BMJ Open

Methodologic approaches for medication error analyses in patient safety- and pharmacovigilance reporting systems:a scoping review protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-057764
Article Type:	Protocol
Date Submitted by the Author:	26-Sep-2021
Complete List of Authors:	Tchijevitch, Olga; University of Southern Denmark Faculty of Health Sciences, Department of Clinical Research, Research Unit OPEN Hansen, Sebrina Maj-Britt; University of Southern Denmark Odense Campus Library Bogh, Soren; University of Southern Denmark Faculty of Health Sciences, Department of Clinical Research, Research Unit OPEN Hallas, Jesper; University of Southern Denmark Faculty of Health Sciences, Department of Clinical Pharmacology and Pharmacy Birkeland, Søren; University of Southern Denmark Faculty of Health Sciences, Department of Clinical Research, Research Unit OPEN
Keywords:	Health & safety < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, PUBLIC HEALTH

Methodologic approaches for medication error analyses in patient safety- and pharmacovigilance reporting systems: a scoping review protocol

Olga Tchijevitch[1*], Sebrina Maj-Britt Hansen[2], Søren Bie Bogh[1], Jesper Hallas[3], Søren Birkeland[1]
[1]Department of Clinical Research, Research Unit OPEN, University of Southern Denmark, J.B Winsloews Vej 9A, 5000 Odense, Denmark.
[2]University Library of Southern Denmark, Campusvej 55, 5230 Odense M.
[3]Department of Clinical Pharmacology and Pharmacy, University of Southern Denmark, J. B. Winsloews Vej 19.2, 5000 Odense, Denmark.
*Correspondence to: otchijevitch@health.sdu.dk

ABSTRACT

Introduction Medication errors (MEs) are associated with patient harm and high economic costs. Healthcare authorities and pharmacovigilance organizations in many countries routinely collect data on MEs via reporting systems for learning purposes. While different approaches have been developed and used for the ME analysis, an overview over the scope of available methods currently is lacking.
This scoping review, aims to identify, explore, and map the available literature on methods used to analyze MEs in reporting systems.

Methods and analyses This protocol describes a scoping review, based on Joanna Briggs Institute methodological framework. A systematic search will be performed in Medline (Ovid), Embase (Ovid), Cinahl (EBSCOhost), Cochrane central, Google Scholar, websites of the major pharmacovigilance centers and national healthcare safety agencies, and citation search in Scopus. All retrieved records will be independently screened by two researchers on the title, abstract and full-text, involving a third researcher in case of disagreement. Data will be extracted and presented in descriptive and tabular form. The extraction will be based on information about methods of MEs analyses, the type of the reporting system and information on medication errors (medication name, ATC- codes, medication error type, medication-event categories, and harm categories).

Ethics and dissemination Ethical approval is not required. The results will be disseminated via publication in peer-reviewed journals, scientific networks and relevant conferences.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This scoping review, based on established scoping review methodology, will be the first to identify and map the existing publications on methods used to analyse medication errors in reporting systems.
- The systematic search strategy was developed in collaboration with an experienced information specialist, and study selection and data extraction will be performed by independent reviewers.
- There will be no formal quality assessment on the included publications, as the review aims to map the scope of publications on methodology of medication error analyses in reporting sytems.
- The search strategy may result in a large number of publications, that may require refinement to the eligibility criteria.

INTRODUCTION

Medication error (ME) is an error in a medication treatment process, and can occur during ordering, dispensing, administering and monitoring.(1) MEs are a recognized patient safety challenge,(2) associated with patient harm and increasing national expenses.(3–5) The prevalence of preventable medication harm has been estimated to be 3% in adult patients in primary and secondary healthcare settings on average, with higher rates in elderly (11%) and intensive care patients (7%).(6) For example, in the UK, error-related harm has been estimated to contribute to more than 1,700 deaths per year, costing 98.5 million GBP (114.6 million EUR) for hospital admissions and extended hospital stay (7). The suggested yearly costs range between 4.5 and 21.8 billion EUR in European healthcare (8) and constitute about 35 billion EUR worldwide.(2)
MEs and harm associated with MEs have been recognized in healthcare for decades.(9,10) Consequently, patient safety reporting systems (PSRS) have been introduced and adopted by many countries. The systems are based on reporting incidents that resulted in harm or could have caused harm. The main intention with the systems is to learn and thereby prevent forthcoming injuries.(11) These systems are organized on different levels (national, regional, institutional, etc.). Some are voluntary and others are mandatory and

some only include MEs, while others may also include other hazardous health care incidents. The share of medication reports is remarkable, corresponding to 11% of nearly 1 200,000 annual incident reports in England and Wales and 56 % of 222,289 incidents, reported in Denmark. (11,12)

In pharmacovigilance, spontaneous reporting systems (SRS) have been initially used for monitoring of *adverse drug reactions* (ADR), but recently these systems became more involved in monitoring of MEs, following WHO and EU recommendations for collaboration between the safety organizations in healthcare (8,13). The European database for ADR (EudraVigilance) and US Adverse Events Reporting System (FAERS) collected 147,824 ME reports in 2002-2015 and over 100,000 reports in 2015.(14,15)

The number of reported incidents has increased rapidly, reaching an overwhelming volume of reports. (11,12,14) Analyzing the large amount of data, collected via reporting systems by national safety authorities and pharmacovigilance centers is increasingly costly and challenging. (16,17) Inefficiently analyzed data may ultimately impede the learning potential, and in the end, compromise patient safety. Moreover, healthcare systems may choose to deprioritize or even phase out parts of the mandatory reporting, thereby taking patient safety a great step backward.(18) Various approaches to MEs analyses have been developed to address challenges, ranging from traditional manual reviewing and arithmetical counting to advanced computerized methods such as natural language processing (NLP) and data mining methods. However, knowledge of the current scope of methodological approaches and the frequency of their use is limited. There is a need to provide an up-to-date overview of the knowledge to understand and make recommendations for necessary developments. A preliminary search in PubMed has not identified systematic or scoping reviews on this topic. In this scoping review, we aim to identify, explore and map the existing publications/scientific literature on methods of MEs analysis in reporting systems.

METHODS

This will be a scoping review following Joanna Briggs Institute methodological framework,(19) initially developed by Arksey and O'Malley,(20). This method is based on five stages.

The proposed review will be reported according to Preferred Reporting Items for Systematic Review and Meta- Analyses extension for Scoping Reviews (PRISMA ScR).(21)

The definition of terms is presented in Table 1.

Table 1 Definitions of terms

Medication error (ME)	*"A medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing, order communication, product labeling, packaging, and nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use"*.(22) MEs can be classified according to their severity in nine categories from "*no harm*" to *"death*", according to MCC MERP classification index.(23)
Adverse drug events (ADEs)	*"Injuries resulting from medical interventions related to a drug. ADE may result from medication errors or from adverse drug reactions (ADR) in which there were no error"*.(24) ADEs can be preventable and non-preventable. Preventable ADE is always a result of an error. Non-preventable ADE is ADR, an injury without an error.(24)

Adverse drug reaction (ADR)	*"A response to a medicine which is noxious and unintended, and which occurs at doses normally used in man".*(25)
Spontaneous reporting system (SRS)	A system, that is relayed on *"an unsolicited communication by a healthcare professional or consumer to a company, regulatory authority or other organization[…], that describes one or more adverse drug reactions in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection scheme".*(26)
Patient safety reporting systems (PSRS)	Systems for reporting of incidents in healthcare, that *"cause an injury to the patient or pose a risk of harm.*(27) *The fundamental role of a PSRS is to enhance patient safety by learning from failures of the healthcare system".*(13)

Identifying the research question

The research question of this scoping review emerged from knowledge gaps identified by the authors. As the availability of methodological approaches and new technologies used to analyze large databases is rapidly developing, the following question was formulated "What is known from the literature about MEs methods of analyses in reporting systems?". The review should help researchers and organizations engaged with medication safety to gain insight into the current methods to analyze MEs and support authorities in considering alternative or supplementary methods for MEs analyses.

Identifying relevant studies

The search strategy was developed in cooperation with the research team and the information specialist **(SH)** using a search guide developed by Bramer.(28) First, we identified elements from the research question: "medication errors" and "system analyses". Secondly, we collected subject-specific headings and key words and their synonyms accordingly. The search was initially performed in Embase (Ovid) and translated to Medline (Ovid), Cinahl (EBSCOhost) and Cochrane Central (se Appendix 1).
Google Scholar, major national healthcare safety agencies and pharmacovigilance centers' websites will be searched for relevant publications. We will review the reference lists of the included studies and use the citation search in Scopus for each reference. The search is limited to 2005 onwards. From this point in time, many countries began to introduce national patient reporting systems. (29,30)

Study selection

All retrieved records from the literature search will be imported and managed in Covidence. Two researchers (OT) and (SH) will independently first screen at title/abstract level and secondly on full-text level according to the in- and exclusion criteria listed below. In case of disagreement, the third researcher (SB) will be involved to achieve consensus.

Inclusion criteria:

- Publications targeting MEs or AEs related to MEs, that have occurred to persons of any age and gender;
- Publications that describe methodologies used to identify and analyze MEs;
- Publications that use reporting systems as a source, including SRS or PSRS on national, regional or local levels;
- Publications reporting on ADE and ADR, will be considered only if there is a described association between these two and MEs.

Exclusion criteria:

- Review articles, editorials and publications that do not provide information on medication involved or ME's category;
- Publications exploring herbal or traditional medicines.

Data extraction

Two researchers (OT) and (SB) will independently extract the data using a charting table, that will be developed by the research team. A priori pilot test will be performed on two or three sources to ensure all relevant results are extracted, iteratively updating a data-charting form.(19)

General characteristics will be extracted from the chosen publications: author(s), year of publication, source of origin/country of origin, study design, settings and population. Next, we will extract information about methods used for MEs' detection and analysis, the type of the reporting system used, and the frequency and characteristics of MEs revealed by the analysis: the most frequent medications involved in MEs (their generic name and ATC-code), and medication-event combinations, based either on stages of medication process (prescribing, preparation, dispensing and monitoring) or medication error category (such as wrong medication, wrong patient, wrong dose, wrong route, wrong time, omission error). Patient demographic characteristics, such as age and gender, categories of medication-related harm and the reporting organization will also be extracted. Additionally, limitations/biases and sources of funding will be noted.

The outcome of ME analyses may vary from study to study. For example, in some studies focus may be on adverse events/patient harm and in others, focus is on hazardous medication-event situations. Likewise, differences can occur as some studies may, e.g., investigate only prescribing or administration errors or MEs connected to a particular drug of interest. In contrast, others may explore MEs more generally.

Data summary

The primary interest of this study is to provide an overview of the methods used for MEs' analysis; these methods will be seen in connection with the type of the reporting system and detailed information on MEs, their types and frequency.

The results will be summarized and presented in descriptive and tabular form.

Patient and public involvement

This protocol was developed without patient or public involvement.

Study status

The study protocol has been completed on 21 September 2021, and the literature search will be started immediately after the publication of the protocol, followed by study selection and data extraction. We plan to fulfill the study by July 2022.

ETHICS AND DISSEMINATION

The review does not require approval from the Ethic Committee, as this is a literature study. Dissemination of the results will take place via publication in peer-reviewed journals and presentations for the interest organizations, that work on patient safety, as well as scientific networks and conferences.

FUNDING

This work was supported by the Faculty of Health Science University of Southern Denmark, the Region of Southern Denmark, Department of Cardiology Lillebaelt Hospital and Helsefonden.

ACKNOWLEDGMENTS

We would like to thank CEMBO/Cochrane Denmark for providing methodological consultancy service and support.

CONTRIBUTORS

All authors contributed to the protocol design and plan. SB and OT have developed the initial draft of the protocol, which has been revised and finally accepted by the research team (OT, SH, SBB, JH and SB). The initial literature search has been developed collaboratively by SH and OT.

REFERENCES

1. Lisby M, Nielsen LP, Brock B, Mainz J. How should medication errors be defined? Development and test of a definition. Scand J Public Health. 2012 Mar 1;40(2):203–10.

2. WHO | The third WHO Global Patient Safety Challenge: *Medication Without Harm* [Internet]. WHO. World Health Organization; [cited 2021 Feb 17]. Available from: http://www.who.int/patientsafety/medication-safety/en/

3. Hoonhout LHF, de Bruijne MC, Wagner C, Asscheman H, van der Wal G, van Tulder MW. Nature, occurrence and consequences of medication-related adverse events during hospitalization: a retrospective chart review in the Netherlands. Drug Saf. 2010 Oct 1;33(10):853–64.

4. Kjellberg J, Wolf RT, Kruse M, Rasmussen SR, Vestergaard J, Nielsen KJ, et al. Costs associated with adverse events among acute patients. BMC Health Serv Res [Internet]. 2017 Dec [cited 2019 Feb 19];17(1). Available from: http://bmchealthservres.biomedcentral.com/articles/10.1186/s12913-017-2605-5

5. de Vries EN, Ramrattan MA, Smorenburg SM, Gouma DJ, Boermeester MA. The incidence and nature of in-hospital adverse events: a systematic review. Qual Saf Health Care. 2008 Jun 1;17(3):216–23.

6. Hodkinson A, Tyler N, Ashcroft DM, Keers RN, Khan K, Phipps D, et al. Preventable medication harm across health care settings: a systematic review and meta-analysis. BMC Med [Internet]. 2020 Nov 6 [cited 2021 Jan 29];18. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7646069/

7. Elliott RA, Camacho E, Jankovic D, Sculpher MJ, Faria R. Economic analysis of the prevalence and clinical and economic burden of medication error in England. BMJ Qual Saf. 2021 Feb;30(2):96–105.

8. Goedecke T, Ord K, Newbould V, Brosch S, Arlett P. Medication Errors: New EU Good Practice Guide on Risk Minimisation and Error Prevention. Drug Saf. 2016 Jun;39(6):491–500.

9. Leape LL, Brennan TA, Laird N, Lawthers AG, Localio AR, Barnes BA, et al. The nature of adverse events in hospitalized patients. Results of the Harvard Medical Practice Study II. N Engl J Med. 1991 Feb 7;324(6):377–84.

10. To Err Is Human: Building a Safer Health System [Internet]. Washington, D.C.: National Academies Press; 2000 [cited 2021 Feb 23]. Available from: http://www.nap.edu/catalog/9728

11. Cousins DH, Gerrett D, Warner B. A review of medication incidents reported to the National Reporting and Learning System in England and Wales over 6 years (2005–2010). Br J Clin Pharmacol. 2012 Oct;74(4):597–604.

12. Styrelsen for Patientsikkerhed. Dansk Patientsikkerhedsdatabase. Årsberetning 2019. [Internet]. [cited 2021 Feb 18]. Available from: https://stps.dk/da/udgivelser/2020/aarsberetning-for-dansk-patientsikkerhedsdatabase-2019/~/media/01707469F7F9446FB3D3FD4EAB99CD6E.ashx

13. WHO | Reporting and learning systems for medication errors: [Internet]. WHO. World Health Organization; [cited 2021 Feb 23]. Available from: http://www.who.int/medicines/areas/quality_safety/safety_efficacy/emp_mes/en/

14. Newbould V, Le Meur S, Goedecke T, Kurz X. Medication Errors: A Characterisation of Spontaneously Reported Cases in EudraVigilance. Drug Saf. 2017;40(12):1241–8.

15. Carnovale C, Mazhar F, Pozzi M, Gentili M, Clementi E, Radice S. A characterization and disproportionality analysis of medication error related adverse events reported to the FAERS database. Expert Opin Drug Saf. 2018 Dec 2;17(12):1161–9.

16. Bate A, Evans SJW. Quantitative signal detection using spontaneous ADR reporting. Pharmacoepidemiol Drug Saf. 2009;18(6):427–36.

17. Ventola CL. Big Data and Pharmacovigilance: Data Mining for Adverse Drug Events and Interactions. Pharm Ther. 2018 Jun;43(6):340–51.

18. Rigsrevisionen 2014. Beretning til Statsrevisorerne om problemerne med at udvikle og implementere Fælles Medicinkort. [Internet]. Available from: http://www.rigsrevisionen.dk/media/1999813/problemerne-med-at-udvikle-og-implementere-faelles-medicinkort.pdf

19. Peters M, Godfrey C, McInerney P, Munn Z, Trico A, Khalil H. Chapter 11: Scoping Reviews. In: Aromataris E, Munn Z, editors. JBI Manual for Evidence Synthesis [Internet]. JBI; 2020 [cited 2021 May 9]. Available from: https://wiki.jbi.global/display/MANUAL/Chapter+11%3A+Scoping+reviews

20. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. Int J Soc Res Methodol. 2005 Feb;8(1):19–32.

21. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. Ann Intern Med. 2018 Oct 2;169(7):467–73.

22. NCC MERP. About Medication Errors [Internet]. 2014 [cited 2021 Feb 17]. Available from: https://www.nccmerp.org/about-medication-errors

23. indexColor2001-06-12.pdf [Internet]. [cited 2021 Feb 23]. Available from: https://www.nccmerp.org/sites/default/files/indexColor2001-06-12.pdf

24. Bates DW, Boyle DL, Vander Vliet MB, Schneider J, Leape L. Relationship between medication errors and adverse drug events. J Gen Intern Med. 1995 Apr;10(4):199–205.

25. safety-of-medicines--adverse-drug-reactions-jun18.pdf [Internet]. [cited 2021 Feb 22]. Available from: https://www.who.int/docs/default-source/medicines/safety-of-medicines--adverse-drug-reactions-jun18.pdf?sfvrsn=4fcaf40_2

26. 2006 - E 2 D Post Approval Safety Data Management.pdf [Internet]. [cited 2021 May 31]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use_en-12.pdf

27. WHO-EIP-SPO-QPS-05.3-eng.pdf [Internet]. [cited 2021 May 31]. Available from: https://apps.who.int/iris/bitstream/handle/10665/69797/WHO-EIP-SPO-QPS-05.3-eng.pdf?sequence=1&isAllowed=y

28. Bramer WM, de Jonge GB, Rethlefsen ML, Mast F, Kleijnen J. A systematic approach to searching: an efficient and complete method to develop literature searches. J Med Libr Assoc JMLA. 2018 Oct;106(4):531–41.

29. NHS England » Introducing our new system for patient safety learning [Internet]. [cited 2021 Sep 21]. Available from: https://www.england.nhs.uk/blog/introducing-our-new-system-for-patient-safety-learning/

30. Bjørn B, Anhøj J, Lilja B. [Reporting of patient safety incidents: experience from five years with a national reporting system]. Ugeskr Laeger. 2009 May 11;171(20):1677–80.

APPENDIX 1 Search protocol for "Methodologic approaches for medication error analyses in patient safety- and pharmacovigilance reporting systems - a scoping review"

Online searches

- Google Scholar
- European Medicines Agency (https://www.ema.europa.eu/en/human-regulatory/research-development/pharmacovigilance/eudravigilance)
- U.S. Food and Drug Administration (https://www.fda.gov/)
- Agency for Healthcare Research and Quality. Patient Safety Network (https://www.ahrq.gov/npsd/index.html)
- Institute for Safe Medication Practices (https://www.ismp.org)
- Australian Commission on Safety and Quality in Health Care (https://www.safetyandquality.gov.au)
- National Health Service (NHS) England (https://www.england.nhs.uk/)
- Norwegian Healthcare Authority (https://helse-nord.no/)
- Danish Patient Safety Authority (https://stps.dk/)
- National Board of Health and Welfare in Sweden (https://www.socialstyrelsen.se)

Search query for online searches:
medication error AND reporting, at title level.

Citation searches

Citation searches will be conducted in Scopus for all identified studies from the electronic databases.

Electronic databases

- Embase (Ovid)
- Medline (Ovid)
- Cochrane Central
- CINAHL (EBSCOhost)

Search strings for electronic databases

Embase (Ovid)

#	Query
1.	exp medication error/
2.	adverse event/
3.	drug overdose/

4. drug underdose/
5. exp inappropriate prescribing/
6. patient harm/
7. patient risk/
8. ((drug$ or medication$ or medicin$ or dose$ or dosage$ or dosing) adj2 (incident$ or adverse event$ or mistake$ or error$ or wrong or inappropriate or safety)).ti,ab.
9. drug overdose.ti,ab.
10. drug underdose.ti,ab.
11. ((pharmacist$ or prescrib$ or prescription$ or dispens$ or dosing) adj2 (error$ or mistake$ or miscalculat$)).ti,ab.
12. near miss$.ti,ab.
13. (patient adj1 (harm or risk)).ti,ab.
14. or/1-13
15. exp pharmacovigilance/
16. exp drug monitoring/
17. incident report/
18. voluntary reporting/
19. system analysis/
20. natural language processing/
21. "root cause analysis"/
22. pharmaco-vigilance.ti,ab.
23. pharmacovigilance.ti,ab.
24. ((drug or medication) adj1 monitoring).ti,ab.
25. incident report$.ti,ab.
26. (voluntary adj2 report$).ti,ab.
27. mandatory report$.ti,ab.
28. ((reporting or monitoring) adj1 system$).ti,ab.
29. system analys?s.ti,ab.
30. natural language processing.ti,ab.
31. "root cause analysis".ti,ab.
32. safety management.ti,ab.
33. or/15-32

34.	14 and 33
35.	limit 34 to yr="2005 -Current"

Medline (Ovid)

#	Query
1.	exp Medication Errors/
2.	Drug Overdose/
3.	Inappropriate Prescribing/
4.	Patient Harm/
5.	((drug$ or medication$ or medicin$ or dose$ or dosage$ or dosing) adj2 (incident$ or adverse event$ or mistake$ or error$ or wrong or inappropriate or safety)).ti,ab.
6.	drug overdose.ti,ab.
7.	drug underdose.ti,ab.
8.	((pharmacist$ or prescrib$ or prescription$ or dispens$ or dosing) adj2 (error$ or mistake$ or miscalculat$)).ti,ab.
9.	near miss$.ti,ab.
10.	(patient adj1 (harm or risk)).ti,ab.
11.	or/1-10
12.	exp Pharmacovigilance/
13.	exp Drug Monitoring/
14.	Natural Language Processing/
15.	"Root Cause Analysis"/
16.	Safety Management/
17.	pharmaco-vigilance.ti,ab.
18.	pharmacovigilance.ti,ab.
19.	((drug or medication) adj1 monitoring).ti,ab.
20.	incident report$.ti,ab.
21.	(voluntary adj2 report$).ti,ab.
22.	mandatory report$.ti,ab.
23.	((reporting or monitoring) adj1 system$).ti,ab.
24.	system analys?s.ti,ab.
25.	natural language processing.ti,ab.

26.	"root cause analysis".ti,ab.
27.	safety management.ti,ab.
28.	or/12-27
29.	11 and 28
30.	limit 29 to yr="2005 -Current"

Cochrane Central

ID	Search
#1	MeSH descriptor: [Medication Errors] explode all trees
#2	MeSH descriptor: [Drug Overdose] this term only
#3	MeSH descriptor: [Inappropriate Prescribing] explode all trees
#4	MeSH descriptor: [Patient Harm] this term only
#5	(drug* or medication* or medicin* or dose* or dosage* or dosing) NEAR/2 (incident* or adverse event* or mistake* or error* or wrong or inappropriate or safety):ti,ab
#6	drug overdose:ti,ab
#7	drug underdose:ti,ab
#8	(pharmacist* or prescrib* or prescription* or dispens* or dosing) NEAR/2 (error* or mistake* or miscalculat*):ti,ab
#9	(patient) NEAR/1 (harm or risk):ti,ab
#10	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9
#11	MeSH descriptor: [Pharmacovigilance] explode all trees
#12	MeSH descriptor: [Drug Monitoring] explode all trees
#13	MeSH descriptor: [Natural Language Processing] this term only
#14	pharmaco-vigilance:ti,ab
#15	pharmacovigilance:ti,ab
#16	(drug or medication) NEAR/1 (monitoring):ti,ab
#17	(incident report*):ti,ab
#18	voluntary NEAR/2 report*:ti,ab
#19	(mandatory report*):ti,ab

#20	(reporting or monitoring) NEAR/1 (system*):ti,ab
#21	(system analysis):ti,ab
#22	(natural language processing):ti,ab
#23	"root cause analysis":ti,ab
#24	safety management:ti,ab
#25	#11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24
#26	#10 and #25 with Publication Year from 2005 to 2021, in Trials

Cinahl

#	Query	Limiters/Expanders
S31	S10 AND S29	Limiters - Published Date: 20050101-20211231 Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S30	S10 AND S29	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S29	S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S28	TI "Safety management" OR AB "Safety management"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S27	TI "Root Cause Analysis" OR AB "Root Cause Analysis"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S26	TI "Natural Language Processing" OR AB "Natural Language Processing"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S25	TI "Systems Analys?s" OR AB "Systems Analys?s"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S24	TI((reporting or monitoring) N1 system*) or AB((reporting or monitoring) N1 system*)	Expanders - Apply equivalent subjects

		Search modes - Boolean/Phrase
S23	TI "mandatory reporting*" OR AB "mandatory reporting*"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S22	TI(voluntary N2 reporting*) OR AB(voluntary N2 reporting*)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S21	TI "incident report*" OR AB "incident report*"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S20	TI((drug or medication) N1 monitoring) or AB((drug or medication) N1 monitoring)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S19	TI "pharmacovigilance" OR AB "pharmacovigilance"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S18	(MH "Root Cause Analysis")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S17	(MH "Natural LanguageProcessing")	Expanders - Apply equivalent subjects Search modes - SmartText Searching
S16	(MH "Systems Analysis")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S15	(MH "Mandatory Reporting")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S14	(MH "Voluntary Reporting")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S13	(MH "Incident Reports")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase

S12	(MH "Drug Monitoring")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S11	(MH"Pharmacovigilance")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S10	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S9	TI(patient N1 (harm or risk)) or AB(patient N1 (harm or risk))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S8	TI "near miss*" OR AB "near miss*"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S7	TI((pharmacist* or prescrib* or prescription* or dispens* or dosing) N2 (error* or mistake* or miscalculat*)) or AB((pharmacist* or prescrib* or prescription* or dispens* or dosing) N2 (error* or mistake* or miscalculat*))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S6	TI "Drug underdose" OR AB "Drug underdose"	Expanders - Apply equivalent subjects Search modes - SmartText Searching
S5	TI "Drug overdose" OR AB "Drug Overdose"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S4	TI((drug* or medication* or medicin* or dose* or dosage* or dosing) N2 (incident* or adverse event* or mistake* or error* or wrong or inappropriate or safety)) OR AB(drug* or medication* or medicin* or dose* or dosage* or dosing) N2 (incident* or adverse event* or mistake* or error* or wrong or inappropriate or safety))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S3	(MH "Inappropriate Prescribing")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase
S2	(MH "Adverse Drug Event")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase

S1	(MH "Medication Errors")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase

BMJ Open

Methodologic approaches for medication error analyses in patient safety- and pharmacovigilance reporting systems:a scoping review protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-057764.R1
Article Type:	Protocol
Date Submitted by the Author:	28-Feb-2022
Complete List of Authors:	Tchijevitch, Olga; University of Southern Denmark Faculty of Health Sciences, Department of Clinical Research, Research Unit OPEN Hansen, Sebrina Maj-Britt; University of Southern Denmark Odense Campus Library Bogh, Soren; University of Southern Denmark Faculty of Health Sciences, Department of Clinical Research, Research Unit OPEN Hallas, Jesper; University of Southern Denmark Faculty of Health Sciences, Department of Clinical Pharmacology and Pharmacy Birkeland, Søren; University of Southern Denmark Faculty of Health Sciences, Department of Clinical Research, Research Unit OPEN
Primary Subject Heading:	Public health
Secondary Subject Heading:	Health services research
Keywords:	Health & safety < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, PUBLIC HEALTH

Methodologic approaches for medication error analyses in patient safety- and pharmacovigilance reporting systems: a scoping review protocol

Olga Tchijevitch[1*], Sebrina Maj-Britt Hansen[2], Søren Bie Bogh[1], Jesper Hallas[3], Søren Birkeland[1]
[1]Department of Clinical Research, Research Unit OPEN, University of Southern Denmark, J.B Winsloews Vej 9A, 5000 Odense, Denmark.
[2]University Library of Southern Denmark, Campusvej 55, 5230 Odense M.
[3]Department of Clinical Pharmacology and Pharmacy, University of Southern Denmark, J. B. Winsloews Vej 19.2, 5000 Odense, Denmark.
*Correspondence to: otchijevitch@health.sdu.dk

ABSTRACT

Introduction Medication errors (MEs) are associated with patient harm and high economic costs. Healthcare authorities and pharmacovigilance organizations in many countries routinely collect data on MEs via reporting systems to improve patient safety and for learning purposes. While different approaches have been developed and used for the ME analysis, an overview over the scope of available methods currently is lacking.

This scoping review, aims to identify, explore, and map the available literature on methods used to analyze MEs in reporting systems.

Methods and analyses This protocol describes a scoping review, based on the Joanna Briggs Institute methodological framework. A systematic search will be performed in Medline (Ovid), Embase (Ovid), Cinahl (EBSCOhost), Cochrane central, Google Scholar, websites of the major pharmacovigilance centers and national healthcare safety agencies, and citation search in Scopus in March 2022. All retrieved records will be independently screened by two researchers on the title, abstract and full-text, involving a third researcher in case of disagreement. Data will be extracted and presented in descriptive and tabular form. The extraction will be based on information about methods of ME analyses, the type of the reporting system and information on MEs (medication name, ATC- codes, ME type, medication-event categories, and harm categories).

Ethics and dissemination Ethical approval is not required. The results will be disseminated via publication in peer-reviewed journals, scientific networks and relevant conferences.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This scoping review, based on an established scoping review methodology, will be the first to identify and map the existing publications on methods used to analyse medication errors in reporting systems.
- The systematic search strategy was developed in collaboration with an experienced information specialist, and study selection and data extraction will be performed by independent reviewers.
- There will be no formal quality assessment on the included publications, as the review aims to map the scope of publications on methodology of medication error analyses in reporting sytems.
- The search strategy may result in a large number of publications, that may require refinement of the eligibility criteria.

INTRODUCTION

A medication error (ME) is an error in the medication treatment process, and it can occur during all stages of medication use from ordering, through dispensing and administration, to monitoring.(1) MEs constitute a major challenge to patient safety(2) and are associated with patient harm and increasing national expenses.(3–5) The prevalence of preventable medication harm has been estimated to be 3% in adult patients in primary and secondary healthcare settings on average, with higher rates in elderly (11%) and intensive care patients (7%).(6) For example, in the UK, error-related harm has been estimated to contribute to more than 1,700 deaths per year, costing 98.5 million GBP (114.6 million EUR) for hospital admissions and extended hospital stay (7). The suggested yearly costs range between 4.5 and 21.8 billion EUR in European healthcare (8) and constitute about 35 billion EUR worldwide.(2)

MEs and harm associated with MEs have been a challenge to safety for decades.(9,10) Consequently, patient safety reporting systems (PSRS) have been introduced and adopted by many countries. Systems are based on reporting incidents that resulted in harm or could have caused harm. The main intention with the systems

is to learn and thereby prevent forthcoming injuries.(11) Systems are organized on different levels (national, regional, institutional, etc.). Some are voluntary and others are mandatory and some only include MEs, while others may also include other hazardous health care incidents. The share of ME reports is remarkable, corresponding to 11% of nearly 1 200,000 annual incident reports in England and Wales and 56 % of 222,289 incidents, reported in Denmark. (11,12)

In pharmacovigilance, spontaneous reporting systems (SRS) have been initially used for monitoring of *adverse drug reactions* (ADR), but recently these systems became more involved in monitoring of MEs, following WHO and EU recommendations for collaboration between the safety organizations in healthcare (8,13). The European database for ADR (EudraVigilance) and US Adverse Events Reporting System (FAERS) collected 147,824 ME reports in 2002-2015 and over 100,000 reports in 2015.(14,15)

The number of reported incidents has increased rapidly, reaching an overwhelming volume of reports. (11,12,14) Analyzing the large amount of data, collected via reporting systems by national safety authorities and pharmacovigilance centers is increasingly costly and challenging. (16,17) Inefficiently analyzed data may ultimately impede the learning potential of ME reports, and in the end, compromise patient safety. Moreover, healthcare systems may choose to deprioritize or even phase out parts of the mandatory reporting, thereby taking patient safety a great step backward.(18) Various approaches to ME analyses have been developed to address challenges, ranging from traditional manual reviewing and arithmetical counting to advanced computerized methods such as natural language processing (NLP) and data mining methods. However, knowledge of the current scope of methodological approaches and the frequency of their use is limited. There is a need to provide an up-to-date overview of the knowledge to understand and make recommendations for necessary developments. A preliminary search in PubMed has not identified systematic or scoping reviews on this topic. In this scoping review, we aim to identify, explore and map the existing publications/scientific literature on methods of ME analysis in reporting systems.

METHODS

This will be a scoping review following Joanna Briggs Institute methodological framework,(19) initially developed by Arksey and O'Malley(20). This method is based on five stages: (1) identifying the research question; (2) identifying relevant studies; (3) study selection; (4) charting the data; (5) collating, summarizing and reporting the results.

The proposed review will be reported according to Preferred Reporting Items for Systematic Review and Meta- Analyses extension for Scoping Reviews (PRISMA ScR).(21)

The definition of terms is presented in Table 1.

Table 1 Definitions of terms

Medication error (ME)	*"A medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing, order communication, product labeling, packaging, and nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use".*(22) MEs can be classified according to their severity in nine categories from "*no harm*" to *"death*", according to MCC MERP classification index.(23) Other definitions on MEs might be applicable and will be labeled during the extraction.

Adverse drug events (ADEs) Adverse drug reaction (ADR)	*"Injuries resulting from medical interventions related to a drug. ADE may result from medication errors or from adverse drug reactions (ADR) in which there were no error".*(24) ADEs can be preventable and non-preventable. Preventable ADE is always a result of an error. Non-preventable ADE is ADR, an injury without an error.(24) *"A response to a medicine which is noxious and unintended, and which occurs at doses normally used in man".*(25) In this study we intend to focus exclusively on preventable ADE.
Spontaneous reporting system (SRS)	A system, that is relayed on *"an unsolicited communication by a healthcare professional or consumer to a company, regulatory authority or other organization[…], that describes one or more adverse drug reactions in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection scheme".*(26) SRS are administered by pharmacovigilance centres, and might be refered to as "*post marketing spontaneous reports*", "*postmarketing surveillance"* or *"adverse events reaction systems"*.
Patient safety reporting systems (PSRS)	Systems for reporting of incidents in healthcare, that *"cause an injury to the patient or pose a risk of harm.*(27) *The fundamental role of a PSRS is to enhance patient safety by learning from failures of the healthcare system".*(13) PSRS are usually administered by the local or national healthcare authorities, and might be reffered to as *"patient incident reporting", "safety database" or "event reporting system".*

Identifying the research question

The research question of this scoping review emerged from knowledge gaps identified by the authors. As the availability of methodological approaches and new technologies used to analyze large databases is rapidly developing, the following question was formulated "What is known from the literature about ME methods of analyses in reporting systems?". The review should help researchers and organizations engaged with medication safety to gain insight into the current methods to analyze MEs and support authorities in considering alternative or supplementary methods for ME analyses.

Identifying relevant studies

The search strategy was developed in cooperation with the research team and the information specialist **(SH)** using a search guide developed by Bramer.(28) First, we identified elements from the research question: "medication errors" and "system analyses". Secondly, we collected subject-specific headings and key words and their synonyms accordingly. The search was initially performed in Embase (Ovid) and translated to Medline (Ovid), Cinahl (EBSCOhost) and Cochrane Central (Appendix 1).

Google Scholar, major national healthcare safety agencies and pharmacovigilance centers' websites will be searched for relevant publications. The final search will be made within two weeks when the protocol is approved with the cut-off date 31 March 2022. We will review the reference lists of the included studies and use the citation search in Scopus for each reference. Additionally, we will contact authors of publications for further information, if necessary. All searches will be limited to 2005 onwards. From this point in time, many countries began to introduce national patient reporting systems. (29,30)

Study selection

All retrieved records from the literature search will be imported and managed in Covidence. Two researchers (OT) and (SH) will independently first screen at title/abstract level and secondly on full-text level according to the in- and exclusion criteria listed below. In case of disagreement, the third researcher (SB) will be involved to achieve consensus.

All publications with titles and abstracts available in English or Scandinavian languages will be mapped in this study without further language restrictions. However, the data extraction will be possible only for publications that are published in full in English or Scandinavian languages.

Inclusion criteria:

- Publications targeting MEs or AEs related to MEs, that have occurred to persons of any age and gender;
- Publications that describe methodologies used to identify and analyze MEs;
- Publications from all healthcare institutions or organizations that use reporting systems as a source, including SRS or PSRS on national, regional or local levels;
- Publications reporting on ADE and ADR, will be considered only if there is a described association between these two and MEs.

Exclusion criteria:

- Review articles, editorials and publications that do not provide information on medication involved or ME's category;
- Publications exploring herbal or traditional medicines.

Data extraction

Two researchers (OT) and (SB) will independently extract the data using a charting table, that will be developed by the research team. A priori pilot testing will be performed on two or three sources to ensure all relevant results are extracted, iteratively updating a data-charting form.(19)

General characteristics will be extracted from the chosen publications: author(s), year of publication, source of origin/country of origin, study design, settings and population. Next, we will extract information about methods used for MEs' detection and analysis, the type of the reporting system used, and the frequency and characteristics of MEs revealed by the analysis: the most frequent medications involved in MEs (their generic name and ATC-code), and medication-event combinations, based either on stages of medication process (prescribing, transcribing, dispencing/preparation, administering/documenting and monitoring) or medication error category (such as wrong medication, wrong patient, wrong dose, wrong route, wrong time, omission error, etc.)(Appendix 2). Patient demographic characteristics, such as age and gender, categories of medication-related harm and the reporting organization will also be extracted. Additionally, limitations/biases, such as the quality of data and funding sources, will be noted.

The outcome of ME analyses may vary from study to study. For example, in some studies focus may be on adverse events/patient harm and in others, focus is on hazardous medication-event situations. Likewise, differences can occur as some studies may, e.g., investigate only prescribing or administration errors or MEs connected to a particular drug of interest. In contrast, others may explore MEs more generally.

Data summary

The primary interest of this study is to provide an overview of the methods used for MEs' analysis; these methods will be seen in connection with the type of the reporting system and detailed information on MEs, their types, and frequency.

The results will be summarized and presented in descriptive and tabular form.

Patient and public involvement

This protocol was developed without patient or public involvement.

Study status

The study protocol was completed on 21 September 2021, and the literature search will be started immediately after the publication of the protocol, followed by study selection and data extraction. We plan to fulfill the study by November 2022.

ETHICS AND DISSEMINATION

The review does not require approval from the Ethic Committee, as this is a literature study. Dissemination of the results will take place via publication in peer-reviewed journals and presentations for the interest organizations, that work on patient safety, as well as scientific networks and conferences.

FUNDING

This work was supported by the Faculty of Health Science University of Southern Denmark (SDU stipendium grant 24.09.2020), the Region of Southern Denmark (grant j.nr.20/45119. Efond 645), Department of Cardiology Lillebaelt Hospital (letter of financial support from 28.05.2020) and Helsefonden (grant 20-B-0189).

ACKNOWLEDGMENTS

We would like to thank CEMBO/Cochrane Denmark for providing methodological consultancy service and support.

CONTRIBUTORS

All authors contributed to the protocol design and plan. SB and OT have developed the initial draft of the protocol, which has been revised and finally accepted by the research team (OT, SH, SBB, JH and SB). The initial literature search has been developed collaboratively by SH and OT.

REFERENCES

1. Lisby M, Nielsen LP, Brock B, Mainz J. How should medication errors be defined? Development and test of a definition. Scand J Public Health. 2012 Mar 1;40(2):203–10.

2. WHO | The third WHO Global Patient Safety Challenge: *Medication Without Harm* [Internet]. WHO. World Health Organization; [cited 2021 Feb 17]. Available from: http://www.who.int/patientsafety/medication-safety/en/

3. Hoonhout LHF, de Bruijne MC, Wagner C, Asscheman H, van der Wal G, van Tulder MW. Nature, occurrence and consequences of medication-related adverse events during hospitalization: a retrospective chart review in the Netherlands. Drug Saf. 2010 Oct 1;33(10):853–64.

4. Kjellberg J, Wolf RT, Kruse M, Rasmussen SR, Vestergaard J, Nielsen KJ, et al. Costs associated with adverse events among acute patients. BMC Health Serv Res [Internet]. 2017 Dec [cited 2019 Feb 19];17(1). Available from: http://bmchealthservres.biomedcentral.com/articles/10.1186/s12913-017-2605-5

5. de Vries EN, Ramrattan MA, Smorenburg SM, Gouma DJ, Boermeester MA. The incidence and nature of in-hospital adverse events: a systematic review. Qual Saf Health Care. 2008 Jun 1;17(3):216–23.

6. Hodkinson A, Tyler N, Ashcroft DM, Keers RN, Khan K, Phipps D, et al. Preventable medication harm across health care settings: a systematic review and meta-analysis. BMC Med [Internet]. 2020 Nov 6 [cited 2021 Jan 29];18. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7646069/

7. Elliott RA, Camacho E, Jankovic D, Sculpher MJ, Faria R. Economic analysis of the prevalence and clinical and economic burden of medication error in England. BMJ Qual Saf. 2021 Feb;30(2):96–105.

8. Goedecke T, Ord K, Newbould V, Brosch S, Arlett P. Medication Errors: New EU Good Practice Guide on Risk Minimisation and Error Prevention. Drug Saf. 2016 Jun;39(6):491–500.

9. Leape LL, Brennan TA, Laird N, Lawthers AG, Localio AR, Barnes BA, et al. The nature of adverse events in hospitalized patients. Results of the Harvard Medical Practice Study II. N Engl J Med. 1991 Feb 7;324(6):377–84.

10. To Err Is Human: Building a Safer Health System [Internet]. Washington, D.C.: National Academies Press; 2000 [cited 2021 Feb 23]. Available from: http://www.nap.edu/catalog/9728

11. Cousins DH, Gerrett D, Warner B. A review of medication incidents reported to the National Reporting and Learning System in England and Wales over 6 years (2005–2010). Br J Clin Pharmacol. 2012 Oct;74(4):597–604.

12. Styrelsen for Patientsikkerhed. Dansk Patientsikkerhedsdatabase. Årsberetning 2019. [Internet]. [cited 2021 Feb 18]. Available from: https://stps.dk/da/udgivelser/2020/aarsberetning-for-dansk-patientsikkerhedsdatabase-2019/~/media/01707469F7F9446FB3D3FD4EAB99CD6E.ashx

13. WHO | Reporting and learning systems for medication errors: [Internet]. WHO. World Health Organization; [cited 2021 Feb 23]. Available from: http://www.who.int/medicines/areas/quality_safety/safety_efficacy/emp_mes/en/

14. Newbould V, Le Meur S, Goedecke T, Kurz X. Medication Errors: A Characterisation of Spontaneously Reported Cases in EudraVigilance. Drug Saf. 2017;40(12):1241–8.

15. Carnovale C, Mazhar F, Pozzi M, Gentili M, Clementi E, Radice S. A characterization and disproportionality analysis of medication error related adverse events reported to the FAERS database. Expert Opin Drug Saf. 2018 Dec 2;17(12):1161–9.

16. Bate A, Evans SJW. Quantitative signal detection using spontaneous ADR reporting. Pharmacoepidemiol Drug Saf. 2009;18(6):427–36.

17. Ventola CL. Big Data and Pharmacovigilance: Data Mining for Adverse Drug Events and Interactions. Pharm Ther. 2018 Jun;43(6):340–51.

18. Rigsrevisionen 2014. Beretning til Statsrevisorerne om problemerne med at udvikle og implementere Fælles Medicinkort. [Internet]. Available from: http://www.rigsrevisionen.dk/media/1999813/problemerne-med-at-udvikle-og-implementere-faelles-medicinkort.pdf

19. Peters M, Godfrey C, McInerney P, Munn Z, Trico A, Khalil H. Chapter 11: Scoping Reviews. In: Aromataris E, Munn Z, editors. JBI Manual for Evidence Synthesis [Internet]. JBI; 2020 [cited 2021 May 9]. Available from: https://wiki.jbi.global/display/MANUAL/Chapter+11%3A+Scoping+reviews

20. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. Int J Soc Res Methodol. 2005 Feb;8(1):19–32.

21. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. Ann Intern Med. 2018 Oct 2;169(7):467–73.

22. NCC MERP. About Medication Errors [Internet]. 2014 [cited 2021 Feb 17]. Available from: https://www.nccmerp.org/about-medication-errors

23. indexColor2001-06-12.pdf [Internet]. [cited 2021 Feb 23]. Available from: https://www.nccmerp.org/sites/default/files/indexColor2001-06-12.pdf

24. Bates DW, Boyle DL, Vander Vliet MB, Schneider J, Leape L. Relationship between medication errors and adverse drug events. J Gen Intern Med. 1995 Apr;10(4):199–205.

25. safety-of-medicines--adverse-drug-reactions-jun18.pdf [Internet]. [cited 2021 Feb 22]. Available from: https://www.who.int/docs/default-source/medicines/safety-of-medicines--adverse-drug-reactions-jun18.pdf?sfvrsn=4fcaf40_2

26. 2006 - E 2 D Post Approval Safety Data Management.pdf [Internet]. [cited 2021 May 31]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use_en-12.pdf

27. WHO-EIP-SPO-QPS-05.3-eng.pdf [Internet]. [cited 2021 May 31]. Available from: https://apps.who.int/iris/bitstream/handle/10665/69797/WHO-EIP-SPO-QPS-05.3-eng.pdf?sequence=1&isAllowed=y

28. Bramer WM, de Jonge GB, Rethlefsen ML, Mast F, Kleijnen J. A systematic approach to searching: an efficient and complete method to develop literature searches. J Med Libr Assoc JMLA. 2018 Oct;106(4):531–41.

29. NHS England » Introducing our new system for patient safety learning [Internet]. [cited 2021 Sep 21]. Available from: https://www.england.nhs.uk/blog/introducing-our-new-system-for-patient-safety-learning/

30. Bjørn B, Anhøj J, Lilja B. [Reporting of patient safety incidents: experience from five years with a national reporting system]. Ugeskr Laeger. 2009 May 11;171(20):1677–80.

Supplementary material

Appendix 1 Search protocol for "Methodologic approaches for medication error analyses in patient safety- and pharmacovigilance reporting systems - a scoping review".

Appendix 2 Guide on stages in the medication use process and error types.

APPENDIX 1 Search protocol for "Methodologic approaches for medication error analyses in patient safety- and pharmacovigilance reporting systems - a scoping review"

The search protocol describes the planned searches in electronic databases (Embase, Medline, Cochrane and Cinahl), citation searches and online searches.

Embase (Ovid) search string

#	Query
1.	exp medication error/
2.	adverse event/
3.	drug overdose/
4.	drug underdose/
5.	exp inappropriate prescribing/
6.	patient harm/
7.	patient risk/
8.	((drug$ or medication$ or medicin$ or dose$ or dosage$ or dosing) adj2 (incident$ or adverse event$ or mistake$ or error$ or wrong or inappropriate or safety)).ti,ab.
9.	drug overdose.ti,ab.
10.	drug underdose.ti,ab.
11.	((pharmacist$ or prescrib$ or prescription$ or dispens$ or dosing) adj2 (error$ or mistake$ or miscalculat$)).ti,ab.
12.	near miss$.ti,ab.
13.	(patient adj1 (harm or risk)).ti,ab.
14.	or/1-13
15.	exp pharmacovigilance/
16.	exp drug monitoring/
17.	incident report/
18.	voluntary reporting/
19.	system analysis/
20.	natural language processing/
21.	"root cause analysis"/
22.	pharmaco-vigilance.ti,ab.
23.	pharmacovigilance.ti,ab.
24.	((drug or medication) adj1 monitoring).ti,ab.
25.	incident report$.ti,ab.
26.	(voluntary adj2 report$).ti,ab.
27.	mandatory report$.ti,ab.
28.	((reporting or monitoring) adj1 system$).ti,ab.
29.	system analys?s.ti,ab.
30.	natural language processing.ti,ab.
31.	"root cause analysis".ti,ab.
32.	safety management.ti,ab.
33.	or/15-32
34.	14 and 33
35.	limit 34 to yr="2005 -Current"

Medline (Ovid) search string

#	Query
1.	exp Medication Errors/
2.	Drug Overdose/
3.	Inappropriate Prescribing/
4.	Patient Harm/
5.	((drug$ or medication$ or medicin$ or dose$ or dosage$ or dosing) adj2 (incident$ or adverse event$ or mistake$ or error$ or wrong or inappropriate or safety)).ti,ab.
6.	drug overdose.ti,ab.
7.	drug underdose.ti,ab.
8.	((pharmacist$ or prescrib$ or prescription$ or dispens$ or dosing) adj2 (error$ or mistake$ or miscalculat$)).ti,ab.
9.	near miss$.ti,ab.
10.	(patient adj1 (harm or risk)).ti,ab.
11.	or/1-10
12.	exp Pharmacovigilance/
13.	exp Drug Monitoring/
14.	Natural Language Processing/
15.	"Root Cause Analysis"/
16.	Safety Management/
17.	pharmaco-vigilance.ti,ab.
18.	pharmacovigilance.ti,ab.
19.	((drug or medication) adj1 monitoring).ti,ab.
20.	incident report$.ti,ab.
21.	(voluntary adj2 report$).ti,ab.
22.	mandatory report$.ti,ab.
23.	((reporting or monitoring) adj1 system$).ti,ab.
24.	system analys?s.ti,ab.
25.	natural language processing.ti,ab.
26.	"root cause analysis".ti,ab.
27.	safety management.ti,ab.
28.	or/12-27
29.	11 and 28
30.	limit 29 to yr="2005 -Current"

Cochrane Central search string

ID	Search
#1	MeSH descriptor: [Medication Errors] explode all trees
#2	MeSH descriptor: [Drug Overdose] this term only
#3	MeSH descriptor: [Inappropriate Prescribing] explode all trees
#4	MeSH descriptor: [Patient Harm] this term only
#5	(drug* or medication* or medicin* or dose* or dosage* or dosing) NEAR/2 (incident* or adverse event* or mistake* or error* or wrong or inappropriate or safety):ti,ab
#6	drug overdose:ti,ab
#7	drug underdose:ti,ab
#8	(pharmacist* or prescrib* or prescription* or dispens* or dosing) NEAR/2 (error* or mistake* or miscalculat*):ti,ab
#9	(patient) NEAR/1 (harm or risk):ti,ab
#10	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9
#11	MeSH descriptor: [Pharmacovigilance] explode all trees
#12	MeSH descriptor: [Drug Monitoring] explode all trees
#13	MeSH descriptor: [Natural Language Processing] this term only
#14	pharmaco-vigilance:ti,ab
#15	pharmacovigilance:ti,ab
#16	(drug or medication) NEAR/1 (monitoring):ti,ab
#17	(incident report*):ti,ab
#18	voluntary NEAR/2 report*:ti,ab
#19	(mandatory report*):ti,ab
#20	(reporting or monitoring) NEAR/1 (system*):ti,ab
#21	(system analysis):ti,ab
#22	(natural language processing):ti,ab
#23	"root cause analysis":ti,ab
#24	safety management:ti,ab
#25	#11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24
#26	#10 and #25 with Publication Year from 2005 to 2021, in Trials

Cinahl (EBSCO) search string

#	Query
S31	S10 AND S29 Limiters - Published Date: 20050101-20211231
S30	S10 AND S29
S29	S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28
S28	TI "Safety management" OR AB "Safety management"
S27	TI "Root Cause Analysis" OR AB "Root Cause Analysis"
S26	TI "Natural Language Processing" OR AB "Natural Language Processing"
S25	TI "Systems Analys?s" OR AB "Systems Analys?s"
S24	TI((reporting or monitoring) N1 system*) or AB((reporting or monitoring) N1 system*)
S23	TI "mandatory reporting*" OR AB "mandatory reporting*"
S22	TI(voluntary N2 reporting*) OR AB(voluntary N2 reporting*)
S21	TI "incident report*" OR AB "incident report*"
S20	TI((drug or medication) N1 monitoring) or AB((drug or medication) N1 monitoring)
S19	TI "pharmacovigilance" OR AB "pharmacovigilance"
S18	(MH "Root Cause Analysis")
S17	(MH "Natural LanguageProcessing")
S16	(MH "Systems Analysis")
S15	(MH "Mandatory Reporting")
S14	(MH "Voluntary Reporting")
S13	(MH "Incident Reports")
S12	(MH "Drug Monitoring")
S11	(MH"Pharmacovigilance")
S10	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9
S9	TI(patient N1 (harm or risk)) or AB(patient N1 (harm or risk))
S8	TI "near miss*" OR AB "near miss*"
S7	TI((pharmacist* or prescrib* or prescription* or dispens* or dosing) N2 (error* or mistake* or miscalculat*)) or AB((pharmacist* or prescrib* or prescription* or dispens* or dosing) N2 (error* or mistake* or miscalculat*))
S6	TI "Drug underdose" OR AB "Drug underdose"
S5	TI "Drug overdose" OR AB "Drug Overdose"
S4	TI((drug* or medication* or medicin* or dose* or dosage* or dosing) N2 (incident* or adverse event* or mistake* or error* or wrong or inappropriate or safety)) OR AB(drug* or medication* or medicin* or dose* or dosage* or dosing) N2 (incident* or adverse event* or mistake* or error* or wrong or inappropriate or safety))
S3	(MH "Inappropriate Prescribing")
S2	(MH "Adverse Drug Event")
S1	(MH "Medication Errors")

Online resources

We will search online resources with following query: “medication error AND reporting”, at title level. The searches will be limited from 2005 and onwards. Following resources will be searched:

- Google Scholar
- European Medicines Agency (https://www.ema.europa.eu/en/human-regulatory/research-development/pharmacovigilance/eudravigilance)
- U.S. Food and Drug Administration (https://www.fda.gov/)
- Agency for Healthcare Research and Quality. Patient Safety Network (https://www.ahrq.gov/npsd/index.html)
- Institute for Safe Medication Practices (https://www.ismp.org)

- Australian Commission on Safety and Quality in Health Care (https://www.safetyandquality.gov.au)
- National Health Service (NHS) England (https://www.england.nhs.uk/)
- Norwegian Healthcare Authority (https://helse-nord.no/)
- Danish Patient Safety Authority (https://stps.dk/)
- National Board of Health and Welfare in Sweden (https://www.socialstyrelsen.se)

Citation searches

We will conduct backward and forward citation searches. We will screen the reference lists of the eligible studies from the electronic searches and online searches. Furthermore, we will search Scopus citation database for forward citations of the eligible studies as well.

Appendix 2 Guide on stages in the medication use process and error types

Stage of medication use process[1]	Definition[2]	Type of error[3]
Prescribing	The process of entering and processing prescriptions for patient care.	Wrong medication, wrong patient, wrong dose, wrong route, wrong/missing time, missing information on discontinuation, drug-drug interaction, allergy (known). Omission of date/ signature.
Transcribing	An identical copy of prescription of medical order.	Any discrepancy between the prescription and other document.
Dispensing (including preparation)	Dispensing of medication in concordance with prescription. The process of preparing medications from a prescription for a patient.	Wrong medication, wrong patient (labeling), wrong dose, wrong time, wrong/missing preparation / mixture.
Administering/documenting	The process of administering and documenting administration of a medication to the right patient, in the write way and the right time.	Wrong patient, wrong medication, wrong time, wrong route, wrong frequency, medication not given, medication not taken. Administering is not documented.
Monitoring/documentation	The process of monitoring for adverse events and therapeutic effectiveness.	Missing follow-up on treatment or documentation on the effects.

[1]Described by the U.S. Pharmacopeia (U.S. Pharmacopeia National Formulary. Revision bulletin: <1006> physical environments that promote safe medication use. [Internet]. [7. februar 2022]; https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/c1066.pdf)

[2]Adapted from: Vest TA, Gazda NP, O'Neil DP, Schenkat DH, Eckel SF. Practice-enhancing publications about the medication-use process in 2020. American Journal of Health-System Pharmacy. 10. november 2021;zxab428.

[3]Adapted from: Lisby M. Errors in the medication process: frequency, type, and potential clinical consequences. International Journal for Quality in Health Care. 1. februar 2005;17(1):15–22.

BMJ Open

Methodologic approaches for medication error analyses in patient safety- and pharmacovigilance reporting systems:a scoping review protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-057764.R2
Article Type:	Protocol
Date Submitted by the Author:	05-May-2022
Complete List of Authors:	Tchijevitch, Olga; University of Southern Denmark Faculty of Health Sciences, Department of Clinical Research, Research Unit OPEN Hansen, Sebrina Maj-Britt; University of Southern Denmark Odense Campus Library Bogh, Soren; University of Southern Denmark Faculty of Health Sciences, Department of Clinical Research, Research Unit OPEN Hallas, Jesper; University of Southern Denmark Faculty of Health Sciences, Department of Clinical Pharmacology and Pharmacy Birkeland, Søren; University of Southern Denmark Faculty of Health Sciences, Department of Clinical Research, Research Unit OPEN
Primary Subject Heading:	Public health
Secondary Subject Heading:	Health services research
Keywords:	Health & safety < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, PUBLIC HEALTH

Methodologic approaches for medication error analyses in patient safety- and pharmacovigilance reporting systems: a scoping review protocol

Olga Tchijevitch[1*], Sebrina Maj-Britt Hansen[2], Søren Bie Bogh[1], Jesper Hallas[3], Søren Birkeland[1]
[1]Department of Clinical Research, Research Unit OPEN, University of Southern Denmark, J.B Winsloews Vej 9A, 5000 Odense, Denmark.
[2]University Library of Southern Denmark, Campusvej 55, 5230 Odense M.
[3]Department of Clinical Pharmacology and Pharmacy, University of Southern Denmark, J. B. Winsloews Vej 19.2, 5000 Odense, Denmark.
*Correspondence to: otchijevitch@health.sdu.dk

ABSTRACT

Introduction Medication errors (MEs) are associated with patient harm and high economic costs. Healthcare authorities and pharmacovigilance organizations in many countries routinely collect data on MEs via reporting systems to improve patient safety and for learning purposes. Different approaches have been developed and used for the ME analysis, but an overview of the scope of available methods currently is lacking.

This scoping review aims to identify, explore, and map available literature on methods used to analyze MEs in reporting systems.

Methods and analyses This protocol describes a scoping review, based on the Joanna Briggs Institute methodological framework. A systematic search will be performed in Medline (Ovid), Embase (Ovid), Cinahl (EBSCOhost), Cochrane central, Google Scholar, websites of the major pharmacovigilance centers and national healthcare safety agencies, and citation search in Scopus in August 2022. All retrieved records are to be independently screened by two researchers on title, abstract and full-text, involving a third researcher in case of disagreement. Data will be extracted and presented in descriptive and tabular form. The extraction will be based on information about methods of ME analyses, type of reporting system and information on MEs (medication name, ATC-codes, ME type, medication-event categories, and harm categories).

Ethics and dissemination Ethical approval is not required. The results will be disseminated via publication in peer-reviewed journals, scientific networks and relevant conferences.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This scoping review, based on an established scoping review methodology, will be the first to identify and map existing publications on methods used to analyze medication errors in reporting systems.
- The systematic search strategy is developed in collaboration with an experienced information specialist, and study selection and data extraction is to be performed by independent reviewers.
- No formal quality assessment on the included publications will be done, as the review aims to map publications on methodology of medication error analyses in reporting systems.
- The search strategy may result in a large number of publications, that may require refinement of eligibility criteria.

INTRODUCTION

A medication error (ME) is an error in the medication treatment process, which may occur during all stages of medication use from ordering, through dispensing and administration, to monitoring.(1) MEs constitute a major challenge to patient safety(2) and are associated with patient harm and increasing national expenses.(3–5) The prevalence of preventable medication harm has been estimated to be 3% in adult patients in primary and secondary healthcare settings on average, with higher rates in elderly (11%) and intensive care patients (7%).(6) For example, in the UK, error-related harm is estimated to contribute to more than 1,700 deaths per year, costing 98.5 million GBP (114.6 million EUR) for hospital admissions and extended hospital stay.(7) In European healthcare, the estimated yearly cost range from 4.5 to 21.8 billion EUR(8) and worldwide, it adds up to about 35 billion EUR.(2)

MEs and harm associated with MEs have been a challenge to safety for decades.(9,10) Consequently, patient safety reporting systems (PSRS) have been introduced to and adopted by many countries. The PSRS are based on reports of incidents that resulted in harm or might have caused harm. The main intention of the PSRS is

to learn and thereby prevent forthcoming injuries.(11) The PSRS are organized on different levels (national, regional, institutional, etc.) Some are voluntary, others are mandatory, some only include MEs, while others may include other hazardous health care incidents. The share of ME reports is remarkably high, corresponding to 11% of nearly 1 200,000 annual incident reports in England and Wales, and 56% of 222,289 annual incident reports in Denmark.(11,12)

In pharmacovigilance, spontaneous reporting systems (SRS) were initially applied when monitoring *adverse drug reactions* (ADR), but recently SRS play a more dominant role when monitoring MEs, quite in accordance with the recommendations from WHO and EU for collaboration between safety organizations in healthcare.(8,13) The European database for ADR (EudraVigilance) and the US Adverse Events Reporting System (FAERS) collected 147,824 ME reports in 2002-2015 and more than 100,000 reports in 2015.(14,15) The number of reported incidents has increased rapidly, reaching an overwhelming volume of reports.(11,12,14) Analyzing the large amount of data, collected via reporting systems by national safety authorities and pharmacovigilance centers, is costly and challenging.(16,17) Inefficiently analyzed data may ultimately impede the learning potential of ME reports, and at the end, compromise patient safety. Moreover, healthcare systems may choose to deprioritize or even phase out parts of the mandatory reporting, thereby taking patient safety a great step backwards.(18) Various approaches to ME analyses have been developed to address challenges, ranging from traditional manual reviewing and arithmetical counting to advanced computerized methods such as natural language processing (NLP) and data mining methods. However, knowledge of the current scope of methodological approaches and the frequency of their use is limited. There is therefore a need to provide an up-to-date overview of the knowledge to understand and make recommendations for necessary developments. A preliminary search in PubMed has not identified systematic or scoping reviews on this topic. In this scoping review, we aim to identify, explore and map the existing publications/scientific literature on methods of ME analysis in reporting systems.

METHODS

The proposed scoping review will be based on Joanna Briggs Institute methodological framework,(19) initially developed by Arksey and O'Malley.(20) This method is based on five stages: (1) identifying the research question; (2) identifying relevant studies; (3) study selection; (4) charting the data; (5) collating, summarizing and reporting the results.

The proposed review is to be reported according to Preferred Reporting Items for Systematic Review and Meta- Analyses extension for Scoping Reviews (PRISMA ScR).(21)

The definition of terms is presented in Table 1.

Table 1 Definitions of terms

Medication error (ME)	*"A medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing, order communication, product labeling, packaging, and nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use".*(22) MEs can be classified according to their severity in nine categories from "*no harm*" to *"death*", according to MCC MERP classification index.(23) Other definitions on MEs might be applicable and will be labeled during the extraction.

Adverse drug events (ADEs) Adverse drug reaction (ADR)	*"Injuries resulting from medical interventions related to a drug. ADE may result from medication errors or from adverse drug reactions (ADR) in which there were no error".*(24) ADEs can be preventable and non-preventable. Preventable ADE is always a result of an error. Non-preventable ADE is ADR, an injury without an error.(24) *"A response to a medicine which is noxious and unintended, and which occurs at doses normally used in man".*(25) In this study we intend to focus exclusively on preventable ADE.
Spontaneous reporting system (SRS) and pharmacovigilance	A system, that relies on *"an unsolicited communication by a healthcare professional or consumer to a company, regulatory authority or other organization[…], that describes one or more adverse drug reactions in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection scheme".*(26) SRS are administered by pharmacovigilance centers, operated at national or international levels, and might be referred to as "*post marketing spontaneous reports*", *"post marketing surveillance"* or *"adverse events reaction systems"*. Pharmacovigilance is defined as *"the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine/vaccine related problem*".(27) Pharmacovigilance is dealing with patient safety issuers and all drug-related problems, resulting in ADEs.(28)
Patient safety reporting systems (PSRS)	Systems for reporting of incidents in healthcare that *"cause an injury to the patient or pose a risk of harm.*(29) *The fundamental role of a PSRS is to enhance patient safety by learning from failures of the healthcare system".*(13) PSRS are usually administered by the local or national healthcare authorities (both private and governmental) and might be referred to as *"patient incident reporting", "safety database" or "event reporting system".*

Identifying the research question

The research question emerged from knowledge gaps identified by the authors. As the availability of methodological approaches and new technologies used to analyze large databases is rapidly growing, the following question was formulated "What is known from the literature about ME methods of analyses in reporting systems?". The intention of the review is to help researchers and organizations engaged with medication safety to get an overview over current methods for ME analyses and to support authorities when considering alternative or supplementary methods for ME analyses.

Identifying relevant studies

The search strategy is developed in cooperation with the research team and an information specialist **(SH)** using a search guide developed by Bramer.(30) First, we identified elements from the research question: "medication errors" and "system analyses". Secondly, we collected subject-specific headings and key words and their synonyms accordingly. The search was initially performed in Embase (Ovid) and translated to Medline (Ovid), Cinahl (EBSCOhost) and Cochrane Central (Appendix 1).

Google Scholar, major national healthcare safety agencies and pharmacovigilance centers' websites will be searched for relevant publications. The final search will be made in August 2022. We will review the reference lists of the included studies and use the citation search in Scopus for each reference. Additionally, we will contact authors of publications for further information, if necessary. All searches will be limited to 2005 onwards. From this point in time, many countries started to introduce national PSRS.(31,32)

Study selection

All retrieved records from the literature search will be imported and managed in Covidence. Two researchers (OT) and (SH) are independently to screen at title/abstract level and secondly at full-text level according to the in- and exclusion criteria listed below. In case of disagreement, the third researcher (SB) will be involved to achieve consensus.

All publications with titles and abstracts available in English or Scandinavian languages will be mapped without further language restrictions. However, the data extraction will be possible only for publications published in full in English or Scandinavian languages.

Inclusion criteria:

- Publications targeting MEs or AEs related to MEs, that have occurred to persons of any age and gender;
- Publications that describe methodologies used to identify and analyze MEs;
- Publications from all healthcare institutions or organizations that use reporting systems as a source, including SRS or PSRS on national, regional or local levels;
- Publications reporting on ADE and ADR, will be considered only if a described association exists between these two and MEs.

Exclusion criteria:

- Review articles, editorials and publications that do not provide information on medication involved or ME's category;
- Publications exploring herbal or traditional medicines.

Data extraction

Two researchers (OT) and (SB) will independently extract data using a charting table, developed by the research team. A priori pilot testing will be performed on two or three sources to ensure that all relevant results are extracted, iteratively updating a data-charting form.(19)

General characteristics are to be extracted from the selected publications: author(s), year of publication, source of origin/country of origin, study design, settings and population. Thereafter following information is to be extracted: methods used for MEs' detection and analysis, the type of the reporting system used, the frequency and characteristics of MEs revealed by the analysis: the most frequent medications involved in MEs (their generic name and ATC-code), medication-event combinations, based either on stages of medication process (prescribing, transcribing, dispensing/preparation, administering/documenting, monitoring) or medication error category (such as wrong medication, wrong patient, wrong dose, wrong route, wrong time, omission error, etc. (Appendix 2)), patient demographic characteristics, such as age and gender, categories of medication-related harm and the reporting organization. Additionally, limitations/biases, such as the quality of data and funding sources, will be noted.

The outcome of ME analyses may vary from study to study. In some studies focus may be on adverse events/patient harm, in other studies focus may be on hazardous medication-event situations. Likewise, differences may occur as some studies may, e.g., investigate only prescribing or administration errors or MEs connected to a particular drug of interest. In contrast, other studies may explore MEs more generally.

Data summary

The primary aim of the scoping review is to provide an overview of the methods used for MEs' analysis; these methods will be seen in connection with the type of the reporting system and detailed information on MEs, their types, and frequency.

The results will be summarized and presented in descriptive and tabular form.

Patient and public involvement

This protocol is developed without patient or public involvement.

Study status

The scoping review protocol was submitted on 21 September 2021 and was last updated on 4 May 2022. The study is to start immediately after the publication of the protocol. We plan to fulfill the study by January 2023.

ETHICS AND DISSEMINATION

The review does not require approval from the Ethic Committee, as it is a literature study. Dissemination of the results will take place via publication in peer-reviewed journals and presentations for the stakeholders that work on patient safety, as well as scientific networks and conferences.

FUNDING

This scoping review protocol is supported by the Faculty of Health Science, University of Southern Denmark (SDU stipendium grant 24.09.2020), the Region of Southern Denmark (grant j.nr.20/45119. Efond 645), Department of Cardiology Lillebaelt Hospital (letter of financial support from 28.05.2020) and Helsefonden (grant 20-B-0189).

COMPETING INTERESTS

There are no competing interests.

ACKNOWLEDGMENTS

We would like to thank CEMBO/Cochrane Denmark for providing methodological consultancy service and support.

CONTRIBUTORS

All authors contributed to the protocol design and plan. SB and OT developed the initial draft of the protocol, which was revised and finally accepted by the research team (OT, SH, SBB, JH and SB). The initial literature search was developed collaboratively by SH and OT.

REFERENCES

1. Lisby M, Nielsen LP, Brock B, Mainz J. How should medication errors be defined? Development and test of a definition. Scand J Public Health. 2012 Mar 1;40(2):203–10.

2. WHO | The third WHO Global Patient Safety Challenge: *Medication Without Harm* [Internet]. WHO. World Health Organization; [cited 2021 Feb 17]. Available from: http://www.who.int/patientsafety/medication-safety/en/

3. Hoonhout LHF, de Bruijne MC, Wagner C, Asscheman H, van der Wal G, van Tulder MW. Nature, occurrence and consequences of medication-related adverse events during hospitalization: a retrospective chart review in the Netherlands. Drug Saf. 2010 Oct 1;33(10):853–64.

4. Kjellberg J, Wolf RT, Kruse M, Rasmussen SR, Vestergaard J, Nielsen KJ, et al. Costs associated with adverse events among acute patients. BMC Health Serv Res [Internet]. 2017 Dec [cited 2019 Feb 19];17(1). Available from: http://bmchealthservres.biomedcentral.com/articles/10.1186/s12913-017-2605-5

5. de Vries EN, Ramrattan MA, Smorenburg SM, Gouma DJ, Boermeester MA. The incidence and nature of in-hospital adverse events: a systematic review. Qual Saf Health Care. 2008 Jun 1;17(3):216–23.

6. Hodkinson A, Tyler N, Ashcroft DM, Keers RN, Khan K, Phipps D, et al. Preventable medication harm across health care settings: a systematic review and meta-analysis. BMC Med [Internet]. 2020 Nov 6 [cited 2021 Jan 29];18. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7646069/

7. Elliott RA, Camacho E, Jankovic D, Sculpher MJ, Faria R. Economic analysis of the prevalence and clinical and economic burden of medication error in England. BMJ Qual Saf. 2021 Feb;30(2):96–105.

8. Goedecke T, Ord K, Newbould V, Brosch S, Arlett P. Medication Errors: New EU Good Practice Guide on Risk Minimisation and Error Prevention. Drug Saf. 2016 Jun;39(6):491–500.

9. Leape LL, Brennan TA, Laird N, Lawthers AG, Localio AR, Barnes BA, et al. The nature of adverse events in hospitalized patients. Results of the Harvard Medical Practice Study II. N Engl J Med. 1991 Feb 7;324(6):377–84.

10. To Err Is Human: Building a Safer Health System [Internet]. Washington, D.C.: National Academies Press; 2000 [cited 2021 Feb 23]. Available from: http://www.nap.edu/catalog/9728

11. Cousins DH, Gerrett D, Warner B. A review of medication incidents reported to the National Reporting and Learning System in England and Wales over 6 years (2005–2010). Br J Clin Pharmacol. 2012 Oct;74(4):597–604.

12. Styrelsen for Patientsikkerhed. Dansk Patientsikerhedsdatabase. Årsberetning 2019. [Internet]. [cited 2021 Feb 18]. Available from: https://stps.dk/da/udgivelser/2020/aarsberetning-for-dansk-patientsikkerhedsdatabase-2019/~/media/01707469F7F9446FB3D3FD4EAB99CD6E.ashx

13. WHO | Reporting and learning systems for medication errors: [Internet]. WHO. World Health Organization; [cited 2021 Feb 23]. Available from: http://www.who.int/medicines/areas/quality_safety/safety_efficacy/emp_mes/en/

14. Newbould V, Le Meur S, Goedecke T, Kurz X. Medication Errors: A Characterisation of Spontaneously Reported Cases in EudraVigilance. Drug Saf. 2017;40(12):1241–8.

15. Carnovale C, Mazhar F, Pozzi M, Gentili M, Clementi E, Radice S. A characterization and disproportionality analysis of medication error related adverse events reported to the FAERS database. Expert Opin Drug Saf. 2018 Dec 2;17(12):1161–9.

16. Bate A, Evans SJW. Quantitative signal detection using spontaneous ADR reporting. Pharmacoepidemiol Drug Saf. 2009;18(6):427–36.

17. Ventola CL. Big Data and Pharmacovigilance: Data Mining for Adverse Drug Events and Interactions. Pharm Ther. 2018 Jun;43(6):340–51.

18. Rigsrevisionen 2014. Beretning til Statsrevisorerne om problemerne med at udvikle og implementere Fælles Medicinkort. [Internet]. Available from: http://www.rigsrevisionen.dk/media/1999813/problemerne-med-at-udvikle-og-implementere-faelles-medicinkort.pdf

19. Peters M, Godfrey C, McInerney P, Munn Z, Trico A, Khalil H. Chapter 11: Scoping Reviews. In: Aromataris E, Munn Z, editors. JBI Manual for Evidence Synthesis [Internet]. JBI; 2020 [cited 2021 May 9]. Available from: https://wiki.jbi.global/display/MANUAL/Chapter+11%3A+Scoping+reviews

20. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. Int J Soc Res Methodol. 2005 Feb;8(1):19–32.

21. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. Ann Intern Med. 2018 Sep 4;169(7):467–73.

22. NCC MERP. About Medication Errors [Internet]. 2014 [cited 2021 Feb 17]. Available from: https://www.nccmerp.org/about-medication-errors

23. indexColor2001-06-12.pdf [Internet]. [cited 2021 Feb 23]. Available from: https://www.nccmerp.org/sites/default/files/indexColor2001-06-12.pdf

24. Bates DW, Boyle DL, Vander Vliet MB, Schneider J, Leape L. Relationship between medication errors and adverse drug events. J Gen Intern Med. 1995 Apr;10(4):199–205.

25. safety-of-medicines--adverse-drug-reactions-jun18.pdf [Internet]. [cited 2021 Feb 22]. Available from: https://www.who.int/docs/default-source/medicines/safety-of-medicines--adverse-drug-reactions-jun18.pdf?sfvrsn=4fcaf40_2

26. 2006 - E 2 D Post Approval Safety Data Management.pdf [Internet]. [cited 2021 May 31]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use_en-12.pdf

27. Pharmacovigilance [Internet]. [cited 2022 Apr 8]. Available from: https://www.who.int/teams/regulation-prequalification/regulation-and-safety/pharmacovigilance

28. Clinical Pharmacy Education, Practice and Research : Clinical Pharmacy, Drug Information, Pharmacovigilance, Pharmacoeconomics and Clinical Research [Internet]. [cited 2022 Apr 8]. Available from: https://web-s-ebscohost-com.proxy1-bib.sdu.dk/ehost/ebookviewer/ebook/bmxlYmtfXzE4NzAwNDRfX0FO0?sid=6f9200dc-99cf-46d1-b942-794bbbacd6d9@redis&vid=0&format=EB&lpid=lp_201&rid=0

29. WHO-EIP-SPO-QPS-05.3-eng.pdf [Internet]. [cited 2021 May 31]. Available from: https://apps.who.int/iris/bitstream/handle/10665/69797/WHO-EIP-SPO-QPS-05.3-eng.pdf?sequence=1&isAllowed=y

30. Bramer WM, de Jonge GB, Rethlefsen ML, Mast F, Kleijnen J. A systematic approach to searching: an efficient and complete method to develop literature searches. J Med Libr Assoc JMLA. 2018 Oct;106(4):531–41.

31. NHS England » Introducing our new system for patient safety learning [Internet]. [cited 2021 Sep 21]. Available from: https://www.england.nhs.uk/blog/introducing-our-new-system-for-patient-safety-learning/

32. Bjørn B, Anhøj J, Lilja B. [Reporting of patient safety incidents: experience from five years with a national reporting system]. Ugeskr Laeger. 2009 May 11;171(20):1677–80.

APPENDIX 1 Search protocol for "Methodologic approaches for medication error analyses in patient safety- and pharmacovigilance reporting systems - a scoping review"

The search protocol describes the planned searches in electronic databases (Embase, Medline, Cochrane and Cinahl), citation searches and online searches.

Embase (Ovid) search string

#	Query
1.	exp medication error/
2.	adverse event/
3.	drug overdose/
4.	drug underdose/
5.	exp inappropriate prescribing/
6.	patient harm/
7.	patient risk/
8.	((drug$ or medication$ or medicin$ or dose$ or dosage$ or dosing) adj2 (incident$ or adverse event$ or mistake$ or error$ or wrong or inappropriate or safety)).ti,ab.
9.	drug overdose.ti,ab.
10.	drug underdose.ti,ab.
11.	((pharmacist$ or prescrib$ or prescription$ or dispens$ or dosing) adj2 (error$ or mistake$ or miscalculat$)).ti,ab.
12.	near miss$.ti,ab.
13.	(patient adj1 (harm or risk)).ti,ab.
14.	or/1-13
15.	exp pharmacovigilance/
16.	exp drug monitoring/
17.	incident report/
18.	voluntary reporting/
19.	system analysis/
20.	natural language processing/
21.	"root cause analysis"/
22.	pharmaco-vigilance.ti,ab.
23.	pharmacovigilance.ti,ab.
24.	((drug or medication) adj1 monitoring).ti,ab.
25.	incident report$.ti,ab.
26.	(voluntary adj2 report$).ti,ab.
27.	mandatory report$.ti,ab.
28.	((reporting or monitoring) adj1 system$).ti,ab.
29.	system analys?s.ti,ab.
30.	natural language processing.ti,ab.
31.	"root cause analysis".ti,ab.
32.	safety management.ti,ab.
33.	or/15-32
34.	14 and 33
35.	limit 34 to yr="2005 -Current"

Medline (Ovid) search string

#	Query
1.	exp Medication Errors/
2.	Drug Overdose/
3.	Inappropriate Prescribing/
4.	Patient Harm/
5.	((drug$ or medication$ or medicin$ or dose$ or dosage$ or dosing) adj2 (incident$ or adverse event$ or mistake$ or error$ or wrong or inappropriate or safety)).ti,ab.
6.	drug overdose.ti,ab.
7.	drug underdose.ti,ab.
8.	((pharmacist$ or prescrib$ or prescription$ or dispens$ or dosing) adj2 (error$ or mistake$ or miscalculat$)).ti,ab.
9.	near miss$.ti,ab.
10.	(patient adj1 (harm or risk)).ti,ab.
11.	or/1-10
12.	exp Pharmacovigilance/
13.	exp Drug Monitoring/
14.	Natural Language Processing/
15.	"Root Cause Analysis"/
16.	Safety Management/
17.	pharmaco-vigilance.ti,ab.
18.	pharmacovigilance.ti,ab.
19.	((drug or medication) adj1 monitoring).ti,ab.
20.	incident report$.ti,ab.
21.	(voluntary adj2 report$).ti,ab.
22.	mandatory report$.ti,ab.
23.	((reporting or monitoring) adj1 system$).ti,ab.
24.	system analys?s.ti,ab.
25.	natural language processing.ti,ab.
26.	"root cause analysis".ti,ab.
27.	safety management.ti,ab.
28.	or/12-27
29.	11 and 28
30.	limit 29 to yr="2005 -Current"

Cochrane Central search string

ID	Search
#1	MeSH descriptor: [Medication Errors] explode all trees
#2	MeSH descriptor: [Drug Overdose] this term only
#3	MeSH descriptor: [Inappropriate Prescribing] explode all trees
#4	MeSH descriptor: [Patient Harm] this term only
#5	(drug* or medication* or medicin* or dose* or dosage* or dosing) NEAR/2 (incident* or adverse event* or mistake* or error* or wrong or inappropriate or safety):ti,ab
#6	drug overdose:ti,ab
#7	drug underdose:ti,ab
#8	(pharmacist* or prescrib* or prescription* or dispens* or dosing) NEAR/2 (error* or mistake* or miscalculat*):ti,ab
#9	(patient) NEAR/1 (harm or risk):ti,ab
#10	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9
#11	MeSH descriptor: [Pharmacovigilance] explode all trees
#12	MeSH descriptor: [Drug Monitoring] explode all trees
#13	MeSH descriptor: [Natural Language Processing] this term only
#14	pharmaco-vigilance:ti,ab
#15	pharmacovigilance:ti,ab
#16	(drug or medication) NEAR/1 (monitoring):ti,ab
#17	(incident report*):ti,ab
#18	voluntary NEAR/2 report*:ti,ab
#19	(mandatory report*):ti,ab
#20	(reporting or monitoring) NEAR/1 (system*):ti,ab
#21	(system analysis):ti,ab
#22	(natural language processing):ti,ab
#23	"root cause analysis":ti,ab
#24	safety management:ti,ab
#25	#11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24
#26	#10 and #25 with Publication Year from 2005 to 2021, in Trials

Cinahl (EBSCO) search string

#	Query
S31	S10 AND S29 Limiters - Published Date: 20050101-20211231
S30	S10 AND S29
S29	S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28
S28	TI "Safety management" OR AB "Safety management"
S27	TI "Root Cause Analysis" OR AB "Root Cause Analysis"
S26	TI "Natural Language Processing" OR AB "Natural Language Processing"
S25	TI "Systems Analys?s" OR AB "Systems Analys?s"
S24	TI((reporting or monitoring) N1 system*) or AB((reporting or monitoring) N1 system*)
S23	TI "mandatory reporting*" OR AB "mandatory reporting*"
S22	TI(voluntary N2 reporting*) OR AB(voluntary N2 reporting*)
S21	TI "incident report*" OR AB "incident report*"
S20	TI((drug or medication) N1 monitoring) or AB((drug or medication) N1 monitoring)
S19	TI "pharmacovigilance" OR AB "pharmacovigilance"
S18	(MH "Root Cause Analysis")
S17	(MH "Natural LanguageProcessing")
S16	(MH "Systems Analysis")
S15	(MH "Mandatory Reporting")
S14	(MH "Voluntary Reporting")
S13	(MH "Incident Reports")
S12	(MH "Drug Monitoring")
S11	(MH"Pharmacovigilance")
S10	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9
S9	TI(patient N1 (harm or risk)) or AB(patient N1 (harm or risk))
S8	TI "near miss*" OR AB "near miss*"
S7	TI((pharmacist* or prescrib* or prescription* or dispens* or dosing) N2 (error* or mistake* or miscalculat*)) or AB((pharmacist* or prescrib* or prescription* or dispens* or dosing) N2 (error* or mistake* or miscalculat*))
S6	TI "Drug underdose" OR AB "Drug underdose"
S5	TI "Drug overdose" OR AB "Drug Overdose"
S4	TI((drug* or medication* or medicin* or dose* or dosage* or dosing) N2 (incident* or adverse event* or mistake* or error* or wrong or inappropriate or safety)) OR AB(drug* or medication* or medicin* or dose* or dosage* or dosing) N2 (incident* or adverse event* or mistake* or error* or wrong or inappropriate or safety))
S3	(MH "Inappropriate Prescribing")
S2	(MH "Adverse Drug Event")
S1	(MH "Medication Errors")

Online resources

We will search online resources with following query: “medication error AND reporting”, at title level. The searches will be limited from 2005 and onwards. Following resources will be searched:

- Google Scholar
- European Medicines Agency (https://www.ema.europa.eu/en/human-regulatory/research-development/pharmacovigilance/eudravigilance)
- U.S. Food and Drug Administration (https://www.fda.gov/)
- Agency for Healthcare Research and Quality. Patient Safety Network (https://www.ahrq.gov/npsd/index.html)
- Institute for Safe Medication Practices (https://www.ismp.org)

- Australian Commission on Safety and Quality in Health Care (https://www.safetyandquality.gov.au)
- National Health Service (NHS) England (https://www.england.nhs.uk/)
- Norwegian Healthcare Authority (https://helse-nord.no/)
- Danish Patient Safety Authority (https://stps.dk/)
- National Board of Health and Welfare in Sweden (https://www.socialstyrelsen.se)

Citation searches

We will conduct backward and forward citation searches. We will screen the reference lists of the eligible studies from the electronic searches and online searches. Furthermore, we will search Scopus citation database for forward citations of the eligible studies as well.

Appendix 2 Guide on stages in the medication use process and error types

Stage of medication use process[1]	Definition[2]	Type of error[3]
Prescribing	The process of entering and processing prescriptions for patient care.	Wrong medication, wrong patient, wrong dose, wrong route, wrong/missing time, missing information on discontinuation, drug-drug interaction, allergy (known). Omission of date/ signature.
Transcribing	An identical copy of prescription of medical order.	Any discrepancy between the prescription and other document.
Dispensing (including preparation)	Dispensing of medication in concordance with prescription. The process of preparing medications from a prescription for a patient.	Wrong medication, wrong patient (labeling), wrong dose, wrong time, wrong/missing preparation/ mixture.
Administering/documenting	The process of administering and documenting administration of a medication to the right patient, in the write way and the right time.	Wrong patient, wrong medication, wrong time, wrong route, wrong frequency, medication not given, medication not taken, or administering is not documented.
Monitoring/documentation	The process of monitoring for adverse events and therapeutic effectiveness.	Missing follow-up on treatment or documentation on the effects.

[1]Described by the U.S. Pharmacopeia (U.S. Pharmacopeia National Formulary. Revision bulletin: <1006> physical environments that promote safe medication use. [Internet]. [7. februar 2022]; https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/c1066.pdf)

[2]Adapted from: Vest TA, Gazda NP, O'Neil DP, Schenkat DH, Eckel SF. Practice-enhancing publications about the medication-use process in 2020. American Journal of Health-System Pharmacy. 10. november 2021;zxab428.

[3]Adapted from: Lisby M. Errors in the medication process: frequency, type, and potential clinical consequences. International Journal for Quality in Health Care. 1. februar 2005;17(1):15–22.