed, enhanced, and then decided upon. Figure 4 summarises the different groups, the exchange of information and the interaction between them.

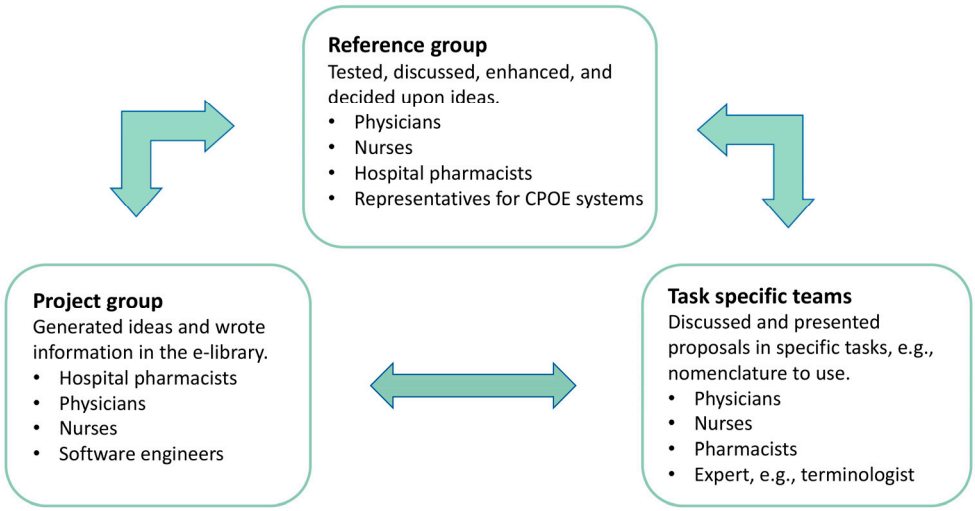

Figure 4. A summary of the different groups working together to form the e-library.

Defining data fields and variables for describing regimens.

One of the task-specific teams presented a proposal that the reference group approved after discussion.

Standardisation of terminology and principles for naming the regimens.

There is no widely accepted naming convention or standard for chemotherapy regimens. The words to use and their meaning had to be determined (e.g., dosage, indication). Another task-specific team was formed including a terminologist to formulate a proposal.

Defining the technical platform.

A crucial step was choosing the technical platform, and whether to develop it within the RCCs or to outsource it. The existing uniform National Platform for Cancer Registration within the RCCs was chosen. Cancer quality registers collect individual data per diagnosis, treatment, and outcome.

Defining medical and pharmaceutical information and creating Basic Facts for drugs.

Important medical and pharmaceutical information on drugs is collected and displayed as Basic Facts. These are defined for a given drug according to the substance name, delivery route, and formulation. Dosing aspects describe how the patient dose is calculated (e.g., body surface area). Drug alerts are displayed for drugs with maximum dose limitations (e.g., vincristine). Pharmaceutical information describes how a drug should be prepared, taken in relation to food, its

shelf life, and storage. Based on the Summary of Product Characteristics (SPC), a physician in the project group identified common or serious adverse drug reactions (ADR) for each substance. Basic Facts information is downloaded automatically when a regimen with that substance is created. Important information will always follow a substance in all regimens and Basic Facts information must exist before the substance can be included in a regimen.

Deciding how to display the regimen information.

Regimens from oncology clinics were used as a basis to determine how to display the regimen information. The guiding principles were: It must be easy for the reader to grasp important information in order to use it safely, and the information should be short, concise and standardised (Norman, 2002). The information is visually divided into three sections: 1) regimen overview including instructions, precautions and recommendations for dose reduction, 2) ADR, and 3) a detailed administration schedule.

Defining details in the first pilot regimens.

To test the workflow, a diagnosis group was chosen with relatively simple regimens including few drugs.

The national e-library

The national e-library can be accessed at https://kunskapsbanken.cancercentrum.se/. It contains the following parts: 1) basic facts, 2) regimens presented per diagnosis, 3) information sheets for patients per regimen, 4) support documents for healthcare professionals, and 5) newsletters published after updates of the e-library. Part of a regimen is shown in Figure 5. The main users (physicians, nurses, and pharmacists) can access the information in the e-library for reading, printing or downloading XML files for the CPOE systems used in Sweden. The patients get access to the information sheets per regimen through their nurse.

Chemotherapy regimen - Lung cancer
Cisplatin-Docetaxel
Indication: Non-small cell lung cancer C34
Cycle intervall: 21 days

Treatment intention: Adjuvant, Curative, Neoadjuvant

Overview

Drug

Substance	Administration	Dilution	Infusion time	Dose/ administration	Dosing	Max dose/ adm.	Max ack. dose
1. Docetaxel	Intravenous infusion	250 mL sodium chloride 0.9% infusion	60 min.	75 mg/m^2	BSA		
2. Cisplatin	Intravenous infusion	1000 mL sodium chloride 0.9% infusion	60 min.	80 mg/m^2	BSA		

Regimen description

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	New cycle day 22
1. Docetaxel	x1																					
2. Cisplatin	x1																					

Emetogenicity: High

Treatment overview: Evaluation after 3-4 cycles.

Instructions for the regimen

Conditions for starting the regimen
Check blood, liver and electrolyte status with renal clearance (Cystatine C, Iohexol, creatinin clearance or equivalent).
Hearing test according to local instructions.
In case of pathological creatinine or if a more favorable side effect profile is desired, switch to Carboplatin-Docetaxel.

Conditions and controls for administration
Cisplatin - Weight or diuresis check.
Docetaxel - Increased preparedness for anaphylactic reaction, greatest risk in cycle 2. Make sure patient has taken premedication.
Check for peripheral neuropathy.

Instructions for prescription
Check blood count including neutrophils, electrolyte status, and creatinine. For start of treatment: neutrophils >1.5, platelets >100 , and leukocytes >2.0.
If S-creatinine above normal value, renal function check with clearance according to local instructions (Cystatine C, Iohexol, creatinine clearance or equivalent). Target value GFR >60.
Docetaxel - Premedication with cortisone, tablet Betamethasone:
Day before treatment give 6 mg Betamethasone, morning and evening.
Day 1 and 2 give 6 mg (total 24 mg) Betamethasone.
The cortisone dose can be reduced in cycle 3 if there is no reaction to the previous treatment.
Cisplatin - during the treatment period at least 4 litres of fluid are given. Intravenous post-hydration can be replaced by liquid.

Dose reduction recommendation
Hematologic toxicities
Nadir for leukocytes <2.0 and/or neutrophils <1.0 - give next cycle with 80% of the doses for both drugs.
If nadir after dose reduction still is leukocytes <2.0 and/or neutrophils <1.0 - reduce doses by an additional 10-15% or change regimen.

Docetaxel - in case of febrile neutropenia or unacceptable adverse drug reactions, consider dose reduction to 75%.

Figure 5. Regimen overview (incomplete) of Cisplatin-Docetaxel for lung cancer from the Swedish national e-library. BSA stands for body surface area.

Usability evaluation of the e-library

The information in the e-library is both complex and extensive and it is central that the users can utilise it as intended. Usability testing focuses on users' needs, uses empirical measurements, and has an iterative design (Abras et al., 2004). The library was evaluated with a combination of methods to obtain a comprehensive view of the usage and usability. Multiple evaluation methods complement each other by providing input from several perspectives (i.e. expert/user, subjective/objective) that may be triangulated and hence identify critical design aspects and user needs (Price et al., 2017). Figure 6 summarises the evaluation, the intended users and the iterative development of the e-library.

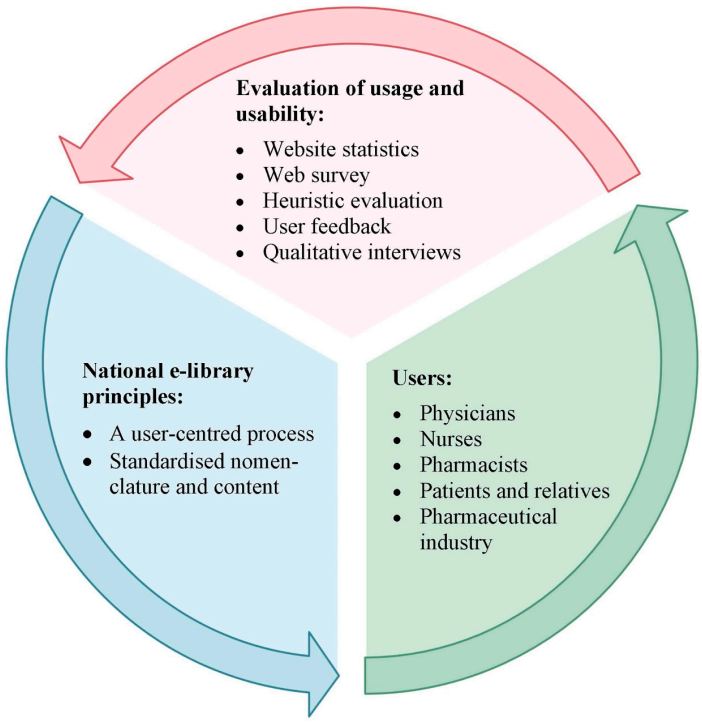

Figure 6. The e-library has been evaluated using multiple methods to draw conclusions about its intended usage and usability, and to iteratively improve the resource.

The evaluation consisted of five methods:

Website statistics collected from May to December 2020 that show the number of users in total, unique users, when they visit the e-library, and from where the visitors came.

A web survey for people visiting the e-library was conducted in January 2020. The survey consisted of questions about the visitors' role and function, what information they were looking for, how pleased they were with the visit, and if they had suggestions of improvements.

A heuristic evaluation of the user interface (Nielsen and Molich, 1990) was performed in June 2020 (Halipi and Lindquist, 2020) to identify details in the user interface design that could be improved to increase usability.

Spontaneous user feedback collected in the form of emails sent to the development team/project leader during 2020, from users presenting their role and question or suggestions.

Qualitative interviews with four nurses, three physicians, and three pharmacists from various regions in Sweden were performed at the end of 2020 and beginning of 2021. No patient interviews were conducted as the intention is that the patients should get regimen information through their nurse and not through the e-library. Interview questions concerned what parts of the e-library they used, how they used it, their experiences of using the e-library in their work compared to how they worked before, and their expectations for further development.

Iterative development of patient information sheets

In 2018, the Swedish government took the initiative to create patient information sheets per regimen. This sheet should include information on the treatment, the most common or important adverse reactions, advice for self-treatment, when to contact the hospital, and lifestyle advice. The development process has not been described in any of the papers and is therefore included here. The project group and the software engineers worked together to elaborate the information and functions needed. Proposals for different regimens were discussed in a workshop with several representatives for the patients, nurses, physicians, and communicators. The patient representatives in particular provided very clear advice on how to improve the information. Examples are to start with patient information sheets for a diagnosis that involves both women and men, not to use italic fonts in the text, and to include advice on how to protect both the patient and their family from the exposure with cancer drugs, since they are classified as hazardous substances (Cass et al., 2017). We changed the information accordingly, using an iterative process. Patient information sheets were first drawn up for colorectal cancer. After being checked and approved by nurses working with these patients and by a linguist, they were released in 2019. Patient information sheets for more diagnoses have been released since then, checked by nurses specialised in that particular diagnosis. The linguist made a new check after half a year.

Summary of papers

Paper I – Characteristics of medication errors with parenteral cytotoxic drugs

The study's aim was to identify the characteristics of the 60 MEs involving parenteral (given as injection or infusion) cytotoxic drugs in Sweden to answer the following questions: Which drugs were involved? What types of errors were made? Where in the medication use process did the errors take place? How were these errors discovered? What were the consequences for the patients?

The results revealed that the most involved cytotoxic drugs were fluorouracil, followed by carboplatin, cytarabine, and doxorubicin. The largest ME category included doses that were too high originating from prescribing and transcribing or preparation. It included tenfold errors. The second largest category was the wrong drug being used during preparation, both by pharmacists and nurses, or in the prescription. In total, there were 18 incidents with mixed-up drugs.

Twenty-five of the 60 MEs (42%) occurred when physicians were prescribing or transcribing an order to the pharmacy. Another 25 of the MEs (42%) occurred within the pharmacies, and the remaining 10 MEs (16%) occurred when the nurses prepared (5 MEs) or administered the drug to the wrong patient (5 MEs). When the ME started at the prescribing stage, all of the 25 cytotoxic preparations were delivered to the patient. When the ME started at the pharmacy, nurses stopped delivery of the infusion to the patient in eight of the 25 incidents. A pharmacist intercepted the ongoing treatment in four cases, and in 13 cases the drug was delivered to the patient. When the erroneous preparations were prepared by a nurse, four of the five were delivered to the patient. It was the same for the administration of a preparation to the wrong patient: four out of five were delivered.

The consequences for the patients were especially severe when the physician made an error in prescribing and transcribing. Six of these MEs were judged as Category I, *Error, Death,* 15 as Category E-H, *Error, Harm*, and five as Category B-D, *Error, No harm*. When the ME started during preparation it led to *Harm* in five and *No harm* in 20 of the reports; 12 of them were intercepted.

Paper II – From a reactive to a proactive safety approach. Analysis of medication errors in chemotherapy using general failure types

The study's aims were to: 1) present the development of a proactive tool for identifying general failure types (GFTs) that fit the process of managing cytotoxic drugs in healthcare; 2) present the results from applying the modified tool to the 60 reported MEs in Paper I and thereby identify the GFTs involved and the active failures; and 3) propose a proactive application of the GFT tool by healthcare providers.

The most frequently encountered GFTs were in *Defences* (35/60), *Procedures* (27/60), *Organisation* (19/60), and *Design* (18/60). Examples in *Defences* were lack of or a failure to double control the patient's or drug's identity or the dose of the drug. Nearly all GFTs in *Procedures* concerned routines: routines that were lacking, were insufficient or were not followed. Examples of *Organisation* GFTs were defective co-operation between different departments necessary for the care of the patient (such as paediatrics and oncology). The GFT *Design* category concerns, for instance, look-alike or sound-alike drugs or ambulatory pumps. Working conditions were often the common denominator underlying the MEs. Examples were high workload, unclear responsibilities, low staffing, and unfamiliar duties.

Among the active failures identified, 19 of the 60 cases were classified as mistakes, 13 of them made by the physician. Examples of mistakes were misinterpreted treatment, protocol or dose, calculation errors, monitoring of the patient, and lack of knowledge. Thirty-five of the reports were classified as slips. Examples of slips were a mix-up of drugs, doses, pumps, patients, documents, and transcription errors. In six of the reports no active failure or error could be determined. This could be because of an error in the protocol due to a miss in proofreading, a planned dose reduction that disappeared in the computer, mixed responsibilities among doctors, or starting a treatment after an erroneous answer that the blood tests were fine.

Paper III – National e-library for standardized chemotherapy regimens

The aim was to develop a national e-library with standardised nomenclature and content in chemotherapy regimens. In developing the tool, an iterative improvement process was applied, following a PDSA Cycle (Plan, Do, Study, Act) (Deming and Kilian, 1992, Deming, 1993). The entire process of developing the e-library was documented, through for example, meeting notes and e-mail archives.

The main result of this study is the e-library itself, available at: https://kunskapsbanken.cancercentrum.se.

The overriding aim of developing the national e-library was to mitigate patient safety risks by using standardised chemotherapy regimens, and to support staff in performing their work. However, the e-library is also part of a wider national context of continuous improvement of cancer care, including organisational learning for improved performance and quality, as presented in Figure 7.

The Swedish NCCC Guidelines should contribute to good care and equality of care for all patients. Based on the best medical knowledge, the Guidelines provide recommendations on the investigation, treatment, care, and follow-up of patients. An NCCC Guideline committee of physicians, nurses, and other relevant experts is responsible for the information being reviewed annually by the committee. The Guidelines contain information especially important for the e-library about which regimens to use, their content (drugs, dosages, on what days, course length), and in what situation (adjuvant, palliative). Regimens are created based on this information. The responsible national physician, appointed by the NCCC Guideline committee, was involved in a dialogue about the details in the regimens, and is responsible for approving the regimens.

A healthcare team using an iterative process over several courses treats a patient with the regimen. Documentation of the treatment – drugs, doses, adverse reactions, and the outcome – is carried out in the CPOE or another system. Information about the patient's illness, treatment and outcome is also reported and entered into national quality registers. The registers are meant to facilitate follow-up and evaluation of the healthcare results and quality of the services.

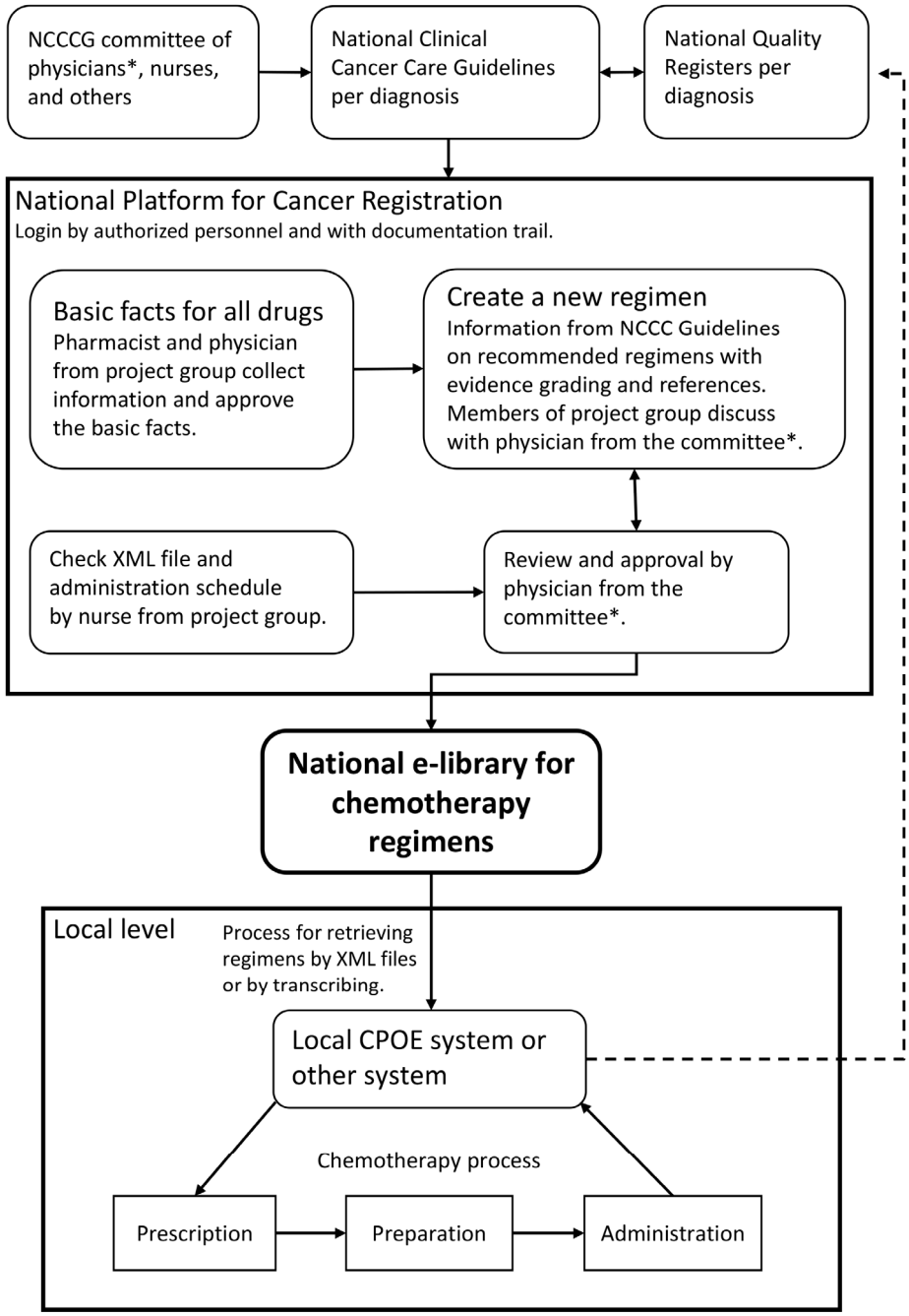

Figure 7. The Swedish e-library in its national and local contexts. Regional Cancer Centres are responsible for the work at the national level, regions are responsible at the local level.

* National Clinical Cancer Care Guidelines' (NCCC Guideline) committee physicians, one of whom consulted with the project group, reviewed, and approved the regimens.

Paper IV – Usage and usability of a national e-library for chemotherapy regimens: a mixed-method study

The aim of this study was to evaluate the usage and usability of the national e-library for chemotherapy regimens in order to see if the users can utilise the library as intended.

The evaluation consisted of a combination of methods to obtain a comprehensive view of the usage and usability. Statistics from the website show an average of just over 2,500 visits and 870 unique visitors per month. Most visits took place Mondays to Fridays, but there were also 5-10 visits per day on weekends. The web survey, with 292 answers, shows that the visitors were mainly physicians and nurses. Almost 80% searched for regimens, 90% found what they were looking for and were satisfied with their visit. The expert heuristic evaluation showed that the e-library follows many of the existing design principles and therefore concluded that it was usable in its current form. Nevertheless, some improvement suggestions were identified, such as moving patient information sheets to a separate tab in the menu.

A total of 86 emails were received in 2020 with user feedback, most of it from nurses. The main part (78%) contained questions such as, “When will the regimens arrive for a given diagnostic group?” The rest had discovered mistakes, mainly in some regimens, such as patient information sheets that lacked a certain side effect. The interviews revealed that most hospitals use a CPOE system, and that they use the e-library in various ways to import XML files, transfer information or as a reference. One hospital without a system uses the administration schedules from the library. Among the expectations for further development included a harmonisation of regimens used in different diagnostic areas, for instance, the same amount of infusion fluid and infusion times for the same drug.

The evaluation indicates that the e-library is used in the intended manner and that the users, with different needs depending on profession and workplace, can interact without problems.

Discussion

The general aims of this thesis were to learn from MEs in the chemotherapy process and to develop a national knowledge source that can mitigate these types of patient safety risks. The studies have been performed in a geographically limited system (Sweden). The studies can contribute with working methods for analysing and learning from serious MEs, and how user-centred development contributes to more standardised working methods, which can also provide safer care. This knowledge is also helpful beyond the Swedish healthcare context.

Learning from medication errors

Medication errors occur at all stages in the chemotherapy process. However, in our study, prescribing stage errors constituted 42% and caused temporary or life-threatening harm to the patients. A similar result has been reported by (Serrano-Fabiá et al., 2010, Gandhi et al., 2005, Watts and Parsons, 2013, Ranchon et al., 2011). All these erroneous medications were delivered to the patients, and none were intercepted, like some of those emanating from pharmacists and nurses. It can be concluded that it is of utmost importance to minimise the potential for errors in the prescribing stage.

The cancer drugs that were found to be most involved in MEs were fluorouracil, carboplatin, cytarabine, and doxorubicin. This is in line with other studies (Chen et al., 1997, Ranchon et al., 2011, Rinke et al., 2007, Phillips et al., 2001, Reinhardt et al., 2019). The platinum-containing drugs (carboplatin and cisplatin) were involved in 9/60 cases where the MEs were judged as *Error, Death* or *Error, Harm*. According to the Calvert formula, carboplatin doses are calculated related to renal function, a complicated process that has led to overdoses, also shown in other studies (Ranchon et al., 2012, Reinhardt et al., 2019, Liem et al., 2003, Duarte et al., 2019, Muller, 2003).

The most found error types were too high doses, followed by the wrong drug. These findings are similar to other studies (Rinke et al., 2007, Phillips et al., 2001). Some of the causes for errors with too high doses or the wrong drug are well described. Tenfold or decimal point errors are a well-recognised risk to patients (Lesar, 2002), especially in children (Doherty and Mc Donnell, 2012). The wrong drug error, made

mainly by pharmacists, involved cases with a mix-up of look-alike, sound-alike drugs (LASA). Examples from the study are vincristine-vinblastine and docetaxel-paclitaxel. LASA may cause or contribute to potentially harmful MEs, and there have been attempts to identify the drugs at risk, often LASA drug pairs (Schulmeister, 2006, Kovacic and Chambers, 2011). LASA drugs mix-ups are also common in a review study of dispensing errors in hospital pharmacies (Aldhwaihi et al., 2016). Several new cancer drugs in the same treatment categories have similar looking and sounding generic names. Examples are palbociclib-ribociklib and sorafenib-sunitinib. This is because the generic name, also known as the international non-proprietary name (INN) established by the WHO, is based on the substance's chemical structure. It would be prudent to be proactive in identifying potential LASA drug pairs. Authorities and the pharmaceutical industry, at the macro-level, ought to deal with the LASA problem. Organisations such as the ISMP and the Food and Drug Administration (FDA) recommend tall man lettering to distinguish drug pairs (Institute for Safe Medication Practice (ISMP), 2013). Tall man lettering means using uppercase and lowercase to highlight a difference. In the example above, it could be SORAfenib-SUNItinib. At the micro-level, barcode reading is a way to check that the right drug is being used (O'Neal et al., 2009).

The most common type of active failure in the study consisted of slips, done by pharmacists and most often concerning a mix-up of drugs or ambulatory pumps. Most of the mistakes were made by the physician, for example, misinterpreted treatment, protocol or dose, calculation errors, inadequate patient monitoring and lack of knowledge. For some of the reports, no active failure could be determined. In all of these, physicians were involved, and the failures were due, for example, to errors in the protocol because of a miss in proofreading, or a planned dose reduction that disappeared in the computer. It is not always necessary that an active error is committed for a ME to occur. However, there are always latent conditions that, together with weak or missing barriers, cause MEs (Reason, 1997).

The most frequently encountered organisational failure types were *Defences* (e.g., double-checking not working), *Procedures* (e.g., poor administrative routines), *Organisation* (e.g., unclear responsibilities), and *Design* (e.g., poor working environment or similarity between names and appearance of drugs). Working conditions were often a common denominator underlying the GFTs. One example was the accumulation of MEs at a pharmacy. The management decided to transfer preparations from one site to another, which resulted in a 35% increase in the number of preparations carried out. The transfer was ill-planned, and six MEs were reported within one month.

Information technology to mitigate errors

The introduction of technology, which started in the 2000s, has reduced the risk of several error types found in the study. The CPOE systems contain information about which drugs and doses to use. The system calculates the correct doses based on the patient's body surface area or other calculation methods. The introduction of CPOE systems has decreased the risks for prescription error types, such as the wrong drug, dose or strength, calculation, and transcribing errors (Vélez-Díaz-Pallarés et al., 2018, Mattsson et al., 2015, Elsaid et al., 2015).

In chemotherapy, with all its different regimens, there needs to be a source of common knowledge that supports organisations using CPOE systems with updated information on the regimens and other related information of interest to the involved professionals. Chemotherapy regimens with updated, standardised nomenclature and content are one way to ensure that all involved healthcare units have access to the same and latest evidence, allowing for increased patient safety (Huertas-Fernández et al., 2017, Classen et al., 2010, Kukreti et al., 2014, Dabliz et al., 2021, Rubinstein et al., 2020, Terkola et al., 2021). The national e-library described in this thesis was developed in and for a Swedish context, is government funded, embedded in a national quality system, freely available, with documents for easy printing, and XML files of the regimens that can be downloaded to a local CPOE system. It also contains information sheets for patients per regimen, support documents for healthcare professionals, and newsletters published after updates of the e-library.

The regimens available in the national e-library are based on recommendations in the NCCC Guideline per diagnosis. A physician from the NCCC Guideline group reviews and approves a regimen before it is available on the website. A nurse from the project group checks the XML file and the administration schedule before it is included on the website. The patient information sheets give the patient and their relatives the essential information about the treatment, making it possible for them to control and contribute to their care. The e-library follows most of the recommendations given in the literature for standardisation, not only concerning nomenclature but also codification in healthcare information systems. A review study of Terkola et al. (2021) has summarised the recommendations. In addition to the examples already provided in the thesis and the papers (vinca alkaloids should only be given intravenously via a mini bag, maximum doses are always included) other examples are not to abbreviate drug names and to use approved generic drug names, never trail a whole number with a decimal point followed by a zero (5 mg instead of 5.0 mg), and always start a regimen on day 1.

The e-library provides users with XML files that can be downloaded to a local CPOE system minimising the risk for errors during transferring of data. The regimen overview and the administration schedule can be used for prescribing and administration if no CPOE system supports the staff. All this taken together means that the e-library can act as a tool for proactive risk reduction in the chemotherapy process.

International outlook

There are not many systems similar to the Swedish e-library internationally, but some have been identified. The Health Service Executive National Cancer Control Programme in Ireland develops national chemotherapy regimens to support safe and evidence-based treatment (Health Service Executive Ireland). The National Comprehensive Cancer Network® in the USA is a not-for-profit alliance of 31 leading cancer centres in the country that provides their members with updated guidelines on treatment by cancer diagnoses and chemotherapy templates (National Comprehensive Cancer Network USA). The Onkopti® in Germany contain more than 1000 updated and available regimens. A licence agreement is needed to access detailed views, and to download and export regimens (ONKODIN, 2022). What these systems have in common is that the regimens are developed jointly by physicians, nurses and pharmacists based on guidelines for each cancer diagnosis in recommending what regimens to use. This is similar to our way of working. Hemonc.org, a haematology oncology Wiki, has used a different approach to developing the regimens through collaboration on the Internet (HemOnc.org, Warner et al., 2015). Healthcare professionals who wish to have editing privileges must contact the administrators to get permission. An editorial board oversees the accuracy and completeness of the content.

The user-centred and iterative development process

As reported in a review study (Carayon and Hoonakker, 2019), usability problems of HIT are continuously experienced by multiple groups of healthcare professionals and patients. Evidence has also been seen of the linkage between poor HIT design and patient safety consequences. There is a lack of attention to human factors issues when designing HIT. The end-users are not sufficiently engaged in the design and implementation processes, which result in negative consequences for patient safety (Carayon and Hoonakker, 2019). The engagement of interprofessional stakeholders, use of the lessons learned from MEs, standardisation, stepwise implementation and

commitment to ongoing quality improvement can reduce the risk of usability problems in HIT.

The current research has been successful in making use of the users' expert knowledge, and knowledge from the MEs and the literature in an iterative development process. The chemotherapy process involves several professions. Their different skills, together with the expertise of software engineers, have been necessary for the development of the national e-library. Other contributions to the success have been the formation of a small, dedicated project group, a reference group with broad representation from the clinics, hospital pharmacies, and CPOE systems, along with the formation of task-specific teams. During the work with patient information sheets, representatives of the patients were also involved and contributed essential points of view. In general, the development efforts have had a significant bottom-up perspective. At the same time, the work has been done within RCCs with their technical platform, quality systems, work with NCCC Guidelines, and government funding. This has resulted in a combination of bottom-up and top-down approach that has proven successful.

User evaluation and user needs

The information in the e-library is both complex and extensive. Therefore, it was essential to evaluate the usage and usability of the e-library. The comprehensive user evaluation conducted is an integral part of continuing the user-centred process that started during the development of the e-library. The evaluation used qualitative and quantitative methods to review the usage and usability comprehensively. Combining several methods, such as expert/users, objective/subjective, provides valuable feedback for further development (Price et al., 2017).

From the web surveys and interviews, it became clear that it was the e-library's content that the users focused on and not on issues related to the website's usability. This may be interpreted as a subjective satisfaction in the interaction with the system. The expert evaluation gave valuable perspectives for presenting the regimens and other information on the website. The web survey showed that the users are substantially satisfied with their visit. Most of them found what they were looking for. Their main feedback was a wish for more regimens, more diagnostic areas to be covered, and more patient information sheets that are continuously added and updated. The number of visits indicates that the resource is used extensively. The geographical span shows that the e-library has emerged as the national resource it is intended to be.

Moreover, the spontaneous user feedback shows clearly that the e-library is used. Contact with the users is vital, and websites generally facilitate a rapid and comprehensive means of knowledge dissemination. The interviews conducted

revealed various ways to use the information in the regimens. Some use the XML files to import the regimen to their CPOE system to ensure that the transmitted data is accurate. Some read the information in the regimen and then transfer it to their CPOE system. Those moving the information from the e-library in this manner explained that they had to adjust the information in their CPOE system. It could concern the local list of drug names or involve local additions and procedures. It is thus easier to copy one of their regimens and make the necessary changes to match the new regimen. Finally, some clinics do not have an CPOE system yet, relying on handwritten orders and documentation. To transfer information manually always presents a risk for introducing errors.

Users have different needs depending on whether they are physicians, nurses or pharmacists and whether they work in a university hospital or a smaller hospital. The e-library can support these different user needs. The expressed needs from the users are helpful to understand which areas and regimens should be prioritised in the improvement efforts.

Dissemination of the national e-library

There is no "magic bullet" or simple solutions to changing or implementing healthcare innovations. The use of "champions" – advocates who are committed to and believe in what they advocate – as implementers is effective. Increased coordination between disciplines and individuals is another implementation strategy used. Multifaceted implementation strategies are considered more effective than single interventions (Nilsen, 2014).

The website was up and running in 2015 with regimens for seven cancer diagnoses. Information about the e-library was disseminated at national healthcare congresses, workshops, articles in oncological journals, and by participants in the reference and project group. There has been a continuous increase in the number of regimens and diagnoses combined with constant website improvements. This has allowed for many contacts with the physicians who approve the regimens and the nurses when discussing patient information sheets for the regimens, which has also contributed to spreading information on and increase the usage of the e-library.

The national e-library of today

Today's Swedish national e-library for chemotherapy regimens contains more than 600 regimens, more than 450 patient information sheets for the regimens, and nearly 300 basic facts on drugs (with significant medical and pharmaceutical information).

The patient information sheets are used as a part of the *My Care Plan via 1177 the Healthcare Guide* and will be available both in English and Arabic in 2022. There are also support documents for healthcare professionals, such as antiemetic guidelines (i.e., information on what medicines can be given to the patient to prevent nausea due to the chemotherapy) and newsletters published after updates.

The e-library, together with NCCC Guidelines, are delivered from the macro-level (RCCs) to be implemented in the meso- and micro-levels (hospitals, ward units). However, there is a risk of mismatch between *work-as-imagined* (information from macro-level) and *work-as-done* (at the micro-level). If the regimens are implemented with standardised content and nomenclature at the micro-level and we at the macro-level are better at listening to and discussing with the healthcare professionals and the patients, the gap between *work-as-imagined* and *work-as done* can be reduced and made as minimal as possible.

Development and implementation are the first phases. In the management phase that follows comes the need for maintenance, monitoring, and continuous improvement. When the NCCC Guidelines are updated, the regimens also need to be reviewed. Information on how to improve the quality of the regimens in a standardised regimen library can be found in (Busby et al., 2011) and in the CPOE system used in 35 hospitals (Crespo et al., 2018).

The project group members have remained nearly the same since the beginning with some minor changes. A new successor in charge is in place and has been trained in co-ordinating the project group. This is a critical element to ensure the continued development of the e-library.

Advances in chemotherapy

The severity and consequences for the patient of a ME committed are often determined by the drug and dose used in the error. Even if cancer drugs are classified as high alert medications by the ISMP (2018), not all have these properties, especially many of those that have been added in recent years. They may have other properties, with different adverse reactions, making premedication or monitoring essential and must not be neglected. Along with the continuous development of treatment options, changes can also occur in how care is delivered and the degree of patient involvement. Examples are the home-based outpatient administration of complex chemotherapy in acute leukaemia and lymphomas (Fridthjof et al., 2018), fixed dosing of monoclonal antibodies (Hendrikx et al., 2017), and changes in what regimens are used (van Herk-Sukel et al., 2013). Put together, this means that patient safety must be constantly improved to meet the changes taking place in healthcare.

Methodological considerations, strengths, and limitations

Learning from the analysis of the medication errors

A set of serious ME cases reported to the national incident reporting system was analysed. The cases came from many clinics and make up a representative sample of serious events. However, the information analysed was limited to the content of the written reports from the national authorities. The reports varied in quality and the amount of the information supplied due to different authors and changes over the years. In the recent years of the investigation period, the healthcare facility or pharmacy carried out a root cause analysis before sending the report to the authorities, thus providing more comprehensive information. Despite these limitations, analysing and drawing conclusions from many nationally reported incidents offers valuable information and can contribute to organisational learning. The retrospective method has also been used to analyse serious MEs with concentrated potassium and sodium solutions (Fyhr and Akselsson, 2011). Medication incidents in the National Reporting and Learning System in England and Wales were reviewed over six years by Cousins, et al. (2012). They concluded that preventable harm from medication incidents can be further minimised by: the continued use of the Reporting and Learning System to identify and prioritise important actions to improve medication safety; having a central organisation that continues to issue medication safety guidance; and using better methods to ensure that these guidelines are implemented.

An option would be to use local incident reports from hospitals, as reported in studies from Spain and Germany (Serrano Fabia et al., 2005, Markert et al., 2009). But then the information would be limited to a few institutions and cover reports with a wide range of severity. Another possible method would be a retrospective medical record review, which often uses triggers as indicators of potential MEs. Examples of triggers could be out-of-bounds laboratory test results or the use of antidote medication. This method has been used in epidemiological studies, and some information from the chemotherapy process is provided (Brennan et al., 1991, Thomas et al., 2000). No such details are shown in the Swedish studies using this method (Soop et al., 2009, Nilsson et al., 2018).

Alternative methods for analysing organisational weaknesses (latent conditions) would be to use the more comprehensive internal incident investigations carried out in today's institutions, supported by the National Manual on Incident Investigation. Most important when investigating organisational weaknesses and what contributed to the incident is to have access to as much information as possible, and that this information can be supplemented if necessary.

Development, implementation, and evaluation of the national e-library

In developing the e-library, we used multidisciplinary teams and their expertise, together with lessons learnt from our studies and those of others in an iterative process. The development work has been financed with government funding and within an existing quality system, combining top-down and bottom-up approaches. The development could have been done with more guidance from the authorities or the clinics. The balance between these two can always be discussed. The important thing is that they work together.

We used standardisation of the terminology and the content, which many supports. The development and expansion of regimens took place over ten years. This could have been accelerated if the physicians had devoted more resources to reviewing and approving the regimens.

A mix of methods was used in evaluating the usage and usability of the e-library. One can always discuss which mix of methods is optimal, and the combination used could be extended to include additional ones, "cognitive walkthrough" being one such method. Its straightforward and detailed procedure to simulate a user's problem-solving process at each step through a dialogue with the system could have provided additional input in evaluating the system's usability (Nielsen and Mack, 1994). Another possible method is "journey mapping", where you map how the user works, which different actors are involved and how the work process can be changed or improved (McCarthy et al., 2020).

In the development of the e-library, the focus has been to increase patient safety as much as possible, but this is not something we have explored yet. There is an interaction between the usability and safety of an e-health system. Different methods can be used to investigate system safety, such as the system theoretic accident model and processes (STAMP), failure modes and effect analysis (FMEA), fault tree analysis (FTA), and hazard and operability (HAZOP) (Price et al., 2017).

Conclusions

By analysing serious MEs and their characteristics the active failures and latent conditions that contributed to their occurrence can be found. *With this knowledge, measures can be proposed to prevent them from happening again.*

Medication errors occur at all stages: prescribing, preparation, and administration in the chemotherapy process. All of the prescribing errors made by physicians were delivered to the patients, and a majority of the errors caused temporary or life-threatening harm to the patients. The most common error types were too high doses, followed by the wrong drug. *Thus, it is of utmost importance to minimise the potential for errors in the prescribing stage.*

There was a great variety in what happened in the various MEs, which professions were involved, and why the errors occurred. *However, working conditions were often a common denominator behind the errors in many cases*.

Healthcare is constantly evolving with new drugs and methods for the treatment of patients. A national e-library with continuously updated and standardised chemotherapy regimens, as a shared knowledge source, is one way to ensure that all involved healthcare units have access to the same and latest evidence. This also allows for increased patient safety.

The national e-library contains regimens and other supportive information based on the latest evidence. *The information is embedded in a national quality system, within the RCCs, and therefore contributes to organisational and national learning in chemotherapy.*

To ensure that the design and content comply with the users' needs, the usage and usability of the national e-library were evaluated using mixed methods. *The e-library was used in the intended way, and the users can interact without any problems. The results show that the e-library supports healthcare professionals in their daily work.*

Future studies

Healthcare is constantly evolving with new drugs and methods for the treatment of patients. Research in MEs must therefore follow the changes that are taking place. Today, oral cancer drugs are the primary treatment that thus need to be followed up in order to investigate the risks for MEs. Methotrexate, a drug used to treat cancer, has also long been used to treat rheumatoid arthritis and psoriasis but on a different administration schedule (once weekly with tablets rather than more often for cancer). This has resulted in a well-known risk (Moore et al., 2004, Vial et al., 2019), highlighted by the EMA recommending new measures to prevent severe and potentially fatal errors (European Medicines Agency, 2019).

Three different CPOE systems are used in Sweden today, but some clinics still use handwritten documentation. Are there any differences in the processes and risks for MEs between clinics using different solutions? To answer this question and further our knowledge a proactive risk analysis method combined with a retrospective analysis from their internal incident reports could be used.

Now that the national e-library is in use at many clinics, it is necessary to examine in more detail how the service is used at the different clinics. What parts are used? How do clinics implement new regimens? Do they use the XML files? Do they have any other needs that an e-library can support? Evaluations of the usage and usability with mixed methods need to be repeated to follow changes in the users' work and their views on the e-library as well as to promote continuous improvement.

Populärvetenskaplig sammanfattning

Varje år får nästan 66 000 människor ett cancerbesked i Sverige. Bröstcancer är vanligast för kvinnor och prostatacancer för män. Kirurgi, strålterapi och cancerläkemedel är basen i behandlingen av cancer och ofta i kombination med varandra. Behandling med cancerläkemedel hjälper patienten bekämpa sin sjukdom.

Cancerläkemedel kan ges som dropp på sjukhus eller tas som tabletter i hemmet. Behandlingen är komplicerad då olika läkemedel kombineras, ges i olika doser och under olika många dagar beroende på vilken cancerform som behandlas. De olika behandlingarna kallas för regimer. Läkare, sjuksköterskor och farmaceuter samarbetar för att ge patienten behandling. För att stödja vårdpersonalen i arbetet och göra behandlingarna mera lika i landet sågs ett behov av att ta fram ett Nationellt regimbibliotek där den viktigaste informationen finns, se https://kunskapsbanken.cancercentrum.se.

Inom verksamheter med cancerläkemedel uppmärksammades runt millennieskiftet att medicineringsfel kunde ske, något som ibland kunde skada patienten. Som apotekare hade jag under många år ansvaret för beredningsverksamheten på ett större sjukhusapotek där man blandade dropp med cancerläkemedel (cytostatika). Vi kunde få felaktiga ordinationer från läkarna som vi farmaceuter stoppade. Men vi gjorde också egna misstag som stoppades av sjuksköterskorna. Trots olika kontroller kunde fel ändå drabba patienten. Det kunde vara fel läkemedel eller för höga doser. Ett litet fel i dosen kan få allvarliga konsekvenser för patienten då skillnaden mellan bästa effekt och svår biverkan kan vara liten. Jag ville därför undersöka vad som blir fel och varför, för att sedan kunna föreslå åtgärder som minskar risken för att felen upprepas.

Forskningen i avhandlingsarbetet har gjorts under 15 år i Sverige. Tillsammans med mina forskarkollegor har jag undersökt allvarliga medicineringsfel med cancerläkemedel som rapporterats in till våra myndigheter. Vi såg att allvarliga fel görs bland läkare, farmaceuter och sjuksköterskor. Misstagen som gav de allvarligaste konsekvenserna för patienten gjordes av läkare när de ordinerade. Ofta var det för höga doser som gavs och som ledde till exempelvis förlängda vårdtider och i värsta fall till att patienten avled. Vi identifierade flera olika orsaker till felen, som att rutiner saknades eller att läkemedlen hade namn som liknade varandra och därför blandades ihop. Brister i arbetsmiljön – som att det var ont om personal eller att personalen inte fått tillräcklig träning – bidrog till att misstagen skedde.

Efter önskemål från cheferna vid Sveriges onkologkliniker utvecklades ett Nationellt regimbibliotek inom Regionala Cancercentrum i samverkan med mig som projektledare. De önskade en nationell källa med regimer som kunde användas i deras olika ordinationssystem. I utvecklingsarbetet användes forskningen som vi gjort kring medicineringsfelen och från litteraturen. Exempelvis bestämdes att vissa läkemedel bara får ges som dropp, därför att det finns risker för fel om man ger dem som injektion. En referensgrupp med företrädare för de olika vårdprofessionerna bidrog med sina expertkunskaper. Viktiga principer som användes har varit att standardisera hur vi namnger regimerna och hur vi skriver texterna i regimerna. En annan att informationen ska vara kort, koncis och lätt att hitta. Regimbiblioteket har ständigt förbättrats utifrån användarnas synpunkter. Vi har också tagit fram information om regimerna till patienterna där de får veta det viktigaste om sin behandling, som hur den ska ges, vilka biverkningar som är vanliga och när de bör kontakta vården.

För att undersöka hur regimbiblioteket används och vad användarna tycker har vi utvärderat användningen av regimbiblioteket med intervjuer, webbundersökning, sammanställning av feed-back och besöksstatistik. En expertundersökning av webbsidans användbarhet gjordes också. Sammantaget visar det att regimbiblioteket används, att användarna är nöjda och hittar det de söker. Återkopplingar från vårdpersonalen gör att vi ständigt kan förbättra innehållet i regimbiblioteket.

Det kommer många nya cancerläkemedel och behandlingarna förändras så behandling i allt högre grad sker i hemmet. Lärdomarna från medicineringsfelen och arbetet med det Nationella regimbiblioteket kan stötta den utvecklingen och bidra till att behandling med cancerläkemedel blir så säker som möjligt.

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About the author

ANNSOFIE FYHR is a registered pharmacist and has worked as manager of and responsible person for the quality of the chemotherapy preparation at the hospital pharmacy in Lund, Sweden. Chemotherapy errors represent potential risks for severe patient harm. The hospital pharmacists could see physicians making mistakes when prescribing, and the pharmacists themselves could make their own mistakes during preparation. Most often, the medication errors were stopped before they reached the patients. The reoccurring question among us pharmacists was: "Why do all these errors occur and what can be done to stop them?"

During my PhD studies at the Department of Design Sciences, Faculty of Engineering LTH, Lund University, I wanted to find answers and conducted research on medication errors. A National e-library for chemotherapy regimens was also developed to improve the chemotherapy process. This thesis is the result of this work.

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