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Impact of medication reconciliation and medication reviews on the incidence of preventable adverse drug reactions during hospitalization of elderly patients. A randomized controlled trial

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Background: Of all adverse drug reactions, 35-45% are due to medication errors and would therefore be preventable. Thus, it is essential to implement effective strategies to prevent medication errors. However, it remains unclear whether medication reviews provide an additional benefit compared to medication reconciliation regarding medication safety. *Aim*: The present study aimed to evaluate whether medication reconciliation and medication reviews affect the incidence of preventable adverse drug reactions in elderly patients. *Method*: Non-elective patients 65 years and above admitted to the hospital, taking at least one high-risk drug, were eligible for participation in a three-armed randomized controlled trial. One group went through the medication reconciliation process, a second group received a comprehensive medication review, including medication reconciliation, and the third group did not receive any pharmaceutical intervention (control group). The incidence of preventable adverse drug reactions during hospitalization was set as the primary endpoint. The severity of the preventable adverse drug reactions and the number and clinical relevance of drug-related problems and discrepancies were defined as secondary endpoints. *Results*: In 207 patients, 74 preventable adverse drug reactions were detected. Neither medication reconciliation nor medication reviews showed a significant impact on the incidence of preventable adverse drug reactions compared to the control group. However, medication reviews significantly reduced the severity of preventable adverse drug reactions (p=0.017). *Conclusion*: The current study results suggest that medication reviews may have an impact on a clinically relevant outcome by reducing the severity of preventable adverse drug reactions. A significant impact of medication reconciliation on clinically relevant outcomes could not be demonstrated. Based on the results of this study, when deciding on a pharmaceutical intervention comprehensive medication reviews should be preferred over sole medication reconciliation whenever possible.

1. Introduction

Medication reconciliation has been proven to be a suitable method to identify and prevent medication errors at interfaces (Lehnbom et al. 2014). Therefore, many international patient safety organizations regard medication reconciliation as an indispensable contribution to safe drug therapy (Donaldson et al. 2017; National Institute for Health and Care Excellence 2015). Many studies have shown that discrepancies can be detected and reduced by medication reconciliation but positive effects on clinically relevant endpoints such as mortality, number of adverse drug events, and length of stay are rare yet (Lehnbom et al. 2014; Redmond et al. 2018; Lee et al. 2023: Chai et al. 2023).

Another intervention to prevent medication errors is a comprehensive medication review. Although a medication review is a more thorough intervention compared to medication reconciliation, studies in the hospital setting have not shown measurable effects on clinically relevant endpoints either (Hohl et al. 2015; Huiskes et al. 2017). Only a few studies have investigated the impact of medication reviews on the incidence of adverse drug reactions (ADR). Whereas two studies reported a reduction in ADR between 66% and 78% (Leape et al. 1999; Kucukarslan et al. 2003), others could not demonstrate an effect of medication reviews on the number of ADRs (Surgery and Pharmacy in Liaison Study Group 2015; Touchette et al. 2012).

When deciding which strategy to implement to prevent medication errors, the effectiveness of the intervention is crucial. Since medication reviews are a more profound but also more time-consuming intervention, it is critical to evaluate whether the higher time requirement translates into a more significant benefit for the patient. To the best of the authors' knowledge, there are no studies available so far comparing the impact of medication reconciliation and additional medication reviews on clinical outcomes. The incidence of preventable ADRs was chosen as the primary endpoint, which is regarded to be more suitable than other common endpoints to prove the effectiveness of medication reviews (Beuscart et al. 2017).

The present study aimed to evaluate whether medication reconciliation or medication reviews reduce the incidence of preventable adverse drug reactions and if this effect is significantly more pronounced in medication reviews than in medication reconciliation.

2. Investigations and results

A total number of 220 patients was recruited for study participation. Thirteen patients dropped out because they no longer met the inclusion criteria or withdrew their consent immediately after randomization. Study data were not collected for any of these drop-out patients; therefore, the evaluation was carried out as per-protocol analysis with 207 patients. Figure 1 provides the patient flow diagram.

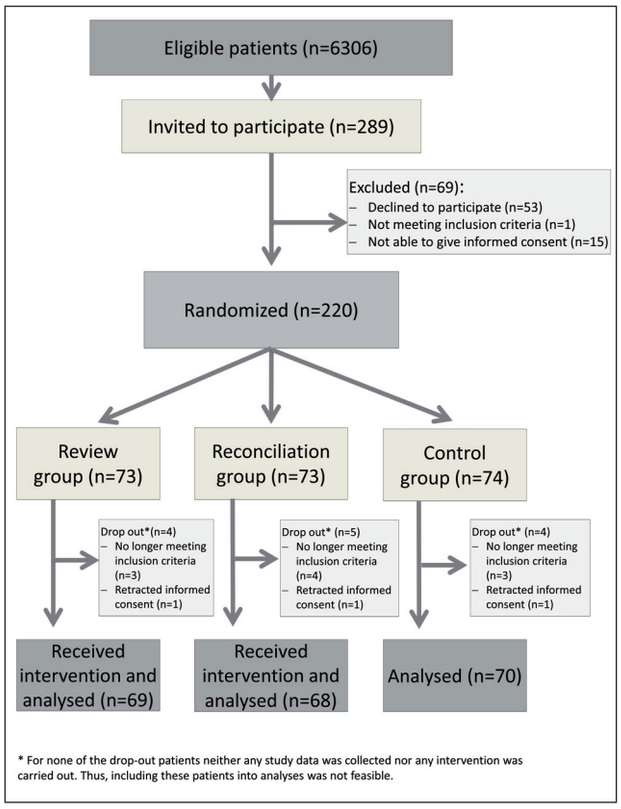

Fig. 1: Patient flow diagram

Sixty-nine patients were assigned to the review group, 68 patients to the reconciliation group and 70 patients to the control group. Table 1 provides demographic data for each study group.

2.1. Incidence of preventable adverse drug reactions

A total of 209 potential ADRs were detected, of which 166 were rated as having a certain or probable causal relationship to drug therapy. This corresponds to 0.8 ADR per patient. Of all ADRs, 74 (44.6% of all ADRs) were rated as preventable. This corresponds to 0.4 preventable ADRs per patient which were distributed among the study arms as follows: Patients of the review group (n=23) and the reconciliation group (n=19) suffered from 0.3 preventable ADRs per patient whereas patients of the control group suffered from 0.5 ADRs per patient (n=32). Over half of all ADRs were rated as probably preventable (n=86, 51.8%) by the expert panel, whereas only 6 ADRs (3.6% of all ADRs) were classified as not preventable.

Univariate Poisson regression analysis showed a statistically significant impact of the variables length of stay, renal function on admission, the number of preadmission drugs, and the number of inpatient drugs (p=0.0003, p=0.003, p<0.0001, p<0.0001) on the incidence of preventable ADRs but not for the variables treatment group, age and sex (p=0.207, p=0.295, p=0.871). Therefore, the variables age and sex were not included in the multivariate Poisson regression model. Correlation analyses showed no significant interaction between the variables; thus, all remaining variables were included in the multivariate regression analysis. The multivariate Poisson regression showed a statistically significant impact for the variables renal function at admission (p=0.024; estimate=-0.011; confidence interval (CI) -0.020--0.001), number of preadmission drugs (p=0.034; estimate= 0.057; CI 0.004-0.110) and number of inpatient drugs (p=0.019; estimate=0.045; CI 0.008-0.083) but not for the treatment group (p=0.142). Thus, no statistically significant effect of medication reconciliation or additional medication reviews on the incidence of preventable ADRs could be demonstrated neither compared to the control group (Review vs Control: p=0.161; estimate= -0.510; CI -1.164-0.144; MedRec vs Control: p=0.313; estimate= -0.423; CI -1.106-0.259) nor against each other (Review vs MedRec: p=0.960 estimate= -0.087; CI -0.829-0.656).

2.2. Severity of preventable adverse drug reactions

Severity assessment was performed by using the National Coordinating Council for Medication Error Reporting and Prevention Index (NCC MERP 2001). The results are shown in Figure 2.

Table 1: Patient characteristics as mean (± SD) or absolute frequency (percentage %)

		Review group (n=69)	Reconciliation group (n=68)	Control group (n=70)
Age [Years]		76.8 (± 6.8)	75.7 (± 5.6)	77.1 (± 6.5)
Sex	Female	30 (43.5%)	28 (41.2%)	24 (34.3%)
	Male	39 (56.5%)	40 (58.8%)	46 (65.7%)
Length of stay [days]		10.4 (± 9.1)	9.1 (± 8.1)	9.8 (± 9.2)
Renal function at admission	eGFR < 30 mL/min	13 (18.8%)	6 (8.8%)	8 (11.4%)
	eGFR 30– 60 mL/min	28 (40.6%)	28 (41.2%)	19 (27.1%)
	eGFR > 60 mL/min	28 (40.6%)	34 (50.0%)	43 (61.4%)
Number of preadmission drugs		10.9 (± 4.8)	10.4 (± 4.0)	10.6 (± 4.3)
Number of inpatient drugs		16.9 (± 8.2)	15.6 (± 6.6)	15.9 (± 7.7)

Notes: eGFR: estimated glomerular filtration rate
SD: standard deviation

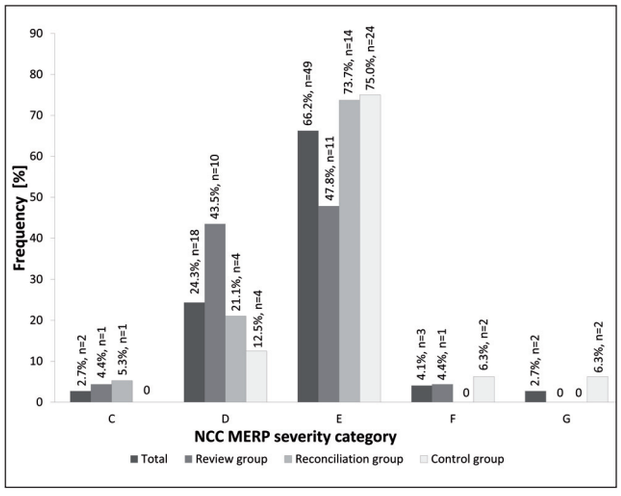

Fig. 2: Severity assessment of preventable adverse drug reactions per study group. No ADRs were classified as category A, B, H or I

Of the review group's preventable ADRs, 52.2% (n=12) were classified into the severity categories E, F, or G and were therefore presumably associated with harm to the patient. This applies to 73.7% (n=14) of preventable ADRs for patients of the reconciliation group and for patients of the control group for 87.5% (n=28) of preventable ADRs.
Using logistic regression, the chance in the control group to suffer from a preventable ADR with harm for the patient was 6.4 times higher than in the review group (Tukey-adjusted p-value=0.017; odds ratio(OR)=6.42; CI: 1.31-31.45). Neither the differences between the review group and the reconciliation group nor between the reconciliation group and the control group reached statistical significance.

2.3. Drug-related problems and discrepancies

A total of 388 drug related problems (DRP) were detected in the 69 patients of the review group. This corresponds to an average number of 5.6 DRPs per patient (SD = 4.19, median = 5, Q1 = 2, Q3 = 8, min = 0, max = 18). Only two patients (2.9%) of this study arm had no DRP at all. 72.4% of all DRPs were solved during the hospital stay. The expert panel assessed DRPs according to their clinical relevance. Figure 3 shows the result of the expert assessment, separately for inpatient care and outpatient care.

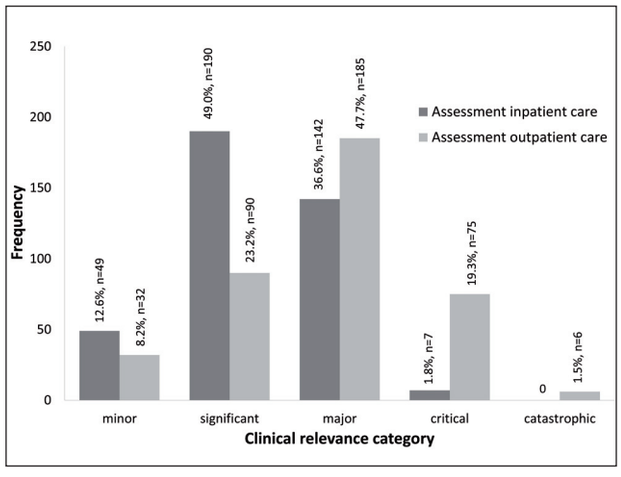

Fig. 3: Clinical relevance of DRPs assessed for inpatient care and outpatient care

For the patients of the reconciliation group, a total of 396 discrepancies were documented. This corresponds to an average number of 5.8 discrepancies per patient (SD = 4.07, median = 5, Q1 = 3, Q3 = 7.25, min = 0, max = 18). No discrepancies were detected in three patients (4.4%). Of all discrepancies 76.8% (n = 304) were classified as medication errors. This corresponds to 4.5 medication errors per patient (SD = 3.51, median = 4, Q1 = 2, Q3 = 6, min = 0, max = 16). The remaining 92 discrepancies (23.2%) were intentional undocumented therapy changes and therefore classified as documentation errors (1.4 documentation errors per patient; SD = 1.64, median = 1, Q1 = 2, Q3 = 2, min = 0, max = 6). Only 26.8% of all discrepancies were solved during hospital stay.
The expert panel assessed the discrepancies according to their clinical relevance. Figure 4 shows the result of the expert assessment for the two settings inpatient and outpatient care.

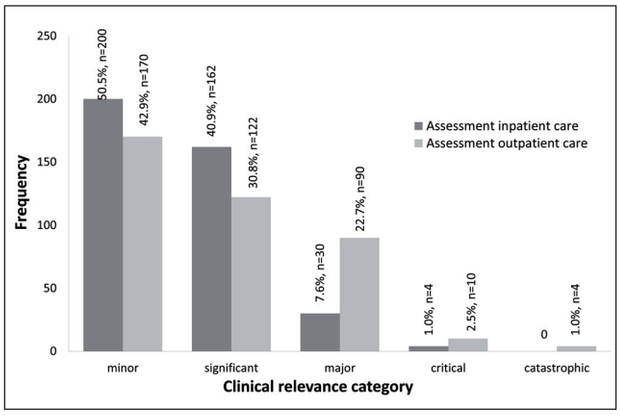

Fig. 4: Clinical relevance of discrepancies assessed for inpatient care and outpatient care

For the comparative analysis, all discrepancies and DRPs classified by the expert panel in the categories 'major', 'critical', or 'catastrophic' were considered 'clinically relevant'.
Whereas in inpatient care, only 8.6% (n=34) of all discrepancies were classified as 'clinically relevant', this applied to 38.4% (n=149) of all DRPs. For outpatient care, 26.3% (n=104) of the discrepancies were classified as 'clinically relevant', whereas this applied to 68.6% (n=266) of all DRPs.
This difference was statistically significant (p <0.0001) for both scenarios. Thus, for inpatient care, the chance that a detected DRP was clinically relevant in preventing harm was 6.6 times higher compared to a detected discrepancy (p=<0.0001, OR=6.64, CI: 4.42-9.97). After discharge, the chance that a detected DRP would prevent harm was still 6.1 times higher compared to a detected discrepancy (p=<0.0001, OR=6.12, CI: 4.49-8.35).

3. Discussion

Although no impact of medication reconciliation or additional medication reviews on the incidence of preventable ADRs could be demonstrated, the present study showed a significant reduction of the severity of preventable ADRs by medication reviews. Thus, the current study results suggest that medication reviews may have an impact on a clinically relevant outcome.
A limitation of the present study may be the limited generalizability to non-academic hospitals and other university hospitals because of the mono-centric study design. Because the study was unblinded, the Hawthorne effect could have affected the behavior of physicians, nurses, patients, and relatives. On the other hand, there are strengths of the present study. The study design was an open, randomized-controlled parallel-group design because randomized-controlled trials are the gold standard for investigating clinical interventions (Schulz et al. 2010). The independent endpoint detection and the systematic endpoint evaluation aimed at meeting the highest scientific standards.
Due to the randomization of participants, it can be assumed that differences between the study arms arose by chance. Nevertheless, it should be mentioned that patients in the review group took on average one more drug during their inpatient stay than patients in the other study arms and had a higher proportion of patients with impaired kidney function.

With 166 ADRs and 74 preventable ADRs, these events' incidence is rather high compared to other studies (Lazarou et al. 1998; Bouvy et al. 2015). This can be attributed to several factors. The detection of ADRs is a highly complex process, and ADRs can often be identified only by considering several clinical parameters (Plank-Kiegele et al. 2017). Therefore, the ADR detection within the present study was done as a prospective, manual file analysis considering all available information sources, including the patient, the caring nurses, and the treating physicians. This is the gold standard of ADR detection and has led to high ADR incidence rates in other studies as well (Alhawassi et al. 2014). Also, only trained pharmacists were responsible for endpoint detection, which improved ADR detection and increased the detection rate (Phansalkar et al. 2007).

With 0.5 preventable ADRs per patient, there were more preventable ADRs in the control group than in the review group or the reconciliation group (0.3 preventable ADRs per patient). Therefore, it is not surprising that the results of the statistical analysis show a trend that medication reviews have an impact on the incidence of preventable ADRs. This trend can also be seen in comparison with the reconciliation group. The expert assessments of the clinical relevance of DRPs and discrepancies underline this conclusion. However, the variable 'treatment group' could not be identified as a risk factor for the number of preventable ADRs in the univariate and multivariate regression models. While pharmaceutical care in internal and intensive care patients was shown to reduce the incidence of preventable ADRs by 66 to 78%, no impact on the ADR incidence could be demonstrated in surgical or geriatric patients (Leape et al. 1999; Kucukarslan et al. 2003; Surgery and Pharmacy in Liaison Study Group 2015; Schmader et al. 2004). Only two out of five studies reported a positive effect of medication reconciliation on ADR incidence (Crotty et al. 2004; Kripalani et al. 2012; Phatak et al. 2016; Boockvar et al. 2006; Lee et al. 2023). All variables determined as risk factors for the number of preventable ADRs in the univariate and multivariate regression models coincide with the risk factors for the occurrence of ADRs published in other studies (Lazarou et al. 1998; Davies et al. 2007, 2009; Zhou and Rupa 2018).

Of all DRPs, 38.4% (assessment inpatient care) and 68.6% (assessment outpatient care) were rated as clinically relevant, whereas this only applies to 8.6% (assessment inpatient care) and 26.3% (assessment outpatient care) of the discrepancies.

This difference was highly statistically significant for both assessments. Surprisingly, the only study that compared the clinical relevance of discrepancies with the clinical relevance of other pharmaceutical services found a higher clinical relevance for discrepancies (Nickerson et al. 2005). However, the design of that study differs vastly from the design of the present work, mainly because the assessment of clinical relevance was carried out exclusively by the treating physician. The findings of the present work are in correlation to Griva et al. (2024) who explored the perspectives of stakeholders in care settings when patients are transferred between care settings. Their finding supported the need for a shift of medication reconciliation towards a more comprehensive medication review model. Others are seeing the value of expanding their services to full medication review (Uhl et al. 2018).

In conclusion, the present study could not demonstrate a significant effect of medication reconciliation and medication reviews on the incidence of preventable ADRs in elderly, non-elective inpatients. Nevertheless, the results suggest that medication reviews are able to reduce the severity of preventable ADRs. Moreover, the DRPs from medication reviews have a significantly higher clinical relevance than discrepancies detected by medication reconciliation. Therefore, medication reviews should be combined with medication reconciliation whenever possible.

4. Experimental

4.1. Ethics approval

Ethics approval was obtained by the ethical review board of the Medical Faculty of RWTH Aachen University (EK-Nr. 206/14). The study was registered at ClinicalTrials.gov (NCT02413957).

4.2. Setting and study design

A three-arm randomized controlled study in a parallel-group design was conducted. Due to the complex interventions, blinding of patients and treating physicians was not feasible.

4.2.1. Patient recruitment

Patients were recruited over a twelve months period between January 2015 and January 2016 at the University Hospital Aachen's emergency department. When the patient was discharged from inpatient care, the data collection process was completed. Enrollment and allocation of patients as well as carrying out the intervention was done by a researcher qualified as a pharmacist.

Due to a lack of comparative studies, a sample size calculation was not feasible. Thus, a one-year recruitment period was set as the enrollment endpoint.

4.2.2. Inclusion criteria

Because this study was part of the WHO High 5's project, inclusion criteria were based on this project's specifications. The criterion "existing drug therapy with a high-risk drug" was added due to the necessary ADR detection. Therefore, the inclusion criteria for this study were defined as follows: the patient is 65 years or older, the patient is admitted via the emergency department (non-elective patients), the patient's written consent to participate in the study and existing drug therapy with at least one high-risk drug when hospitalized.

Previous participation in the study was defined as an exclusion criterion.

Based on a literature search, high-risk drugs for ADRs were defined as diuretics, antihypertensives (ß–blocking agents, ACE inhibitors/Angiotensin-II-receptor antagonists, calcium antagonists), digitalis glycosides, antidepressants, neuroleptics/sedatives, antiepileptics, non-steroidal anti-inflammatory drugs, opioids, antibiotics, anticoagulants, and antidiabetics. After inclusion, patients were randomized to one of the three study arms. Study participants were allocated to the three study arms by permuted block randomization with block length 9. The allocation sequence was generated by using a randomization plan generator [http://www.randomization.com. accessed 02 April 2024].

4.2.3. Pharmaceutical interventions

The three study arms are referred to as the 'review group', 'reconciliation group', and 'control group'.

Patients who were randomized to the review group received comprehensive pharmaceutical care. A type 3 medication review was carried out following a guideline that had been tested in a previous study at the University Hospital Aachen (Lenssen et al. 2016). First step for any medication review was the creation of a best possible medication history (BPMH) and the comparison of the BPMH with the patient's current medication order as described below. Thus, medication reconciliation was part of the comprehensive medication review. In contrast to the reconciliation group, all discrepancies were subjected to a pharmaceutical evaluation. Only those discrepancies that were classified as clinically relevant by the study pharmacist were considered as DRP. The medication was then checked for plausibility, guideline conformity, interactions, contraindications, potentially inadequate medications for elderly patients and correct dosage. The patient's current laboratory values were also included in the evaluation of the drug therapy so that an adjustment of the medication to the current kidney and liver function could be checked and possible undesirable drug effects could be discovered. For patients who were about to undergo surgery or special examinations, the medication was evaluated for necessary adjustments. Existing or newly initiated antibiotic therapies were critically questioned, especially the duration of therapy. For drugs with a narrow therapeutic index, therapeutic drug monitoring (TDM) was recommended where necessary. Additionally, patient training on the correct use of medications or to increase adherence was offered. A medication review was performed upon admission and for every change in drug therapy or the patient's state of health. For patients in the review group, there was a daily visit by the study pharmacist, to give patients the opportunity to address problems with drug therapy, clarify open questions and request training.

Patients randomized to the reconciliation group went through the medication reconciliation process described in detail elsewhere (Schmitz et al. 2022). First, the BPMH was created. The BPMH included all medications used by the patient (pre-scribed and non-prescribed) as well as herbal products, food supplements, vitamins, minerals and trace elements. A minimum of two sources had to be used for every BPMH. All of the gathered information about medications was reviewed with the patient, and the drug name, dose, route of administration and timing was verified for each drug. The BPMH was then checked against the admission medication order (AMO). All discrepancies between the BPMH and the AMO were recorded. Clarification was obtained regarding whether or not the identified discrepancies were intentional or unintentional. Intentional discrepancies were then classified as documentation errors, whilst unintentional discrepancies were classified as medication errors.

Based on experiences from a previous study documentation errors were only passed on to the treating physician if clinically relevant. This should increase the acceptance of the intervention. Medication errors, however, were generally passed on to the treating physician without any pharmaceutical evaluation. Patients in the reconciliation group underwent the medication reconciliation process only once upon admission. After completion of the medication reconciliation process, no further pharmaceutical services were provided for this study group.

Patients randomized to the control group received routine care by physicians and nurses without any pharmaceutical intervention.

4.2.4. Endpoints

The primary endpoint of the study was defined as the incidence of preventable adverse drug reactions. Four independent pharmacists observed symptoms of potential adverse drug reactions. Uniform ADR detection was ensured by using a standard operating procedure (SOP). The severity of the detected preventable ADRs, the number of DRPs, the number of discrepancies, and the clinical relevance of these events were defined as secondary endpoints.

4.2.5. Expert assessment

All potential ADRs identified were assessed by a three-member expert panel for causality, preventability, and severity. The expert panel consisted of a pharmacist and two physicians (one specialist in anesthesiology, the other specialist in internal medicine, and hematology and oncology).

The WHO-UMC tool was used for the assessment of causality [https://www.who.int/medicines/areas/quality_safety/safety_efficacy/WHOcausality_assessment.pdf., accessed 02 April 2024]. The assignment of an event to a causality level was based on the majority decision of the experts. For a potential ADR to be rated as an ADR, it was necessary to classify it the category "Certain" or "Probable". The preventability was assessed according to Lau et al. (2003), using a three-point rating scale with the preventability categories 'preventable', 'probably preventable' and 'not preventable'. The severity was assessed using the National Coordinating Council for Medication Error Reporting and Prevention (NCC-MERP) index.

The documented discrepancies for patients in the reconciliation group and the documented DRPs for patients in the review group were assessed for their clinical relevance by using the assessment tool of Doerper et al. (2015). This enables the categorization of discrepancies and DRPs into one of five relevance categories by using a decision tree (minor, significant, major, critical, and catastrophic). Each discrepancy or DRP was assessed in two different scenarios. First of all, the experts evaluated the clinical relevance of the discrepancy or DRP in case the patient stays in the hospital under daily supervision (laboratory value, vital parameters, ...). Next, the same discrepancy or DRP was assessed if the patient is discharged into the outpatient area, in which, at best, only sporadic monitoring takes place. The two types of assessment are referred to as 'assessment inpatient care' and 'assessment outpatient care'.

4.3. Statistical analyses

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary NC, USA.). A p-value < 0.05 was considered statistically significant. Multiple comparisons regarding the treatment groups were adjusted by using the Tukey-Kramer correction.

Continuous variables are expressed as the mean ± standard deviation (SD) or as the median and lower and upper quartile (Q1 and Q3) in case of skewed data. Categorical data are presented as absolute frequencies and percentages.

The incidence of preventable adverse drug reactions was analyzed by fitting a Poisson regression model (PROC GENMOD in SAS) to the data. A correction for over-dispersion was not necessary because the assumption of equal mean and variance was fulfilled (Chi-square test, p=0.573). Seven variables (Treatment group, age, sex, renal function at admission, length of stay, number of preadmission drugs, and number of inpatient drugs) were included in univariate Poisson regression models. For the multivariate regression model, the variable treatment group and all variables that achieved a p-value of <0.05 in the univariate Poisson regression model (renal function at admission, length of stay, number of preadmission drugs, and number of inpatient drugs) were included. Correlations between continuous and quasi-continuous variables were assessed using Pearson's correlation coefficient. Correlations between class variables were assessed using Spearman's correlation coefficient.

The severity of preventable ADRs was analyzed using logistic regression (PROC LOGISTIC in SAS). Events categorized as NCC MERP category E and above were defined as severe preventable ADRs. Clinical relevance of discrepancies and DRP was analyzed using the Chi-Square Test, and Odds ratios (OR) were calculated. Events categorized as major, critical or catastrophic were defined as clinically relevant.

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Conflicts of interest: The authors declare no conflict of interest.

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