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Characterization of Drug-Related Critical Incidents from Multiple Settings in the Critical Incident Reporting System North Rhine-Westphalia

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Abstract

Introduction

Incident reporting systems have been implemented in health care for over a decade and contain reports of critical incidents (CI). These must be analyzed in order to suggest, implement and evaluate solutions for minimizing the risk of future CIs to occur, thereby increasing patient safety. Drug-related CIs (DRCI) are one type of CI which may represent up to 1/3rd of all CIs, therefore this CI-type is characterized in this study.

Aim

To categorize and characterize DRCIs reported in the Critical Incident Reporting System North Rhine-Westphalia (CIRS-NRW).

Materials & Methods

In this explorative, retrospective, descriptive study, 553 reports from the CIRS-NRW, reported between the 1st of January 2019 and the 15th of September 2021, were analyzed. These were categorized by setting, medication use process stage, ATC-code, patient age and look-alike, sound-alike (LASA), and then analyzed via descriptive statistics. Various subgroup analyses were also conducted.

Results

DRCIs occurred mostly in the hospital (48,5%) and pharmacy (40,7%) settings, during the prescribing (33,8%) and administration (33,5%) of drugs and the ATC-codes N02 (9,4%), B01 (6,9%) and N05 (5,4%) were commonly involved. Patient age contained >50% missing data and LASA was involved in 16,5% of DRCIs. Subgroups were often small, likely resulting in low statistical power.

Conclusion

By successfully characterizing the DRCIs, some potential areas of improvement for reducing future DRCIs were highlighted, however there are many more variables of relevance for patient safety than those analyzed in this study, underlining the need for further studies characterizing more DRCIs including additional variables.

Populärvetenskaplig sammanfattning

Händelser som kan leda till eller signifikant ökar risken för patientskador, såkallade kritiska händelser, är inte ovanliga inom sjukvården. För att förebygga dessa händelser och därmed minska risken för patientskador har system implementerats på olika områden inom sjukvården dit dessa händelser rapporteras. Händelserna måste därpå analyseras och utvärderas för att hitta områden som kräver förbättring, varpå förslag till åtgärder måste ges, implementeras och sedan utvärderas, innan en ökad patientsäkerhet kan uppnås. Detta görs generellt endast för ett sjukvårdsområde i taget.

I denna studie har kritiska händelser där läkemedel spelade en signifikant roll, såkallade läkemedelsrelaterade kritiska händelser, karakteriserats, detta i ett system som innefattar ett flertal olika sjukvårdsområden. Först exporterades 2796 rapporter kring kritiska händelser från detta system, varpå dessa filtrerades baserat på rapporteringsdatum, bidragande faktorer, händelsetyp och fyra fritextsökningar. Några av de resulterande 586 rapporterna ansågs, efter läsning av rapporterna, vara potentiellt irrelevanta och diskuterades därför inom forskningsteamet, varpå 33 av dessa exkluderades. Detta gav i slutändan 553 rapporter som beskrev läkemedelsrelaterade kritiska händelser. Dessa karakteriserades sedan med avseende på sjukvårdsområde, steg i läkemedelsanvändningen, läkemedel/läkemedelsgrupp, åldersfördelningen av involverade patienter, samt om en läkemedelsförväxling på grund av namn- eller utseendelikheter skett. Därtill utfördes flertalet explorativa analyser där dessa variabler kombinerades på olika sätt.

Resultaten i denna studie blev följande: läkemedelsrelaterade kritiska händelser sker mest på sjukhus och i apotek och vid förskrivningen och administreringen av läkemedel. Smärtstillande läkemedel, blodförtunnande och psykoleptika är de tre läkemedelsgrupper som är involverade mest. Avseende ålder saknades mycket data (>50%), varför inte mycket kunde sägas angående fördelningen av kritiska händelser baserat på ålder. Läkemedelsförväxling på grund av namn- eller utseendelikheter skedde i 16,5% av alla händelser. Analyser av kombinerade variabler visade bland annat att läkemedelsförväxlingen på grund av namn- eller utseendelikheter skedde framför allt i sjukhus och apotek, under förskrivning och dispensering av läkemedel och att läkemedel inom grupperna smärtstillande läkemedel och psykoleptika var mest involverade vid

sådana förväxlingar. Dessa analyser innehöll ofta väldigt lite data, varför de troligtvis ej är tillräckliga för att tydligt klarlägga specifika områden som kan kräva förbättring.

Denna studie ger således en uppfattning av vissa områden där förbättring är möjlig, men är i vissa avseenden otillräcklig på grund av avsaknad av data. Genom att dock föreslå några områden för förbättring kan processen av att hitta, implementera och utvärdera lösningsförslag startas i alla fall för dessa områden, vilket kan medföra en ökad patientsäkerhet och färre skador för patienter. Studien är även en av få som karakteriserar läkemedelsrelaterade kritiska händelser från flera sjukvårdsområden samtidigt, vilket kan möjliggöra framtida liknande studier genom de i denna studie föreslagna metoderna.

List of abbreviations

AIMS = Australian Incident Monitoring System

BÄK = Bundesärztekammer (eng. German Medical Association)

CI = Critical Incident

CIR = Critical Incident Report

CIRRNET = Critical Incident Reporting & Reacting NETwork

CIRS = Critical Incident Reporting System

CIRS-NRW = Critical Incident Reporting System North Rhine-Westphalia

DRCI = Drug-Related Critical Incident

EMA = European Medicines Agency

IRA = Interrater Agreement

IRR = Interrater Reliability

IRS = Incident Reporting System

LASA = Look-Alike Sound-Alike

LTCPLC = Long Term Care Professional Leadership Council

ME = Medication Error

MedDRA = Medical Dictionary for Regulatory Activities

MUP = Medication Use Process

USP = US Pharmacopeia

PSRS = Patient Safety Incident Reporting System

WHO = World Health Organization

ÄZQ = Ärztliches Zentrum für Qualität in der Medizin (eng. The Medical Center for Quality in Medicine)

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1. Introduction

1.1. History of Incident Reporting Systems

In the 1930s travel by airplane was still very dangerous and accidents were common. Because of this, authorities came together in Chicago in 1944 to discuss regulations, which ultimately lead to a general form for reporting incidents, an Incident Reporting System (IRS). This form was extensively used and resulted in the aviation industry we have today through diligent incident reporting, risk factor analysis and implementation of security protocols [1].

Beside the aviation industry, different IRSs with names varying by country, commonly called Critical Incident Reporting Systems (CIRS) [2, 3, 4], Patient Safety Incident Reporting Systems (PSRS) [5] or Australian Incident Monitoring Systems (AIMS) [6] among others, have been implemented in various settings in health care for over a decade [7]. Some of these settings are intensive care units [8, 9] or a tertiary care clinic for internal medicine [10], among many others. The implementation of IRSs is however only part of the process, where an understanding of how the incidents occur and effective ways to implement solutions are also essential to achieve benefits for the patient.

1.2. Potential Benefits and Challenges of Incident Reporting Systems

In a study by Carlfjord, Öhrn and Gunnarsson, benefits such as an increased patient safety, as well as a development and maintenance of risk awareness were noted, following the implementation of an IRS [11].

In addition to the benefits however, many challenges were noted by Carlfjord, Öhrn and Gunnarsson as well. Challenges mentioned include confusion among staff what to report, the non-reporting of incidents where the problem is easily fixed, a general difficulty of evaluating the effects of IRSs and the process of learning from incident data being complex and difficult [11]. The World Health Organization (WHO) brings up underreporting specifically as a weakness for most reporting systems in health care, but also the potentially large volume of reports requiring time, resources and expertise to analyze [12].

1.3. Incident Reports in Health Care Settings

An IRS within a health care setting contains incident reports that detail incidents that could have led, or did lead, to patient harm, also called critical incidents (CI). A CI is defined by the Ärztliches Zentrum für Qualität in der Medizin (ÄZQ) as "an incident that could lead to an undesirable event or significantly increases the risk of an undesirable event to occur" [13]. These CIs can in turn be categorized in different ways, such as by error type, *e.g.*, human errors or errors due to insufficient communication or if they are connected to drugs or not [10], *i.e.,* if they are drug-related critical incidents (DRCI) or not. In this study a DRCI was defined as a CI where a drug mentioned in the Critical Incident Report (CIR) played a significant role. In other studies, DRCIs have been found to make up between 19-36% of CIs [14, 15, 16], giving ample reason to analyze this specific type of CI in further studies like this one. As pharmacists are considered experts on drugs, this profession may be particularly suited for the analysis of DRCIs, hopefully leading to less DRCIs occurring and thus less potential drug-related patient harm.

1.4. Previous Evaluations of IRSs

Studies evaluating IRSs are not uncommon, but most studies evaluate IRSs used in hospitals with the primary care or mental health care settings being evaluated less [12].

Scharein and Trendelenburg evaluated CIs from a web based CIRS in a tertiary care clinic for internal medicine in Switzerland, analyzing the incidents according to the reporting profession, time point during hospitalization process, content and potential causes. Most incidents occurred on medical wards, during prescribing and/or administering drugs and were most frequently categorized as human errors and communication errors, leading to the suggestion that an improvement in communication and medication delivery are most promising to avoid CIs [10].

Khan and Hoda instead reviewed DRCIs reported from the main operating theatre suite in a teaching hospital in a developing country specifically, finding that underdosage, side-effect/drug reaction and syringe swap were common drug errors [15].

Patient safety incidents from intensive care or high dependency units reported to the UK National Patient Safety Agency were reviewed by Thomas and Panchagnula, where they categorized incidents involving drugs. The most common drugs involved in the reports were

morphine, gentamicin and noradrenaline (norepinephrine) and most incidents occurred during drug administration and prescription [17].

Chacko *et al.* evaluated CIs in a multidisciplinary intensive care unit in India, finding that airway-related incidents were the most frequent incidents reported, followed by line-related incidents and then DRCIs. The study also evaluated the resulting damage following the CIs, where four deaths occurred as a direct consequence or were contributed to by the CI [9].

CIs were analyzed and categorized based on drug group, the involved medication use process step and by error category by Kerker-Specker *et al* in Switzerland. Intravenously administered drugs were the most common, analgesics the most frequent affected/involved drug group and the preparation/calculation step the most prevalent step in the medication use process [2].

Meyer-Massetti *et al.* assessed CIs in the home care setting in Switzerland, describing errors of omission, wrong dose and wrong time as common. Underlying causes were assessed as well, finding that working conditions, lacking attention, time pressure and interruptions by patients were most frequent [3].

Alghamdi *et al.* examined the nature of contributing factors associated with medication-related safety incidents reported in neonatal and pediatric intensive care units within the UK. They found that incidents commonly occurred during the prescribing and administration MUP-stages, frequently involving anti-infectives and the error types drug omission and dosing errors. Common contributing factors to harmful incidents noted were staff-related errors like documenting errors and more, often associated with inadequate guidelines, working conditions and design of systems and protocols [8].

The above studies show the variety of ways in which CIs can be evaluated. Additionally, all of the above studies evaluate CIs in one setting, confirming the statement by the WHO at the start of this subsection [12] and pointing out the lack of studies evaluating IRSs containing CIRs describing CIs across multiple settings.

1.5. About the Critical Incident Reporting System North Rhine-Westphalia

The CIRS-North Rhine-Westphalia (CIRS-NRW) is a learning- and reporting system for CIs in patient care in North Rhine-Westphalia, Germany. It was started at the end of 2012 with the intention of promoting open discussion of CIs and thus providing opportunities for learning from these CIs. CIRs can be viewed on the CIRS-NRW homepage and can also be commented on [18]. This may lead to a discussion of ways to decrease risks and the development of solution strategies, hopefully leading to improvements in patient safety in the long run.

The CIRS-NRW is directed towards people working in health care and consists of reports from over six settings, including the hospital, doctor´s office and pharmacy settings among others. The reports are reviewed by a group of representatives from all CIRS-NRW partners (different chambers of pharmacists, chambers of doctors, hospitals etc.) before publication in the CIRS-NRW database [18], which serves as a form of report validation.

Many different kinds of CIs in health care are reported to the CIRS-NRW by the users, which are mainly health care workers within the NRW. Some relate to drugs *i.e.,* are DRCIs, and some relate to other aspects of health care relevant for patient safety. The reporting is done via a form found on the homepage of the CIRS-NRW. In this form the patient´s age group and sex, the setting where the CI occurred, a description of the CI, contributing factors, the reporting person´s profession and more is filled in (Appendix 1). The filled-out form is then sent to be reviewed by the group of representatives as mentioned above, where it is anonymized if needed and modified to secure a freedom of sanctions, after which it may eventually be published as a CIR [18].

1.6. Reasons for Conducting this Study

The CIRs in the CIRS-NRW have not, in a larger scale, been systematically categorized and characterized to this date, which is what this study aims to do, this with the end-goal of utilizing the potential for learning from the CIRS-NRW to the fullest, thereby decreasing future occurrence of CIs and therefore increasing patient safety.

In addition to this, studies taking multiple settings into account simultaneously are rare, as described in section 1.4. Studies including multiple settings may give a broader view of shortcomings in health care systems in regard to patient safety, potentially highlighting areas in

need of improvement common to entire health care systems. The CIRS-NRW contains CIs from multiple settings, *e.g.*, the hospital, doctor's office and pharmacy settings. By evaluating CIs from multiple settings concurrently in this study a categorization method is proposed, hopefully simplifying future studies evaluating IRSs across multiple settings.

2. Aim and objectives

The aim of this study was to categorize and characterize critical incidents related to the use of drugs *i.e.*, drug-related critical incidents reported in the Critical Incident Reporting System North Rhine-Westphalia.

2.1. Research Questions

- In which setting do DRCIs commonly occur?

- At which stage of the medication use process do DRCIs often occur?

- Which medication groups are commonly involved in critical incidents?

- What does the age distribution of affected patients look like?

- How common are DRCIs related to look-alikes or sound-alikes?

In addition to the above research questions, the variables were also analyzed in an explorative manner, grouping variables into subgroups and analyzing these, to indicate specific areas of interest.

3. Materials and methods

3.1. Setting

The study was conducted in Münster, North Rhine-Westphalia, Germany at the Institute for Health Services Research in Community Pharmacies of the Chamber of Pharmacists Westphalia-Lippe [19], in collaboration with the University of Münster [20].

3.2. Study Design

This study is an explorative, retrospective, descriptive study [21] of DRCIs reported in the CIRS-NRW between the 1st of January 2019 and the 15th of September 2021. This time interval was chosen to include the most recent CIs reported to the CIRS-NRW, while also taking the limited study period into account, which was 4 months.

3.3. Study Units

All CIRs in the CIRS-NRW added before the 15th of September 2021 were exported from the CIRS-NRW. Following the filtering process described under section 3.6., 586 of the 2796 CIRs in the original exported dataset were categorized. 553 of the 586 categorized CIRs were analyzed with descriptive statistics following inclusion/exclusion according to the following criteria.

3.3.1. Inclusion Criteria

- The CIR describes a CI as defined by the ÄZQ [12].

- The CI is drug-related, *i.e.*, the CI is a DRCI.

For inclusion, both inclusion criteria had to be met.

3.3.2. Exclusion Criteria

- The CIR describes a CI, and a drug is mentioned, but it cannot be determined whether the CI is a DRCI or not and it is not deemed relevant for patient safety in regard to the mentioned drug following discussion within the research team.

3.4. Collection of Data

All CIRs that were characterized in this study were already publicly available at the homepage for the CIRS-NRW [18] and were directly exported from the CIR-database found on this homepage.

3.5. Software Used

Microsoft® 365 Excel® was used during the categorization of the CIRs and partly for the creation of figures and tables for the presentation of data. IBM SPSS Statistics 28.0.1.0 (142) was used for the descriptive statistics and for the creation of the majority of figures and some tables.

3.6. Filtering of the CIRs

The original dataset containing 2796 CIRs was first filtered by date, only including the CIRs that were added to the CIRS-NRW between the 1st of January 2019 and the 15th of September 2021, resulting in 1302 remaining CIRs. Then, multiple separate filtrations of the remaining 1302 CIRs followed; one by contributing factors categorized by the Bundesärztekammer (BÄK) in the original dataset beforehand, where all CIRs having medication as a contributing factor were included, and one by incident type, also categorized by the BÄK in the original dataset beforehand, where all CIRs of the incident type medication/infusions were included. Four separate free text searches were also conducted by reverse filtering the 1302 CIRs with the incident type filter first *i.e.,* the 792 CIRs that were filtered away by this filter were the result of the reverse filtering. These 792 CIRs were then filtered by using the words “Arzneimittel”, “Medikament”, “Medikation” and “Präparat”, yielding 8, 37, 23 and 9 CIRs respectively. After the above filtrations a total of 1058 CIRs remained, including some duplicates. After removing all duplicates 586 CIRs were left. These 586 CIRs were categorized and potentially irrelevant CIRs marked, later to be discussed within the research team, resulting in the exclusion of another 33 CIRs using the criteria mentioned under sections 3.3.1. and 3.3.2., leaving 553 CIRs to be analyzed with descriptive statistics. The complete filtering process is also described in Figure 1.

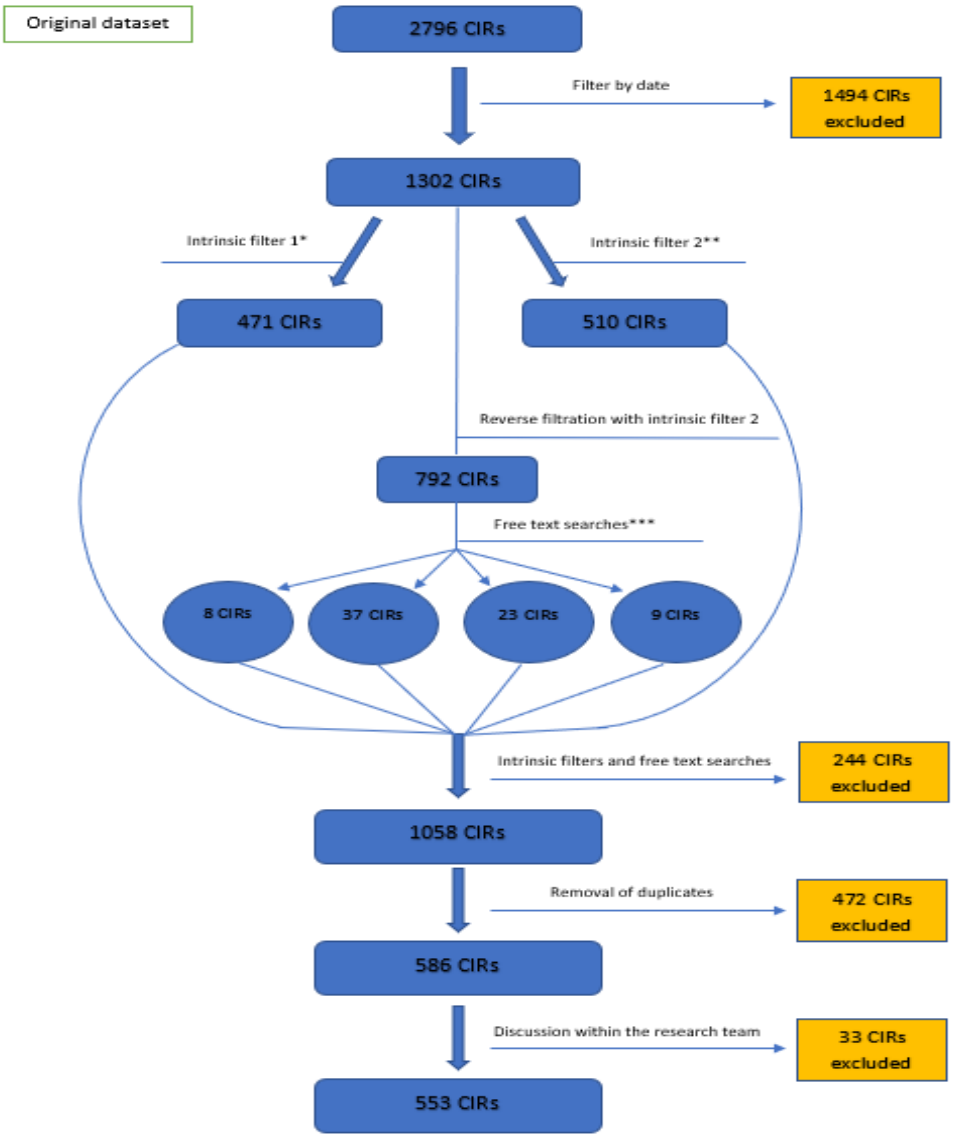

Figure 1: Filtering process for the 2796 CIRs in the original dataset exported from the CIRS-NRW on the 15th of September 2021. The dates used for the first filtration were the 1st of January 2019 and the 15th of September 2021.

*Intrinsic filter 1: Contributing factors categorized by the BÄK beforehand. All CIRs having medication as a contributing factor were included.

**Intrinsic filter 2: Incident type, also categorized by the BÄK beforehand. All CIRs of the incident type medication/infusions were included.

***Free text search words: “Arzneimittel”, “Medikament”, “Medikation” and “Präparat” yielding 8, 37, 23 and 9 CIRs as results respectively. These were applied on the 792 CIRs remaining after a reverse filtration with intrinsic filter 2.

The discussion within the research team that lead to the exclusion of 33 further CIRs after the removal of duplicates was based on the criteria mentioned under sections 3.3.1. and 3.3.2.

3.7. Establishing of Categorization Rules

Because the categorization of the CIRs was done over the course of multiple months, general categorization rules were established following individual categorization of 30 randomly selected CIRs by two people from the research team, followed by a discussion of 14 of these CIRs with a third person within the research team regarding thoughts and comments surrounding the categorization. This was relevant because most CIRs contained missing, incomplete or vague information, resulting in an otherwise highly subjective categorization of these CIRs, warranting th16establishment of these rules to decrease the intra- and inter-individual variation in the categorization of the CIRs.

Rules were established for the variables ATC-code, Medication Use Process (MUP) stage and Look-Alike Sound-Alike (LASA), described under the relevant subsection of section 3.8.

3.8. Categorization of CIRs

There are multiple ways of categorizing CIs in IRSs described by the WHO and European Medicines Agency (EMA) regarding Medication Errors (ME). MEs are defined by the EMA as "an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient" [22]. The WHO recommends four categories for initial analysis and prioritization: patient outcome, MUP, medication problem and therapeutic group or individual medicine [23]. The EMA also recommends following up these four categories, in addition to six others like setting, contributing factors and seriousness [24]. CIs have been categorized by some of these categories in multiple studies, categories used varying between studies, as mentioned under section 1.4.

Because the definitions for MEs and CIs overlap, all MEs are also CIs. Even though this may not always be the case for DRCIs as defined in this study, meaning MEs are not always DRCIs, the categorization of the MUP and therapeutic group was also deemed relevant for DRCIs. This was due to the guaranteed inclusion of at least one drug in the CIRs characterized in this study due to the inclusion criteria set up. Due to the explorative nature of this study, when noticing LASA commonly being mentioned while reading the CIRs, this category was added as an additional variable to categorize the CIRs by. LASA is also mentioned by the WHO as a contributing factor to the occurrence of MEs [23].

Some variables such as age and setting, among others not categorized in this study, had already been categorized by the BÄK as far as possible before they had been added to the CIRS-NRW. After exporting the original dataset from the CIRS-NRW, Ms. Monique Geisler from the BÄK provided a detailed description of the categories for all variables in the exported dataset (Appendix 2), thus these variables did not have to be categorized again.

3.8.1. Categorization of the ATC-code

All 586 CIRs following filtration and removal of duplicates (Figure 1) were read, during which drugs or drug groups mentioned were categorized based on the Anatomical Therapeutic Chemical Classification System *i.e.*, by ATC-code. This was done at the 2nd level, resulting in 94 different possible ATC-codes. The ATC/DDD Index 2022 by the WHO Collaborating Centre for Drug Statistics Methodology (WHOCC) [25] and the ATC-Datenbank der Gelben Liste by Vidal MMI Germany GmbH [26] were used to check the correct ATC-codes of drugs mentioned in the CIRs.

Only CIRs where the indication and drug were clearly stated in the CIRs, or if there was only one possible ATC-code for any given drug mentioned, were categorized. CIRs where the indication was unclear or where data was otherwise missing, making an accurate categorization impossible, were marked and coded as containing missing data. In CIRs where multiple drugs with different ATC-codes were mentioned, every ATC-code was only coded for once. In some CIRs multiple drugs or drug groups were mentioned, where some of these could be categorized and some not, sometimes resulting in both a “successful” categorization of the ATC-code into one of the 94 ATC-code categories and a “missing data” categorization in the same CIR.

See Appendix 3 for a detailed list of all 94 ATC-codes at the 2nd level including the coding and rules used for this variable.

3.8.2. Categorization of the MUP

Because the CIRs in the CIRS-NRW contained CIs from multiple settings and every setting included did not include the exact same MUP-stages, a method that took this into account had to be used for the categorization of the MUP. Evaluations of IRSs are usually done for IRSs

containing CIRs for only one setting, *e.g.*, a hospital or a specific hospital ward. Because multiple settings were included in this study, an aggregation of MUP-stages mentioned in the US Pharmacopoeia (USP) [27], by Diedrich, Zúñiga and Meyer-Massetti [28], by the Long Term Care Professional Leadership Council (LTCPLC) [29], in the Medical Dictionary for Regulatory Activities (MedDRA) [30] and by the EMA [24] was made, resulting in 9 MUP-stages. Important to note is that the order of the MUP-stages does not reflect a timeline of care in any setting, meaning all 9 MUP-stages are not always included for any given setting or CI.

Any category of the MUP-stages was only chosen when an error occurred at that stage that was not the direct result of an error during a previous MUP-stage. This means that error chains, for example when a prescription error leads to a transcribing error because the error is not intercepted, were not considered in this study, because only the first error in any potential error chain was categorized.

In cases where it was not clear whether the CI occurred during the prescribing or transcribing & order entry stages and where both categories were plausible, the CI was categorized as a CI during the prescribing stage. The reasoning behind this was that errors in both stages result in an incorrect drug receipt, meaning errors in these MUP-stages have a similar outcome. The transcribing & order entry stage is also sometimes not separated from the prescribing process [24, 28, 30], thus warranting the categorization as a CI during prescribing.

A similar rule was established for the MUP-stages preparation for administration and administration, where preparation for administration is sometimes not seen as its´ own MUP-stage *e.g.,* like described by the LTCPLC [29] or by Hughes and Blegen [31]. This is why CIs where both preparation for administration and administration were plausible categories, were categorized as CIs occurring during the administration process.

See Appendix 4 for coding, rules and descriptions of the MUP-stages used in this study.

3.8.2.1. Interrater Agreement Test

Because the final MUP-stages used were aggregated from multiple different sources and this method had not been used before, it had to validated in some way. In an article by Gisev, Bell

and Chen the terms interrater agreement (IRA) and interrater reliability (IRR) are described. In this article IRA is described as relating to “the extent to which different raters assign the same precise value for each item being rated”, whereas the term IRR describes “the general trend in ratings, not the absolute value assigned by each of the raters, and the variation between ratings and measurement error is accounted for in IRR” [32]. Because the variable MUP consists of categorical data, meaning the values are not on a scale but instead each have their own meaning, an IRA-test was deemed appropriate in this study. This test was conducted by randomly selecting 10 CIRs via an algorithm in Microsoft® 365 Excel®, after which these were categorized individually by two people within the research team and the resulting categorizations compared.

3.8.2.2. Calculation of Cohen´s Unweighted Kappa (*κ)*

A commonly used index for IRA/IRR is Cohen´s unweighted kappa (κ), often called Cohen´s kappa. Cohen´s kappa provides a chance-corrected index of IRA/IRR in studies where the same two raters rate items on a nominal scale, which was the case in this study. When using Cohen´s kappa, three assumptions must be met [32]:

1. The items to be rated are independent.
2. The categories are independent, mutually exclusive, and exhaustive.
3. The raters are independent.

All of these assumptions were met in this study, making the use of Cohen´s kappa possible. Cohen´s kappa was calculated for the 10 categorized CIRs mentioned above using descriptive statistics in SPSS, resulting in an agreement of 0,744 between the two people from the research team, with an asymptotic standard error of 0,150 and an approximate significance of <,001. A value of 0,61-0,80 for the agreement is considered a substantial agreement [32, 33].

3.8.3. Categorization of LASA

CIRs where LASA was explicitly mentioned, or where LASA was clearly indicated as a contributing factor for the CI, were categorized as LASA. CIRs where patients´ names had been confused were not categorized as LASA. CIRs where drugs had been mixed up for other reasons

e.g., if the drug had been put in the wrong spot and was picked up or taken without looking, were not categorized as LASA either.

3.9. Data Analysis

After categorizing the CIRs they were exported to SPSS creating a new dataset. Because some of the variables, like ATC-code and the MUP, were coded in separate columns, new variables for each of the MUP-stages and for the 12 most commonly mentioned ATC-codes in the CIRs were created. Other modifications of the dataset were also made, enabling the analysis of the data via descriptive statistical analyses using the related functions in SPSS. This was done for the setting, age and LASA variables as well as a total ATC-codes variable and a total MUP-stages variable, resulting in descriptive tables and figures including frequencies and more, some of which are presented in the results section.

The 12 most commonly mentioned ATC-codes in the CIRs categorized were determined by descriptive statistics of an ATC-codes total variable, where a cut-off >10 CIRs was applied, resulting in 12 ATC-codes. Due to the coding of the ATC-codes and MUP-stages in separate columns, the total ATC-codes and total MUP-stages variables were created in separate datasets, resulting in a total of 666 categorized ATC-codes and 727 categorized MUP-stages.

Due to the explorative nature of this study, the variables were also grouped together in subgroups where analyses were performed using descriptive statistics in a similar manner as for the ungrouped variables. The different ways that variables were grouped were:

- LASA – Setting
- LASA – 12 most common ATC-codes variables + 1 ATC-code missing data variable
- LASA – 9 MUP-stage variables + 1 MUP missing data variable
- Setting – 12 most common ATC-codes variables + 1 ATC-code missing data variable
- 12 most common ATC-codes variables + 1 ATC-code missing data variable
  – 9 MUP-stage variables + 1 MUP missing data variable

Because multiple variables for the ATC-codes and MUP-stages were grouped with other variables, many subgroups were created. Instead of separately analyzing all of these subgroups, cross-tabulations were generated showing frequencies for each subgroup. Some CIRs contained

missing data for one variable, but not the other variables, resulting in the inclusion of the ATC-code missing data and the MUP missing data variables.

The LASA – Setting subgroup could help to describe in which setting CIs involving LASA may commonly occur, while the LASA – 12 most common ATC-codes subgroups could hint at which of the 12 most commonly involved ATC-codes in the CIs characterized are possibly mostly affected by LASA. The LASA – MUP-stage subgroups could indicate during which MUP-stage LASA might frequently occur and the Setting – 12 most common ATC-codes subgroups could imply in which setting CIs involving these 12 ATC-codes may regularly occur. The 12 most common ATC-codes – MUP-stage subgroups may describe which of the 12 ATC-codes may be most prevalent in CIs occurring during each MUP-stage.

Important to note is that these subgroup analyses were not constructed and performed in a way proving significance, but only in an explorative manner to indicate possible areas of improvement in the overall drug use relating to the analyzed variables. In other words, no statistical tests were performed for any results from the subgroup analyses.

3.10. Ethical considerations

During this study data analysis of pre-collected/-submitted data was conducted. The data was reported anonymously or anonymized by medical experts that had evaluated the information contained in the CIR before it was published in the database CIRS-NRW. To enable users to report incidents pertaining information regarding actual harm to a patient, a freedom of sanctions is essential and anonymity of both the reporting user and the victim of the harm has to be ensured. In larger CIRSs anonymity is still possible due to the number of reports, but in smaller CIRSs even anonymized cases could be recognized by fellow employees in the institution where the CIRS is implemented [13]. Thus, to ensure the freedom of sanctions in the CIRS-NRW, CIs that did not lead to actual harm were published in the CIRS-NRW, and CIs that lead to actual harm were generally modified in a way so that they instead depicted an incident where no actual harm was done, and then published in the CIRS-NRW. This results in an environment where users can report CIs safely and the anonymization contributes to neither patient nor medical professional being able to be identified. Patient safety is improved by analyzing where and why potentially harmful incidents occur and then improving *e.g.,* working protocols, equipment, or

expertise of workers to prevent any harmful incidents of the same type to occur in the future. An ethical approval was not required for this study because the data was publicly available.

4. Results

The total amount of CIRs remaining of the 2796 CIRs from the original dataset following the complete filtration process was 553, hereafter described as "the total CIRs categorized", correlating to 19,8% of the total amount of CIRs in the original dataset. Thus, 1/5th of CIRs described DRCIs, following the inclusion criteria established (section 3.3.1.).

4.1. Setting

From the total 553 CIRs categorized, 268 (48,5%) occurred in the hospital setting, while 225 (40,7%) occurred in the pharmacy setting. The setting where the third most CIs occurred was the doctor´s office, where 33 (6,0%) of the categorized CIs occurred (Figure 2).

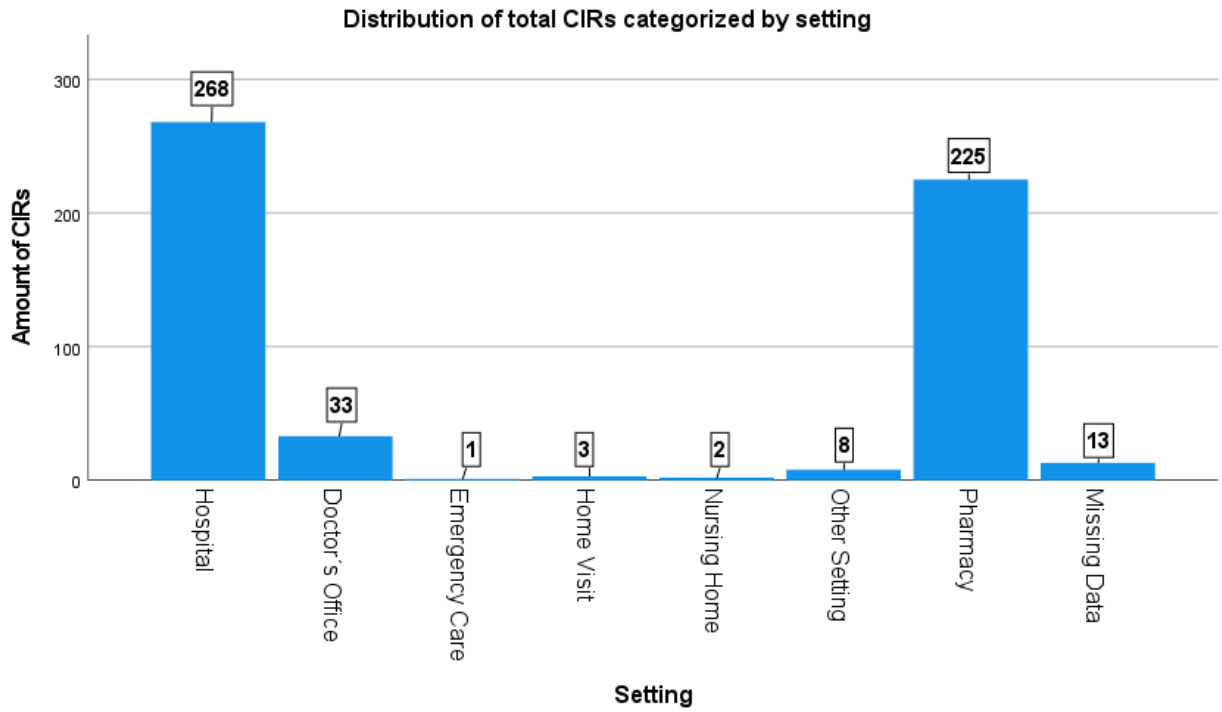

Figure 2: Distribution of the total 553 CIRs categorized by setting.

4.2. MUP

Out of 553 categorized CIRs, 187 (33,8%) described CIs occurring during the prescribing MUP-stage and 185 (33,5%) CIs occurring during administration. CIs were described during dispensing, preparation for administration and documenting in 120 (21,7%), 76 (13,7%) and 62 (11,2%) of the categorized CIRs respectively (Figure 3).

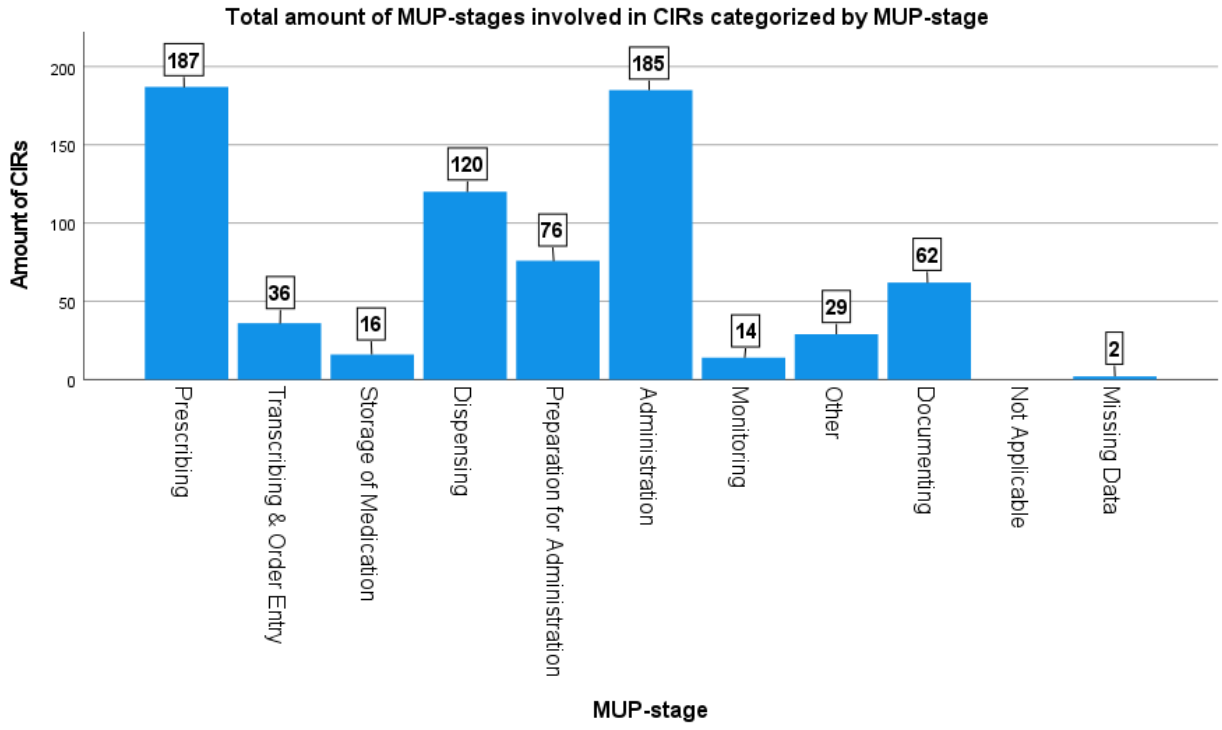

Figure 3: Total amount of MUP-stages involved in CIRs categorized by MUP-stage. Multiple CIs at different MUP-stages are described in some CIRs, resulting in a total of 727 categorized MUP-stages. Total amount of CIRs categorized = 553.

4.3. ATC-code

The three most common ATC-codes involved in CIs were, in order, N02 Analgesics (52; 9,4%), B01 Antithrombotic Agents (38; 6,9%) and N05 Psycholeptics (30; 5,4%). In 195 (35,3%) of CIRs there was at least one drug or drug group that could not be categorized by ATC-code (Figure 4).

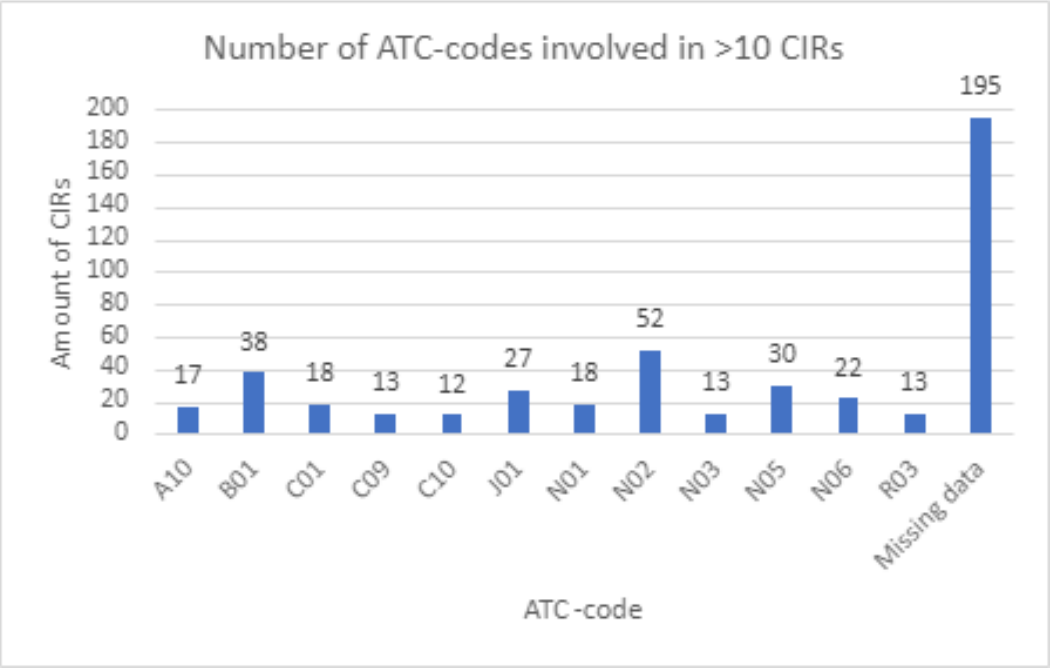

Figure 4: Number of ATC-codes involved in >10 CIRs by ATC-code. Total amount of different ATC-codes included in this study = 94, total amount of ATC-codes categorized = 666, total amount of CIRs categorized = 553.

4.4. Age Distribution

In 294 (53,2%) of CIRs the age of the patient was unknown/missing. The three most common age groups were 71-80 years (45; 8,1%), 61-70 years (38; 6,9%) and 81-90 years (34; 6,1%) (Figure 5).

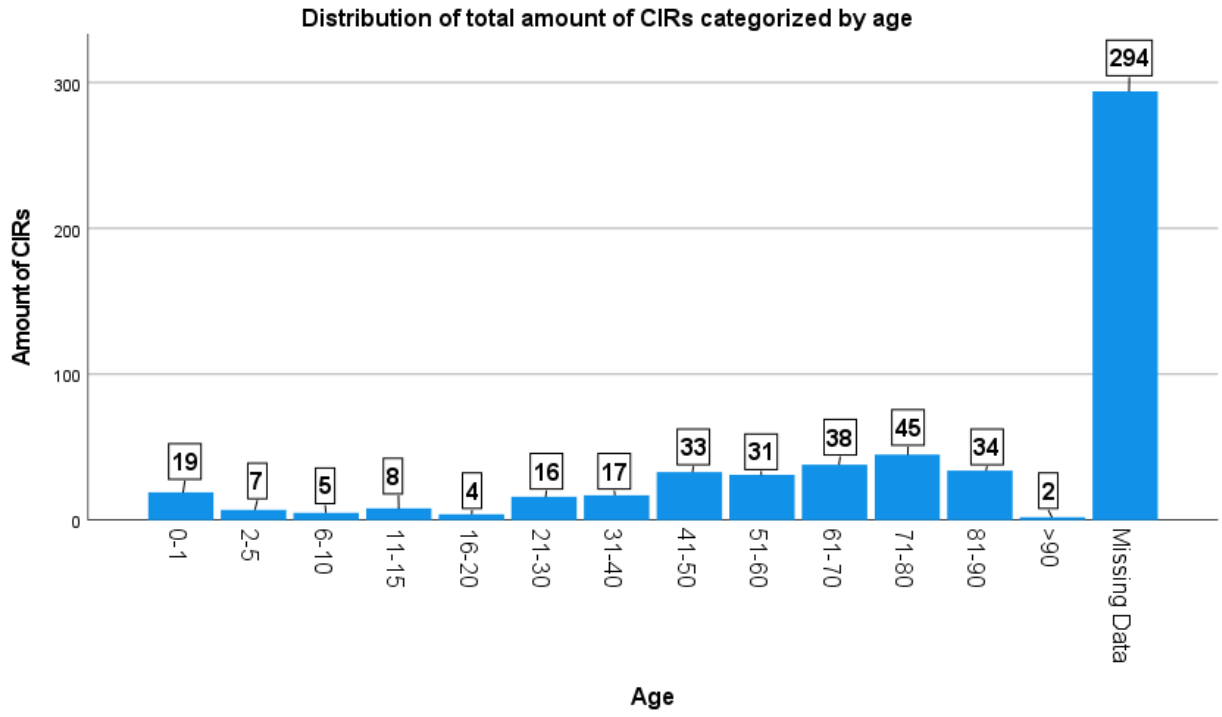

Figure 5: Distribution of the total 553 CIRs categorized by age.

4.5. LASA

In 91 (16,5%) of the total 553 CIRs categorized LASA was mentioned or indicated as a potential contributing factor to the occurrence of the CI.

4.6. Results from Grouped Variables

4.6.1. LASA – Setting

In 42 (46,2%) of the total 91 CIRs mentioning or indicating LASA, the CIs mentioned occurred in the pharmacy, while this number was 39 (42,9%) for the hospital setting. For the categories doctor´s office, other setting and missing data, the amount of CIRs mentioning LASA was 6 (6,6%), 2 (2,2%) and 2 (2,2%) respectively (Figure 6), while it was 0 for the remaining settings.

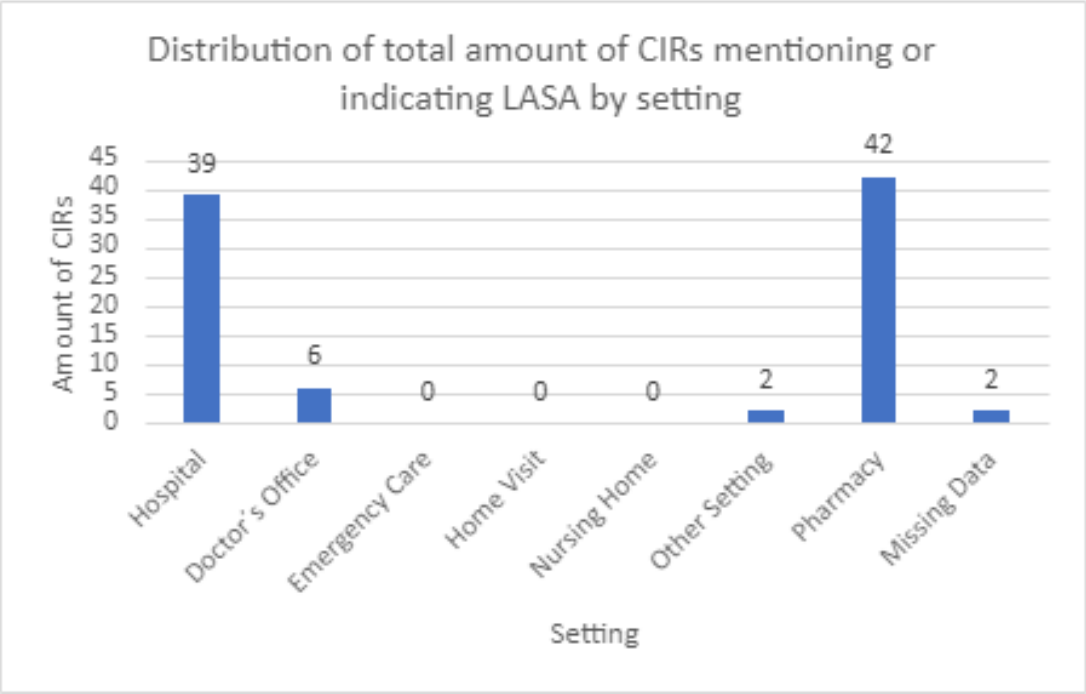

Figure 6: Distribution by setting of the total 91 CIRs mentioning or indicating LASA.

4.6.2. LASA–- MUP-related variables

LASA was a contributing factor during the prescribing MUP-stage in 27 (29,7%) out of the 91 total CIRs involving LASA. For the dispensing MUP-stage this number was 22 (24,2%), for the administration MUP-stage 16 (17,6%) and for the preparation for administration MUP-stage 15 (16,5%) (Figure 7).

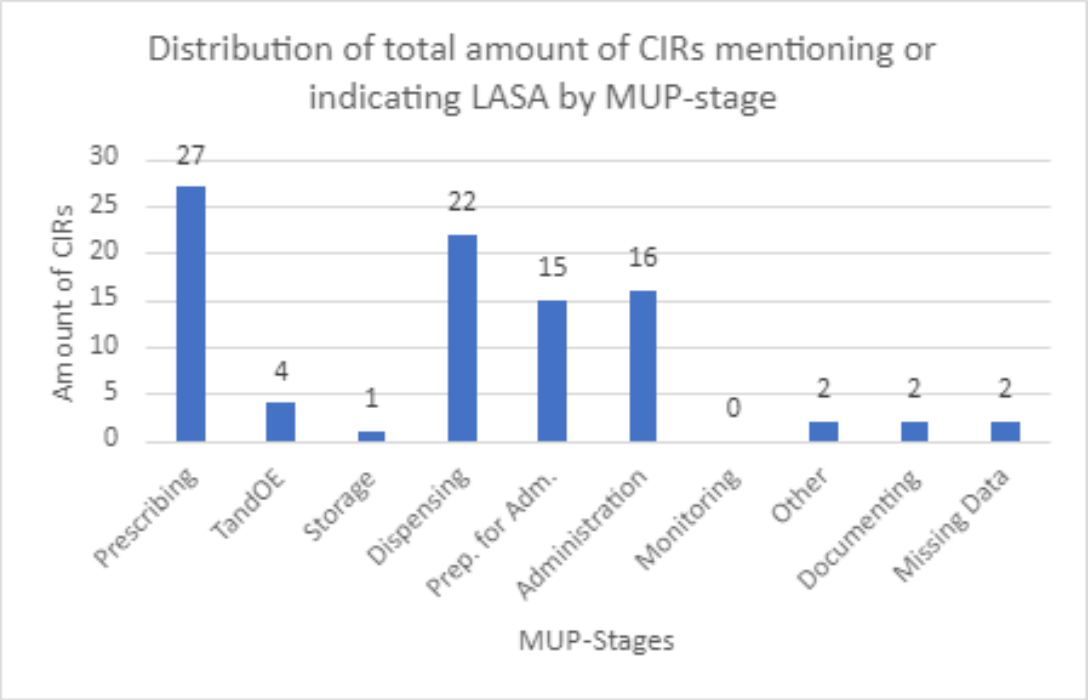

Figure 7: Distribution by MUP-stage of the total 91 CIRs mentioning or indicating LASA. "TandOE" stands for Transcribing & Order Entry and "Prep. for Adm." stands for Preparation for Administration.

4.6.3. LASA–- ATC-code-related variables

Both the ATC-codes N02 and N05 were mentioned or indicated in 13 (14,3%) out of a total 91 CIRs related to LASA, while the ATC-codes N06 and J01 were mentioned in 8 (8,8%) and 7 (7,7%) CIRs respectively, followed by the ATC-code C01 being mentioned in 6 (6,6%) CIRs (Figure 8).

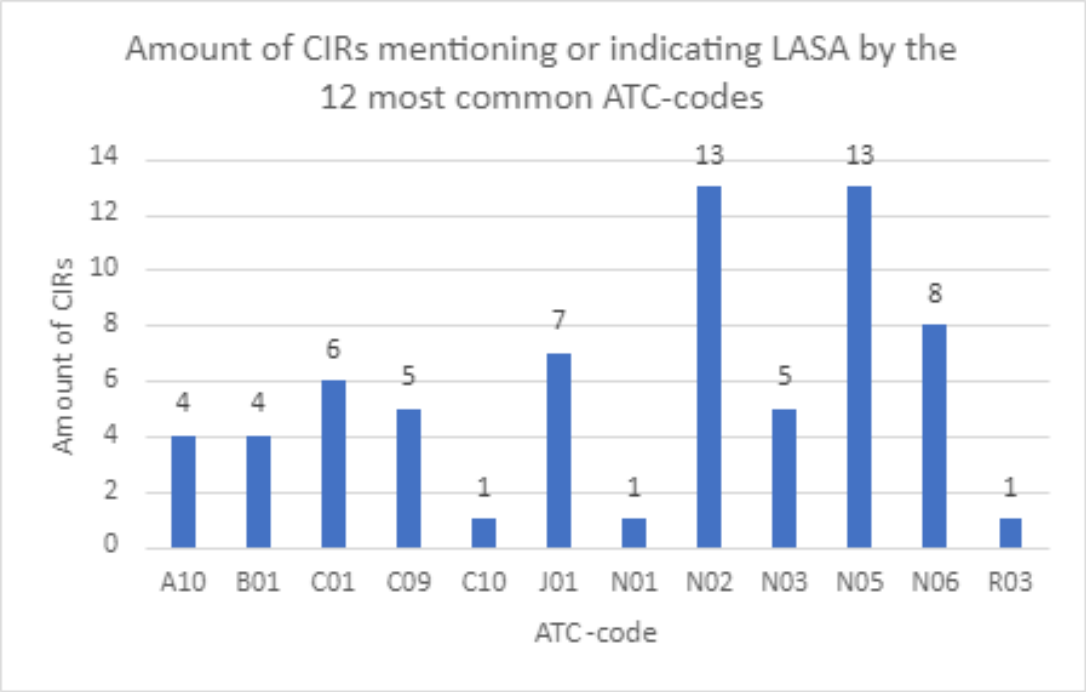

Figure 8: Amount of the total 91 CIRs mentioning or indicating LASA by the 12 most commonly mentioned ATC-codes in the CIRs categorized by ATC-code.

4.6.4. Setting–- ATC-code-related variables

For both of the settings hospital and pharmacy, the ATC-code most commonly involved in the CIs reported for these settings was N02 with 26 (4,7%) and 22 (4,0%) CIRs respectively of the total 553 CIRs categorized. The ATC-codes C09, C10, J01, N06 and R03 were more frequently categorized for the hospital setting, while the ATC-codes more commonly reported in the pharmacy setting included A10, B01, C01, N01, N02, N03 and N05 (Figure 9).

No ATC-code for the missing data category or any of the four remaining settings, besides the hospital setting and the pharmacy setting, was involved in ≥ 5 CIRs, which is why these categories are not presented.

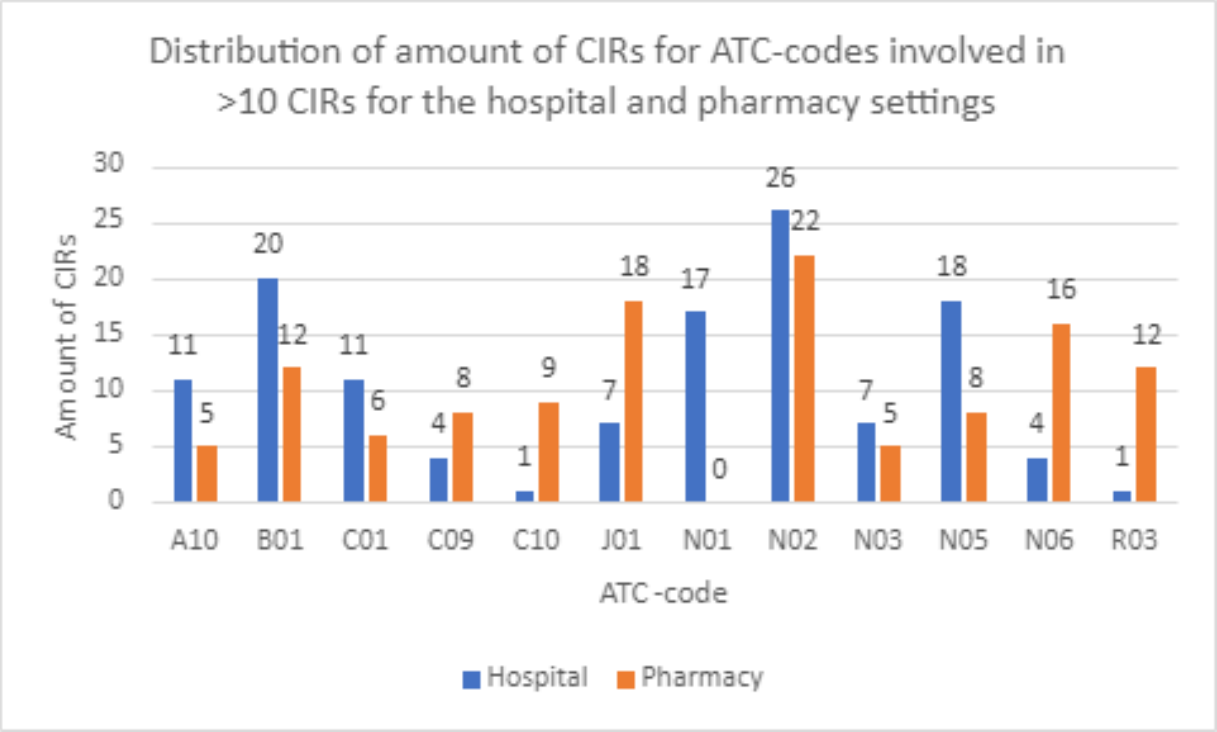

Figure 9: Distribution of CIRs involving ATC-codes involved in more than 10 CIRs by the hospital and pharmacy settings.

4.6.5. ATC-code-related variables – MUP-related variables

The ATC-codes J01 and N02 were the most commonly mentioned ATC-codes during the MUP-stage prescribing, both being involved in 17 (9,1%) out of 187 CIs occurring at the prescribing MUP-stage. The most commonly mentioned ATC-codes for the administration MUP-stage was B01 (15; 8,1%, total: 185 CIRs), for the dispensing MUP-stage it was N02 (10; 8,3%, total: 120 CIRs), and for the preparation for administration MUP-stage there were two equally common ATC-codes; N01 and N05, both being involved in 6 (7,9%) out of 76 CIs occurring during the preparation for administration MUP-stage. For all other MUP-stages the most common ATC-codes were all involved in three or less CIs occurring during the respective MUP-stage (Table 1).

Table 1: Most common ATC-codes out of the 12 ATC-codes involved in >10 CIRs for each MUP-Stage, including the amount of CIRs written in parentheses and the total amount of CIs occurring at the respective MUP-stage.

MUP-Stage	Most common ATC-codes (cut-off >10 CIRs)	Total amount of CIs occurring at the MUP-stage
Prescribing	**J01** (17; 9,1%)/ **N02** (17; 9,1%)	187
Transcribing & Order Entry	-*	36
Storage of Medication	-*	16
Dispensing	**N02** (10; 8,3%)	120
Preparation for Administration	**N01** (6; 7,9%)/ **N05** (6; 7,9%)	76
Administration	**B01** (15; 8,1%)	185
Monitoring	-*	14
Other	-*	29
Documenting	-*	62

*For all 12 ATC-codes involved in >10 CIRs, the amount of times involved during the MUP-stages transcribing & order entry, storage of medication, monitoring, other and documenting was 3 or less, resulting in multiple ATC-codes being the most common for the respective MUP-stage.

5. Discussion

A total of 553 CIRs describing DRCIs were categorized, finding that most DRCIs occur in the hospital and pharmacy settings during the prescribing or administration of drugs. The ATC-code N02 seems to be most prevalent in DRCIs followed by the ATC-codes B01 and N05. LASA seems to occur in 1/6th of DRCIs. Age distribution included a lot of missing data, making the characterization of this variable hard. Thus, answers for all research questions mentioned under section 2.1. have been found, thereby fulfilling the aim of this study.

5.1. Discussion of Results

Almost 19,8% of the CIRs from the original dataset exported from the CIRS-NRW were included, meaning they described DRCIs following the inclusion criteria set up in this study. In other studies, the portion of CIs involving drugs was noted to be 19,4% [14], 21% [15], or 36% [16]. This indicates the relevance of characterizing DRCIs in IRSs to cast light upon potential areas of improvement with the end goal of increasing patient safety.

5.1.1. Setting

Looking at the setting variable, it is clear that most DRCIs seem to occur in the hospital and pharmacy settings (Figure 2). This may be due to the fact that IRSs and the practice of incident reporting were first implemented in the hospital setting [34] and, at least in Germany, have also spread to the pharmacy setting through the use of *e.g.*, the CIRS-NRW (implemented at the end of 2012). For the other settings, a lack of access to computers or forms for incident reporting, lack of time or just the lack of knowledge about IRSs and incident reporting in general may be reasons for the low amount of CIRs in those settings. Specific settings may also have their own IRS that is preferably reported to *e.g.,* like “Jeder Fehler zählt” [35], which is used for reporting CIs occurring in doctors´ offices, potentially resulting in fewer of these CIs being reported to the CIRS-NRW.

5.1.2. Age

When looking at the results concerning the age distribution of the patients mentioned in the CIRs, one should immediately note the apparent amount of missing data, where over half of

CIRs (Figure 5) were missing data regarding the age of the patient. In many cases, the age of the patient may not be relevant when reporting the DRCIs, *e.g.,* when a drug was confused with another drug due to LASA, whereas it could be relevant in some cases, *e.g.*, when a drug that is contraindicated for patients below the age of 18 is prescribed for a teenage patient by mistake. In these cases, the age should be noted, but because these cases are very specific, they most likely do not make up the majority of DRCIs. In cases where the age is deemed irrelevant by the reporter, the risk of omission of the age of the patient is therefore likely high. In addition to this, sometimes the exact age of the patient could simply be unknown, which in addition to the other factor mentioned, results in the missing data in more than half of DRCIs not being very surprising. Besides the missing data category, not much can be said about the age variable, more than that DRCIs seem to occur more commonly in patients aged 0-1 and in patients between the ages of 41-90 (Figure 5).

5.1.3. LASA

Regarding LASA, 16,5% of DRCIs may have LASA as a contributing factor, a similar number to the one described by the WHO (15%), referring to the USP 2004 [23]. Because LASA could theoretically be related to human error due to lack of concentration, stress or lack of knowledge etc., DRCIs involving LASA may be hard to prevent. Nonetheless, the WHO suggests the alerting of health providers and taking of additional safety precautions where name confusion is identified and urges health-care organizations to actively identify and manage risks associated with LASA-drugs [23]. Potential ways to prevent LASA from occurring in specific institutions could be organizational, meaning storage of LASA-drugs in separate places or avoiding of buying drugs with similar package design, if possible, etc., though these solutions might not be practically feasible or very effective in the long run. Systemic changes to the regulatory requirements for package design could be a potentially effective option for reducing LASA but may be hard to achieve.

5.1.4. ATC-code

The three most common ATC-codes were N02 Analgesics, B01 Antithrombotic Agents and N05 Psycholeptics (Figure 4). Interestingly, all of these ATC-codes include drugs that are frequently

classified as high-risk, meaning they are commonly associated with harm when used in error [36, 37]. On one side, this seems logical because errors while using drugs commonly associated with harm would likely lead to CIs in more cases than drugs who are usually not associated with harm. On the other side, drugs that are known to be harmful when involved in errors, should have additional safety measures described in guidelines and special care should be highlighted during training of the handling of these drugs. Because these three ATC-codes are still the most frequently mentioned in the categorized CIRs, the improvement and evaluation of guidelines and the handling of these drugs could therefore be considered areas of interest.

Thomas and Panchagnula found morphine, gentamicin and norepinephrine to be the most common drugs in CIs involving drugs [17]. Both morphine and gentamicin are included in multiple ATC-codes, where N02 and J01 are possible for morphine and gentamicin respectively. Norepinephrine is only included in one ATC-code; C01. Relating this to the results in this study, where the ATC-codes N02, B01 and N05 were the most common, with J01 being the 4th most common and C01 one of two of the 6th most common ATC-codes, some discrepancies can be seen in the exact order of the ATC-codes relating to their frequency of involvement in CIs (Figure 4). A 4th and 6th place for the ATC-codes J01 and C01 respectively could still be seen as rather high, making the results of this study and the one by Thomas and Panchagnula similar.

Kerker-Specker *et al.* found the most common drug group involved in CIs to be N02 Analgesics [2], mirroring the results of this study (Figure 4). However, only CIRs forwarded to the Critical Incident Reporting & Reacting NETwork (CIRRNET) database by CIRS managers of health institutions participating in CIRRNET, where many members work in the hospital setting, were analyzed, meaning CIs occurring in the hospital could make up a majority of CIs analyzed by Kerker-Specker *et al.* Because roughly half of CIs categorized in this study also occurred in the hospital setting (Figure 2), even though multiple settings were included, a relatively similar result could be expected, nonetheless.

Alghamdi *et al.* found anti-infectives to be commonly involved in medication related incidents, which could be related to the ATC-code J01 Antibacterials for systemic use. Because this is not the only ATC-code containing anti-infectives however, a direct comparison to the results of Alghamdi *et al*. cannot be made.

5.1.5. MUP

The MUP-stages where most DRCIs occur are evident from Figure 3, where prescribing and administration are the most frequent MUP-stages categorized. This may be a slight misrepresentation of reality, because of the categorization rules established, leading to the categorization of potential DRCIs during the transcribing & order entry MUP-stage as DRCIs during prescribing, and potential DRCIs during the preparation for administration MUP-stage as DRCIs during administration. This results in the potential underrepresentation of two categories and the potential overrepresentation of two categories. Because most of the categorized CIRs could be categorized without needing to apply these rules however, the degree of misrepresentation should not be large.

Scharein and Trendelenburg also found the prescribing and administration MUP-stages to be the most common in their evaluation of a web based CIRS in a tertiary care clinic for internal medicine [10], which Thomas and Panchagnula found as well when reviewing patient safety incidents from intensive care or high dependency units reported to the UK National Patient Safety Agency [17]. Alghamdi *et al.* also described incidents most commonly occurring during the prescribing and administration MUP-stage [8].

Kerker-Specker *et al.* instead found the MUP-stage preparation/calculation to be the most common [2]. This MUP-stage was not used in this form in this study, but rather as the MUP-stage preparation for administration, where miscalculations when preparing a drug were categorized. In this study, the preparation for administration MUP-stage was the 4th most common MUP-stage (Figure 3), differing from the findings of Kerker-Specker *et al.*

DRCIs during the dispensing and the documenting MUP-stages were also relatively common in this study (Figure 3). The documenting MUP-stage is of interest because the DRCIs reported in the CIRs categorized as documenting errors usually contain very clear descriptions of the error, specifically describing which document or part in documenting went wrong. This leads to the opportunity of fixing the error relatively fast by adjusting guidelines, training staff or through other relevant measures.

5.1.6. Grouped Variables

According to Figure 6, LASA seems to occur most frequently in the hospital and pharmacy settings, following the trend of DRCIs regarding the setting. This is not surprising simply because of the lack of DRCIs in settings other than the hospital and pharmacy.

Looking at Figure 7, the MUP-stages where LASA most commonly occurs seem to be prescribing and dispensing, but the MUP-stages preparation for administration and administration are also often involved. Similar to the setting variable, a lack of DRCIs in MUP-stages other than prescribing, dispensing, preparation for administration and administration could describe this finding. The documenting MUP-stage however does not include many DRCIs where LASA was a contributing factor, even though there were relatively many DRCIs in this category (Figure 3). A possible explanation for this lies in the description of the MUP-stage attached in Appendix 4, where documenting errors do not commonly include confusion of drugs, but instead focus on the handling of documents specifically.

Figure 8 once again indicates the ATC-codes N02 and N05 as commonly occurring, this time in regard to LASA. Because these drug groups include drugs commonly classified as high-risk, as mentioned above, this gives another potential reason for improvement regarding the use of drugs from these drug groups. It also shows a possible contributing factor to be improved on in LASA.

Figure 9 indicates potential trends between drug groups between the hospital and pharmacy settings, giving a hint at which drug groups could potentially be relevant to improve on in which of the two settings.

Table 1 could indicate which specific ATC-codes are relevant to improve on when looking at a specific MUP-stage. Because DRCIs seem to be most common in the prescribing and administration MUP-stages (Figure 3), it may be relevant to evaluate the use of drugs from the ATC-code J01 and N02 when trying to prevent further DRCIs occurring during the prescribing MUP-stage, and the ATC-code B01 when looking at the administration MUP-stage.

Because the subgroups analyzed were relatively small in some cases and all of them may not accurately represent reality due to this, but also due to other reasons like the categorization itself, these results can only be used as implications for areas of improvement.

5.2. Previous Evaluations of IRSs – Comparison of Variables Analyzed

Variables that were analyzed in this study include setting, age, drug group (ATC-code) and MUP-stage, as well as LASA, where these variables were also combined in different ways described in the materials and methods section. In contrast, the variables analyzed in some of the seven studies mentioned under section 1.4., included variables such as incident type (*e.g.*, airway-related incident), error type (*e.g.,* human error or system error), patient outcome and underlying causes/contributing factors in addition to the variables age, MUP-stage and drug group also analyzed in this study [2, 3, 8-10, 15, 17]. The exact variables analyzed in each of these seven studies differed between the studies. The variable setting was not analyzed in the mentioned studies, likely because they mostly only included one setting, but was possible to analyze in this study due to the inclusion of multiple settings. The mentioning of LASA was not common in these seven studies either, where the term look-alike was only mentioned by Kerker-Specker once, but seemingly not considered as a contributing factor for the CIs analyzed [2]. In conclusion, the diversity of variables that can be analyzed when characterizing CIs in an IRS is rather large, resulting in many possible analyses potentially highlighting different areas of interest.

5.3. Problems Faced During Categorization

Patient outcome, categorized in some studies like Chacko *et al.* [9] and recommended by the WHO as a category for initial analysis and prioritization [23], could not be categorized in this study because the CIs in the CIRS-NRW were mostly adjusted to describe CIs where no harm occurred (so called “near-misses”) before being published [13], leading to a potential overrepresentation of this category if the variable would have been categorized, nonetheless.

Because this study involved multiple settings, a new categorization method for categorizing the medication problem would have needed to be constructed, similar to what was done for the MUP. This turned out to be a very time-consuming process, out of the scope of this study, which

is why the CIRs were not categorized by the medication problem as recommended by the WHO [23].

5.4. Study Strengths and Limitations

For some variables, it is clear that a considerable amount of data is missing. This is most true for the age of the patients, but also the ATC-code variable to a certain degree. In 294 of 553 of the CIRs analyzed, the age was missing (Figure 5), most probably making further analyses involving this variable unrepresentative. Regarding the ATC-code variable 195 CIRs had missing data, but because multiple ATC-codes were often involved in one CIR, this does not mean that 195 CIRs could not be analyzed by this variable at all, instead meaning that there is a possibility that the actual results relating to the ATC-code could be misrepresented. For example, if just 5% of the missing data (10 CIRs) would in truth be categorized as psycholeptics (ATC-code N05) if the data was not missing, N05 would change from the 3rd most common ATC-code to the 2nd most common ATC-code. If this happens for multiple ATC-codes, which is likely with 195 counts of missing data, the results most likely look very different. The problem of missing data is an inherent problem with the CIRs in the CIRS-NRW and is most likely not uncommon in other IRSs either, clearly showing a challenge when evaluating IRSs.

The free text searches during the filtering of the CIRs serve as a kind of quality control of the categorization by the BÄK by filtering the 792 CIRs not included by intrinsic filter 2 (Figure 1) by free text search as well, thus expanding the filtering process and potentially including relevant CIRs that intrinsic filter 2 by the BÄK did not include. If the free text searches do not result in many CIRs, the filter by the BÄK could be considered good because it probably included most relevant CIRs. Out of a total 77 results following the free text searches, only 58 were not duplicates of the CIRs found via the filters by the BÄK. Out of these 58 CIRs, 22 were excluded following discussions within the research team. Thus, the free text searches added 36 CIRs to the final dataset, increasing its´ size and making a more accurate analysis possible.

Subgroups were formed and analyzed in this study. Because only 553 DRCIs were included in total, the resulting subgroups sometimes consisted of very few DRCIs, diminishing the power of the results to indicate relationships between different variables and the occurrence of DRCIs. This is clearly a limitation of this study, but because only DRCIs in the CIRS-NRW from the 1st

of January 2019 – 15th of September 2021 were characterized in this study, the impact of this limitation can be reduced in future similar studies, at least of the CIRS-NRW, by analyzing DRCIs from before and after the mentioned time period.

In section 3.8.2. two categorization rules are described that were applied when the MUP-stages prescribing and transcribing & order entry or preparation for administration and administration could not be accurately categorized. These rules may be seen as a limitation in this study, potentially leading to the overrepresentation/underrepresentation of the concerned MUP-stages. By instead categorizing the CIRs where these rules had to be applied as missing data, this may be avoided. Luckily, these rules did not have to be applied for many CIRs, leading to the overrepresentation/underrepresentation, in regard to the concerned MUP-stages, likely being small.

The characterization of DRCIs using different variables than commonly used, such as LASA, could be considered a strength, relating to the statement by the WHO that no studies are available "reporting the incidence of errors that result from confusing the names of medicines" [23], although stated in 2014. By analyzing LASA, this need of studies is met in part.

In addition to the inclusion of LASA, this study characterizes CIRs in the CIRS-NRW across multiple settings and presents a method for categorizing *e.g.,* the MUP over multiple settings simultaneously, which can be seen as a strength due to the lack of similar studies.

5.5. Future Research

Since this study is an explorative, retrospective, descriptive study, causation and strong relations cannot be established from this study alone. For this, multiple more rigorous studies characterizing DRCIs across multiple settings have to be conducted, after which concrete ways of improvement can be suggested, implemented and tried out, and then be evaluated in further studies, hopefully resulting in an increased patient safety in the long run. Looking at the results of this study, improvements regarding *e.g.*, the use of drugs included under the ATC-codes N02, B01 and N05 could be suggested, implemented, tried out and then evaluated in future studies, among other things relating to the other variables analyzed in this study.

As discussed under section 5.2., not many studies analyzed LASA as a specific contributing factor to the DRCIs analyzed in these studies. LASA was found to be involved in 1/6th of DRCIs in this study, warranting the categorization and analysis of this variable in future studies evaluating DRCIs in IRSs.

In this study only the 553 DRCIs reported in the CIRS-NRW from the start of 2019 until the 15th of September 2021 were categorized and characterized, leaving room for multiple future studies of CIs in the CIRS-NRW. An analysis of all DRCIs in the entire CIRS-NRW would increase the amount of data and thus the ability to see strong relations between variables and different outcomes. There are also multiple variables not analyzed for the DRCIs included in this study, like patient outcome or error type, that are commonly analyzed in similar studies as described under section 5.2., calling for further studies analyzing these variables specifically either with the aim of completing the characterization of the DRCIs from the CIRS-NRW included in this study, or of doing a complete comprehensive analysis of all DRCIs in the CIRS-NRW including all commonly used variables.

In addition to DRCIs, the CIRS-NRW also includes many other CIs; only 19,8% of all CIs in the original dataset from the CIRS-NRW were defined as DRCIs (section 4.). Other CIs not involving drugs could also be relevant for patient safety, meaning future studies analyzing these non-drug-related CIs in *e.g.*, the CIRS-NRW could be warranted.

6. Conclusion

A categorization method to categorize CIs from multiple settings concurrently, specifically in regard to the MUP, was proposed in this study. This may simplify future studies of IRSs containing CIs from multiple settings, which in turn can give valuable information surrounding areas of improvement common to multiple settings in health care systems.

Twenty percent of CIs reported in the CIRS-NRW between the 1st of January 2019 and the 15th of September 2021 were DRCIs, seemingly occurring mostly in the hospital and pharmacy settings during the prescribing and administration MUP-stages. The most frequently involved ATC-codes in the DRCIs characterized were found to be N02, B01 and N05 and LASA was a potential contributing factor in 1/6th of the characterized DRCIs. The age distribution of patients affected by DRCIs could not be properly determined due to half of CIRs missing data concerning the patient´s age. Subgroup analyses indicated LASA to be involved mostly in the hospital and pharmacy settings, during the prescribing and dispensing MUP-stages and related to drugs included under the ATC-codes N02 and N05. The subgroup analyses also indicated the ATC-code N02 to be the most commonly involved ATC-code, both in DRCIs occurring in the hospital setting and in DRCIs occurring in the pharmacy setting. The ATC-codes N02 and J01 were the most common in DRCIs occurring during prescribing and B01 was the most common ATC-code in DRCIs occurring during administration. Because the subgroups in some cases consisted of few DRCIs however, clear trends could not be determined, resulting in the need for further studies of DRCIs in IRSs including more DRCIs from multiple settings in the future.

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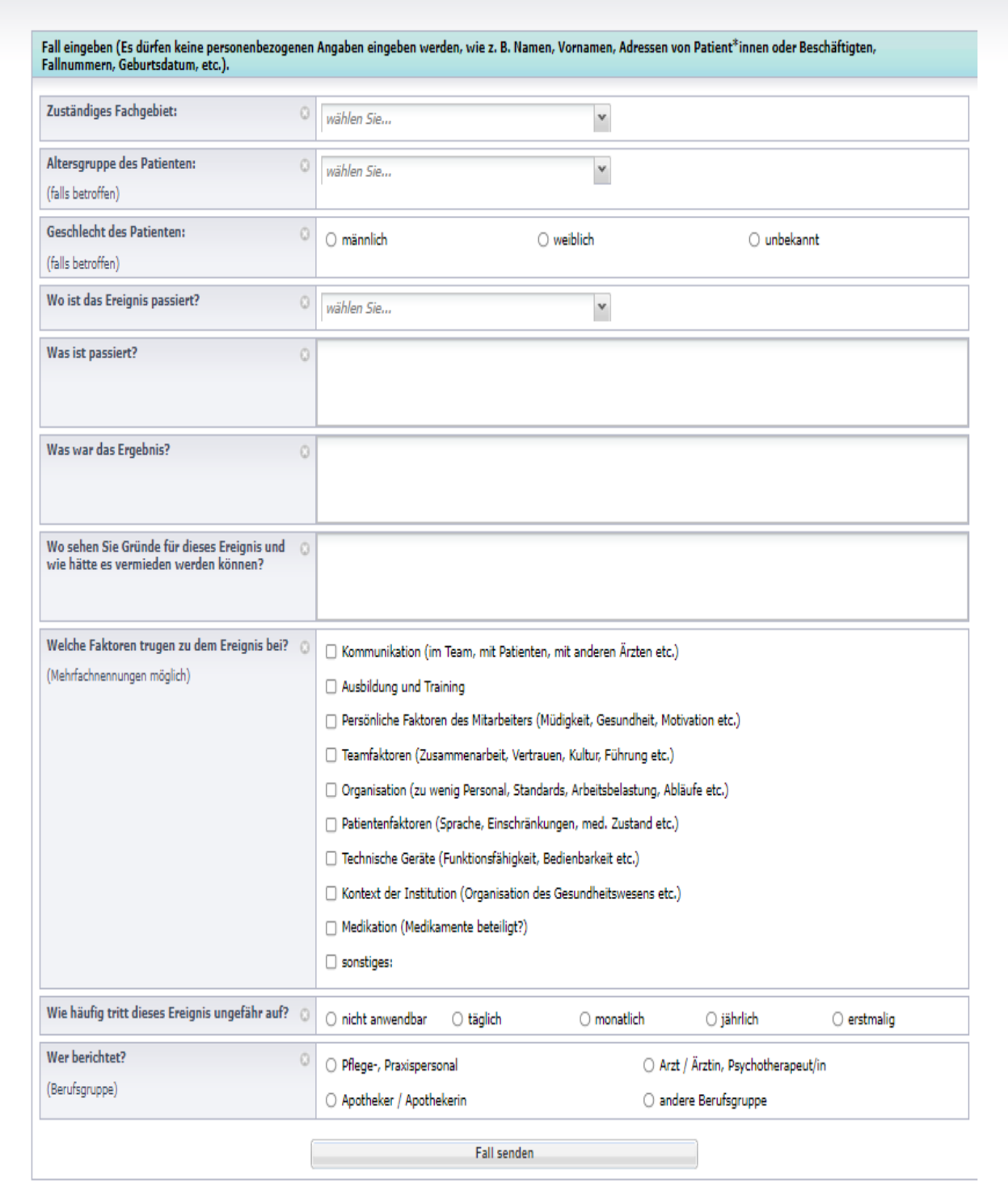
9. Appendixes

9.1. Appendix 1: Reporting Form for CIs reported to the CIRS-NRW (in German)



Fall eingeben (Es dürfen keine personenbezogenen Angaben eingeben werden, wie z. B. Namen, Vornamen, Adressen von Patient*innen oder Beschäftigten, Fallnummern, Geburtsdatum, etc.).

Zuständiges Fachgebiet:	*wählen Sie...*
Altersgruppe des Patienten: (falls betroffen)	*wählen Sie...*
Geschlecht des Patienten: (falls betroffen)	○ männlich ○ weiblich ○ unbekannt
Wo ist das Ereignis passiert?	*wählen Sie...*
Was ist passiert?	
Was war das Ergebnis?	
Wo sehen Sie Gründe für dieses Ereignis und wie hätte es vermieden werden können?	
Welche Faktoren trugen zu dem Ereignis bei? (Mehrfachnennungen möglich)	☐ Kommunikation (im Team, mit Patienten, mit anderen Ärzten etc.) ☐ Ausbildung und Training ☐ Persönliche Faktoren des Mitarbeiters (Müdigkeit, Gesundheit, Motivation etc.) ☐ Teamfaktoren (Zusammenarbeit, Vertrauen, Kultur, Führung etc.) ☐ Organisation (zu wenig Personal, Standards, Arbeitsbelastung, Abläufe etc.) ☐ Patientenfaktoren (Sprache, Einschränkungen, med. Zustand etc.) ☐ Technische Geräte (Funktionsfähigkeit, Bedienbarkeit etc.) ☐ Kontext der Institution (Organisation des Gesundheitswesens etc.) ☐ Medikation (Medikamente beteiligt?) ☐ sonstiges:
Wie häufig tritt dieses Ereignis ungefähr auf?	○ nicht anwendbar ○ täglich ○ monatlich ○ jährlich ○ erstmalig
Wer berichtet? (Berufsgruppe)	○ Pflege-, Praxispersonal ○ Arzt / Ärztin, Psychotherapeut/in ○ Apotheker / Apothekerin ○ andere Berufsgruppe

Fall senden

9.2. Appendix 2: Detailed Description of Categories for every Variable in the CIRS-NRW by the BÄK (in German)

Fallexport CIRS-NRW Felddefinitionen

Spalte	Wert	Bezeichnung
A	Fall-Nr	
B	Fall-Eingangsdatum	
C	Fall-Status	
	1	Neuer Fall
	2	Fall anonymisieren
	3	Fall veröffentlichen
	4	Fall beurteilen
	5	Fallrückmeldung veröffentlichen
	6	Fall abgeschlossen
	7	Fall nachbearbeiten
D	Zuständiges Fachgebiet	
	1	Allgemeinmedizin
	2	Anästhesiologie
	3	Augenheilkunde
	4	Chirurgie
	5	Frauenheilkunde / Geburtshilfe
	6	Haut- und Geschlechtskrankheiten
	7	HNO-Heilkunde
	8	Innere Medizin
	9	Kinder- und Jugendmedizin
	10	Neurologie
	11	Orthopädie
	12	Psychiatrie
	13	Psychotherapie
	14	Radiologie
	15	Urologie

	16	anderes Fachgebiet:
E	Zuständiges Fachgebiet Freitext	
F	Altersgruppe des Patienten	
	1	0-1
	3	2-5
	8	6-10
	13	11-15
	18	16-20
	25	21-30
	35	31-40
	45	41-50
	55	51-60
	65	61-70
	75	71-80
	85	81-90
	95	>90
	?	unbekannt
G	Geschlecht des Patienten	
	1	männlich
	2	weiblich
	3	unbekannt
H	Wo ist das Ereignis passiert	
	1	Krankenhaus
	2	Praxis
	3	Notfalldienst / Rettungswesen
	4	Hausbesuch
	5	Pflege / Altenheim
	6	anderer Ort:
	7	Apotheke
I	Wo ist das Ereignis eingetreten Freitext	

J	In welchem Bereich ist das Ereignis aufgetreten	
	1	Einleitung
	2	OP
	3	Ausleitung
	4	AWR
	5	Transport
	6	Funktions-/Diagnostikraum
	7	ITS / IMC
	8	PM-Ambulanz
	9	Schmerzambulanz
	10	Notfall-Team-Einsatz
	11	Normalstation
	12	Akutschmerzdienst
	13	anderer Bereich:
K	In welchem Bereich ist das Ereignis aufgetreten Freitext	
L	Tag des berichteten Ereignisses	
	1	Wochentag
	2	Wochenende / Feiertag
M	Welche Versorgungsart	
	1	Routinebetrieb
	2	Notfall
N	In welchem Kontext fand das Ereignis statt?	
	1	Prävention
	2	Diagnosestellung
	3	Nichtinvasive Massnahmen (Diagnostik / Therapie)
	4	Invasive Massnahmen (Diagnostik / Therapie)
	5	Organisation (Schnittstellen / Kommunikation)
	6	anderer Kontext:
O	In welchem Kontext fand das Ereignis statt Freitext	
P	ASA Klassifizierung	

1	ASA I
2	ASA II
3	ASA III
4	ASA IV
5	ASA V

Q	Patientenzustand
R	Wichtige Begleitumstände
S	Was ist passiert
T	Was war das Ergebnis
U	Was war besonders gut
V	Was war besonders ungünstig
W	Wo sehen Sie Gründe für dieses Ereignis und wie hätte es vermieden werden können
X	Kam der Patient zu Schaden

1	nicht anwendbar (kein Patient beteiligt)
2	nein
3	Minimaler Schaden / Verunsicherung des Patienten
4	Passagerer Schaden leicht - mittel
5	Passagerer Schaden schwer
6	Dauerschaden leicht - mittel
7	Dauerschaden schwer
8	Tod

Y	Welche Faktoren trugen zu dem Ereignis bei

1	Kommunikation (im Team, mit Patienten, mit anderen Ärzten etc.)
2	Ausbildung und Training
3	Persönliche Faktoren des Mitarbeiters (Müdigkeit, Gesundheit, Motivation etc.)
4	Teamfaktoren (Zusammenarbeit, Vertrauen, Kultur, Führung etc.)
5	Organisation (zu wenig Personal, Standards, Arbeitsbelastung, Abläufe etc.)

	6	Patientenfaktoren (Sprache, Einschränkungen, med. Zustand etc.)
	7	Technische Geräte (Funktionsfähigkeit, Bedienbarkeit etc.)
	8	Kontext der Institution (Organisation des Gesundheitswesens etc.)
	9	Medikation (Medikamente beteiligt?)
	10	sonstiges:
Z	Welche Faktoren trugen zu dem Ereignis bei Freitext	
AG	Wie häufig tritt dieses Ereignis ungefähr auf	
	1	nicht anwendbar
	2	täglich
	3	monatlich
	4	jährlich
	5	erstmalig
AH	Wer berichtet	
	1	Pflege-, Praxispersonal
	2	Arzt / Ärztin, Psychotherapeut/in
	3	andere Berufsgruppe
	4	Apotheker / Apothekerin
AI	Bemerkungen zum Berichtssystem	
AJ	Titel	
AK	Verantwortlich	
AL	Interne Notizen	
AM	Risk	
	Erste Ziffer: Konsequenzen	
	1	Katastrophal
	2	Schwer
	3	Moderat
	4	Minimal
	5	Keine
	Zweite Ziffer: Wahrscheinlichkeit	

	1	Selten
	2	Unwahrscheinlich
	3	Denkbar
	4	Wahrscheinlich
	5	Fast sicher
AN	Klassifikation	
	1	Typischer Fall
	2	Fall des Monats
	3	Alert
	4	Interessanter Fall
AO	Beitragende Faktoren	
	1	Kommunikation (im Team, mit Patienten, mit anderen Ärzten etc.)
	2	Ausbildung und Training
	3	Persönliche Faktoren des Mitarbeiters (Müdigkeit, Gesundheit, Motivation etc.)
	4	Teamfaktoren (Zusammenarbeit, Vertrauen, Kultur, Führung etc.)
	5	Organisation (zu wenig Personal, Standards, Arbeitsbelastung, Abläufe etc.)
	6	Patientenfaktoren (Sprache, Einschränkungen, medizinischer Zustand etc.)
	7	Technische Geräte (Funktionsfähigkeit, Bedienbarkeit etc.)
	8	Kontext der Institution (Organisation des Gesundheitswesens etc.)
	9	Medikation (Medikamente beteiligt?)
AP	Ereignis-Typ	
	1	Verwaltung im Rahmen der Patientenversorgung
	2	Klinischer Prozess / Eingriff
	3	Dokumentation
	4	Krankenhausinfektion
	5	Medikation / Infusionen

	6	Blut / Blutprodukte
	7	Ernährung
	8	Sauerstoff / Narkosegase
	9	Medizinische Geräte / Ausstattung
	10	Verhalten (Mitarbeiter / Patient)
	11	Patientenunfälle
	12	Infrastruktur / Gebäude / Inventar
	13	Ressourcen / Organisatorisches Management
AQ	Getroffene Massnahmen	
	1	keine (z.K. notwendig)
	2	Kommunikation / Guideline / Info
	3	Technisch, Material
	4	Organisatorisch / Prozesse
	5	Ausbildung / Supervision
AR	Kommentare des CIRS-Teams	
AS	Risiko-Matrix veröffentlichen:	
	<leer>	Risiko-Matrix nicht veröffentlicht
	1	Risiko-Matrix veröffentlicht
AT	Anzahl Kommentare	

9.3. Appendix 3: List of ATC-codes used in this Study, Including Coding and Categorization Rules

Coding of the 2nd level of ATC-codes

https://www.whocc.no/atc_ddd_index/

A **ALIMENTARY TRACT AND METABOLISM**

A01 **STOMATOLOGICAL PREPARATIONS** = **1**
A02 **DRUGS FOR ACID RELATED DISORDERS** = **2**
A03 **DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS** = **3**
A04 **ANTIEMETICS AND ANTINAUSEANTS** = **4**
A05 **BILE AND LIVER THERAPY** = **5**
A06 **DRUGS FOR CONSTIPATION** = **6**
A07 **ANTIDIARRHEALS, INTESTINAL ANTIINFLAMMATORY/ANTIINFECTIVE AGENTS** = **7**
A08 **ANTIOBESITY PREPARATIONS, EXCL. DIET PRODUCTS** = **8**
A09 **DIGESTIVES, INCL. ENZYMES** = **9**
A10 **DRUGS USED IN DIABETES** = **10**
A11 **VITAMINS** = **11**
A12 **MINERAL SUPPLEMENTS** = **12**
A13 **TONICS** = **13**
A14 **ANABOLIC AGENTS FOR SYSTEMIC USE** = **14**
A15 **APPETITE STIMULANTS** = **15**
A16 **OTHER ALIMENTARY TRACT AND METABOLISM PRODUCTS** = **16**

B **BLOOD AND BLOOD FORMING ORGANS**

B01 **ANTITHROMBOTIC AGENTS** = **17**
B02 **ANTIHEMORRHAGICS** = **18**
B03 **ANTIANEMIC PREPARATIONS** = **19**
B05 **BLOOD SUBSTITUTES AND PERFUSION SOLUTIONS** = **20**
B06 **OTHER HEMATOLOGICAL AGENTS** = **21**

C **CARDIOVASCULAR SYSTEM**

C01 **CARDIAC THERAPY** = **22**
C02 **ANTIHYPERTENSIVES** = **23**
C03 **DIURETICS** = **24**
C04 **PERIPHERAL VASODILATORS** = **25**
C05 **VASOPROTECTIVES** = **26**

R06 **ANTIHISTAMINES FOR SYSTEMIC USE = 81**
R07 **OTHER RESPIRATORY SYSTEM PRODUCTS = 82**

S **SENSORY ORGANS**

S01 **OPHTHALMOLOGICALS = 83**
S02 **OTOLOGICALS = 84**
S03 **OPHTHALMOLOGICAL AND OTOLOGICAL PREPARATIONS = 85**

V **VARIOUS**

V01 **ALLERGENS = 86**
V03 **ALL OTHER THERAPEUTIC PRODUCTS = 87**
V04 **DIAGNOSTIC AGENTS = 88**
V06 **GENERAL NUTRIENTS = 89**
V07 **ALL OTHER NON-THERAPEUTIC PRODUCTS = 90**
V08 **CONTRAST MEDIA = 91**
V09 **DIAGNOSTIC RADIOPHARMACEUTICALS = 92**
V10 **THERAPEUTIC RADIOPHARMACEUTICALS = 93**
V20 **SURGICAL DRESSINGS = 94**

Missing Data = **999**

Not applicable = **333**

Rules: Only CIRs where the drug used and the indication for which the drug is used, or is intended to be used for, are clearly indicated or mentioned should be categorized as 1-94. The CIRs where this information is not provided or is not apparent in any other way, should be categorized as 999 (missing data) with a 1 in the variable *ind. uncl.*

If there are multiple drugs with different ATC-codes involved in a CI, they should be categorized separately in ATC-code 1-3, where the drug with the ATC-code resulting in the lowest number should be put in the ATC-code 1 column, followed by the second lowest number in the ATC-code 2 column etc.

If an ATC-code is involved in the CIs multiple times it should only be categorized once.

9.4. Appendix 4: Coding, Categorization Rules and Descriptions of the MUP-stages used in this Study

Medication Use Process:

(*MUP1-3) + stages nr.*

- Prescribing = **1**
- Transcribing & order entry = **2**
- Storage of medication = **3**
- Dispensing = **4**
- Preparation for administration = **5**
- Administration = **6**
- Monitoring = **7**
- Other – (specify in column *MUP free*) = **8**
- Documenting = **9**

Missing Data = **999**

Not Applicable = **333**

Rules:

- When there are DRPs at multiple MUP-stages, MUP1 should correspond to the "first" medication use process stage *i.e.*, have the lowest number, followed by MUP2 etc.

- Only MUP-stages where an error occurred that is not the direct result of an error during a previous MUP-stage should be categorized, *i.e.*, not every stage up until detection.

- If it is unclear whether the CI occurred during the prescribing or the transcribing & order entry MUP-stage and both are plausible options, the CI should be categorized as having occurred during the prescribing MUP-stage.

- If it is unclear whether the CI occurred during the preparation for administration or the administration MUP-stage and both are plausible options, the CI should be categorized as having occurred during the administration MUP-stage.

Descriptions of stages in the medication use process used above:

Prescribing:

Prescribing of a drug by a medical professional with the necessary qualifications. Involves the entire process from patient meeting until the prescription is handed out to the patient or relayed to a helper responsible for transcribing and ordering the prescribed drug(s).

Transcribing & order entry:

Transcribing of prescriptions by doctors or other personnel from a physical paper into a digital system or from one digital system to another, as well as the ordering of the prescribed drug(s). The ordering of the drug(s) written on the prescription can be done in conjunction with the transcribing process, which is why both parts are defined as one MUP-stage.

Storage of medication:

Storage of medication in the hospital, pharmacy, at the patients´ home or any other setting. Can in some cases also include logistics involved immediately before delivery of medication to be stored.

Dispensing:

Dispensing of orders from a hospital pharmacy to a hospital ward, from a medical institution to the patient *e.g.,* from the pharmacy to the patient, or from a pharmaceutical company to a pharmacy, meaning logistics is included in this category.

Preparation for administration:

Involves all kinds of preparation of the medication for a successful administration to be possible, *i.e.,* putting the right medications for the right patient at the right place, shaking, mixing or dissolving the medicine in relevant media needed for optimal administration. Also includes the correct installing of solutions for injections/infusions in/on tubes and catheters before *e.g.,* an upcoming anesthesia or other medical procedure in hospitals or similar medical facilities.

Administration:

The immediate timeframes before, during and after the administration of any medication or medicinal product in any setting.

Monitoring:

All errors relating to inadequate monitoring of the drug treatment process as a whole *e.g.*, non-optimal phasing out of a medication or no phasing out at all even though needed. Also includes all errors relating to the monitoring of vitals or other relevant parameters during a patients visit in the hospital or another care instance, related to the administration of medication or the lack thereof.

Documenting:

All errors that can be traced back to incorrect filling of documents such as writing information in the wrong place, not adding relevant information at all while filling out a document, the relevant documents missing all together, incorrect, inadequate or misleading guidelines etc. were categorized as CIs occurring during the documenting MUP-stage.