The REporting of A Disproportionality analysis for drUg Safety signal detection using individual case safety reports in PharmacoVigilance (READUS-PV): explanation and elaboration

SUPPLEMENTARY MATERIAL: Examples of reporting for each item

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We provide below a list of examples of reporting for each item of the READUS-PV guideline. Since this is the first guideline on this topic, no disproportionality analysis published so far has adopted these reporting recommendations. Therefore, examples have been *created* using ChatGPT 3.5, using as a prompt the description of the item. Appropriate changes were performed to comply with READUS-PV guidelines and based on authors' experience. The content of the example boxes has not been screened for correctness but only for adherence to READUS-PV reporting recommendations.

Title

Item 1. Title Information

The title should comprehensively but succinctly convey the study's focus, using clear language, and avoiding ambiguity and striking titles that could generate unjustified alerts [16].

Item 1a. *If disproportionality analyses are a prominent component of the published study, the study should be identified as a "disproportionality analysis". The type of data and name of the database(s) should be specified.*

Item 1b. *Report the name of adverse event(s) and/or drug(s) under study, when applicable.*

Example of items 1a and 1b of READUS-PV checklist
A specific drug-event combination "Investigating Cardiovascular Events with NSAIDs: A Disproportionality Analysis on the FAERS." **The overall safety profile of a drug** "Mapping the Overall Safety Profile of COVID-19 Vaccine-Related Adverse Events: a Disproportionality Analysis on Spontaneous Reports Collected by the FDA VAERS." **The spectrum of potential iatrogenic determinants of a disease** "A Disproportionality Analysis Approach to Identifying Potential Iatrogenic Determinants of QT Prolongation in VigiBase." **Methodological developments** "Exploring Adverse Event Patterns: A Methodological Study to Implement Disproportionality Analysis on Social Media Data."

Introduction

Item 2. Background

Item 2a. *Describe the drug(s) and its utilization, the nature of the adverse event(s) under study and its frequency, and the existing knowledge on the drug-event combination.*

Example of item 2a of READUS-PV checklist
Description of drug of interest: In this study, we focus on the disproportionality analysis of adverse events related to HCTZ (Hydrochlorothiazide), a widely prescribed medication used for managing hypertension and cardiovascular diseases. HCTZ belongs to the class of thiazide diuretics. Its primary mode of action involves promoting diuresis, thus reducing blood volume and consequently lowering blood pressure. The drug is indicated for adult patients with essential hypertension, edema, and as an adjunctive therapy for congestive heart failure. **Description of event of interest:** The adverse event under investigation is hypokalemia, a condition characterized by low potassium levels in the blood. Hypokalemia is of significant concern due to its potential to cause cardiac arrhythmias and other serious complications. Clinical manifestations include muscle weakness, fatigue, and irregular heartbeat, impacting the patient's quality of life and overall well-being. **Safety Issue Under Study:** Based on the mechanism of action of HCTZ, we can expect that long-term use of HCTZ may increase the risk of hypokalemia, but the available evidence is inconclusive and lacks a comprehensive understanding of the magnitude of this risk. Expected risk factors include concurrent use of other medications, such as certain diuretics or laxatives, and underlying health conditions like kidney disorders. However, the specific extent of HCTZ's contribution to hypokalemia remains unclear. **Specific Gap in Knowledge:** Despite some studies suggesting a link between HCTZ and hypokalemia, there is a significant gap in our understanding of this relationship. Moreover, the impact of varying dosages and duration of HCTZ use, and the role of concomitants on the incidence of hypokalemia, have not been thoroughly explored.

Item 2b. *Specify the rationale for performing the analysis, e.g., as part of routine pharmacovigilance, to investigate an overall safety profile, or to assess a pre-specified hypothesis.*

Item 2c. *Explain why ICSR databases and disproportionality analysis are suitable to fill the knowledge gap.*

Example of item 2b and 2c of READUS-PV checklist

Routine pharmacovigilance

a) During routine pharmacovigilance activities, we identified cases of hypokalemia reported for HCTZ. This study described these post-marketing reports.

Overall safety profile investigation

b) The analysis of spontaneous reporting systems is pivotal to monitor post-marketing safety of medications and is particularly suitable to detect rare and delayed adverse events, which are likely to escape detection from clinical trials. Drug X has been granted accelerated marketing approval because it targets unmet needs. Strict monitoring is needed in these situations to minimize risks and maximize benefits. For this reason, we analyzed post-marketing reports to describe the safety profile of Drug X after 2 years on the market.

c) Even if Drug X is an old medication, the recent increase in prescribed dosages raises interest in potential dose-related safety issues that may have, up to now, gone unnoticed.

Assessment of a pre-specified hypothesis

d) In this study, the disproportionality analysis is conducted with a specific rationale aimed at assessing a pre-specified hypothesis regarding the association between Hydrochlorothiazide (HCTZ) and hypokalemia.

e) This study stems from recent case reports documenting the occurrence of hypokalemia after exposure to HCTZ.

f) In the pre-marketing clinical trials, an imbalance was noted for cases of hypokalemia, although not reaching statistical significance. Considering well-known limitations of clinical trials to detect rare adverse events, this post-marketing study investigated the reporting of hypokalemia with HCTZ.

Item 3. Objectives

The aims should directly align with the research question(s) and provide specific objectives to address them.

Item 3. *State specific objectives, identifying the adverse event(s), the drug(s), and the reference group, including any pre-specified hypothesis, if applicable.*

Example of item 3 of READUS-PV checklist
To systematically assess the disproportionality between reporting Hydrochlorothiazide (HCTZ) usage and the occurrence of hypokalemia in a diverse patient population, elucidating the magnitude of this association, its dosages and durations dependency, and potential risk factors.

Methods

Item 4. Study design

Presenting key elements of the study design early in the paper allows readers to quickly grasp the context and framework of the study, ensuring greater comprehension.

Item 4a. *Identify the study (i.e., "disproportionality analysis") and the type of data used (e.g., "individual case safety reports").*

Item 4b. *Provide an outline of the entire study design, including primary and sensitivity analyses performed, and other designs such as case-by-case analysis or literature review.*

Example of item 4a and 4b of READUS-PV checklist
Study Design: This disproportionality analysis used spontaneous reports collected from the ICSR database X, encompassing a diverse patient population across multiple healthcare facilities. **Primary Analysis:** The primary analysis was restricted to patients using any antihypertensive medication to take into account the possible indication bias by which hypokalemia may be more common in individuals with high blood pressure. Adjustments for potential confounding factors, such as age, gender, concurrent medication usage, and underlying health conditions, were made using multivariate logistic regression models. **Sensitivity Analyses:**

1. **Dosage and Duration Stratification:** To explore dosage and duration dependency, sensitivity analyses stratified HCTZ usage into different dosage regimens and durations. This allowed for a detailed examination of the association's strength concerning varying levels of drug exposure.
2. **Subgroup Analyses:** Sensitivity analyses were performed within specific subgroups, including age groups, sex, and patients with comorbidities to identify potential effect modifiers and assess whether the association between HCTZ and hypokalemia varies across different patient populations.
3. **Temporal Analysis:** A temporal analysis was conducted to examine the association over time, considering the duration of HCTZ usage and the occurrence of hypokalemia. This provided insights into the time-dependent nature of the association and potential trends in reporting patterns.

Case-by-Case Analysis and Literature Review: A case-by-case analysis of selected adverse event reports was conducted to validate the accuracy of the data and assess the clinical context of reported hypokalemia cases associated with HCTZ usage. A systematic literature review was performed to compare the findings of this analysis with existing studies.

Item 5. Data description, access, and pre-processing

Provide a well-referenced description of the database(s), including information about access and data processing procedures.

Item 5a. *Specify the name of the database(s), the database(s) custodian, and the coverage. Specify the type/number of drugs included within the database and the thesaurus, taxonomies, or ontologies used for coding drugs and events.*

Item 5b. *Specify the extraction date and the access and describe and justify all choices used for data pre-processing, including any data transformation or exclusion, if appropriate.*

Example of item 5a and 5b of READUS-PV checklist

Database description: The primary database utilized for this disproportionality analysis is the FDA Adverse Event Reporting System (FAERS), a publicly available spontaneous reporting system born in 2004 (reports up to the end of March 2022) and managed by the U.S. Food and Drug Administration (FDA). Anonymized spontaneous reports of adverse events are submitted to the FDA by pharmaceutical industries, healthcare professionals, and consumers. The FAERS, mainly representative of the United States, gathers also serious adverse events from the rest of the world, providing a global perspective. Adverse events are codified through the Medical Dictionary for Regulatory Activities (MedDRA, version 24.0) terminology at the preferred terms (PTs) level. FAERS comprises a wide array of drugs, entered as free text by reporters, encompassing prescription medications, over-the-counter drugs, biologics, and advanced therapies.

Database preprocessing: On May 21, 2022, we downloaded the entire database up to March 2022 as raw quarterly data (see URL). The data accessed for this analysis was already anonymized and did not contain any personally identifiable information, complying with privacy regulations and ensuring ethical data usage. Free-text drug names were standardized using the WHO Drug Dictionary from the WHO Collaborating Centre for International Drug Monitoring, Uppsala Monitoring Centre, ensuring consistent coding and classification of drugs.

1. **Deduplication:** Duplicate entries were identified and removed checking for the same value in the fields of sex, age, country of occurrence, event date, and the lists of drugs and events, thus increasing the probability that each adverse event report was unique.
2. **Management of Nullified ICSRs:** Reports nullified by the reporter or by the FDA were excluded from the analysis to maintain data reliability.
3. **Handling Incongruous Data Values:** Incongruous or inconsistent data values were flagged, and the respective entries were thoroughly reviewed. Data with inconsistencies were either corrected or excluded from the analysis.
4. **Data Transformation:** Time to onset was calculated as the time occurred between the first administration of the drug of interest and the event date. Comorbidity were computed based on indications and concomitants provided (in particular…).
5. **Data Exclusion:** Reports lacking essential information, including drug names, adverse events, or patient demographics, were excluded from the analysis to ensure data quality.
6. **Case versions:** When multiple versions of a case were available, only the last one was retained.

These data pre-processing steps were implemented to enhance data accuracy and reliability, ensuring the integrity of the subsequent disproportionality analysis results.

Item 6. Variables definition

Clearly define the population, events, drugs, potential confounders, and effect modifiers investigated.

Item 6a. *Describe the study population, including any restriction.*
Item 6b. *Describe the nature and the meaning of key variables assessed in the work.*
Item 6c. *Specify and justify any grouping of drugs or events. For drugs, specify and justify whether active ingredients/trade names/salts were considered and/or the selected role.*
Item 6d. *Describe any additional data source used, the type of data, and how they interact with ICSRs.*

Example of item 6a, 6b, 6c, 6d of READUS-PV checklist
Study Population: The study population comprises only individuals reported in the FAERS database who have experienced adverse events while taking antihypertensive medications (either suspect or concomitant). This restriction was performed considering drugs from the ATC classes x, y, and z. **Key Variables:** In the course of the analyses we looked, along with drugs and events, also to two binary (sex, seriousness) and two continuous variables (age, dose). Events were considered serious if resulted in congenital anomalies, death, life-threatening, persistent or significant disability or incapacity, hospitalization or prolongation of hospitalization, other medically important condition. **Drugs:** Only suspected drugs were considered in the analysis to include only reports in which the reporter already suspected the drug of interest. Drugs were primarily identified by their active ingredients to ensure consistency and comparability across different formulations and trade names. **Events:** For the retrieval of the events, we used the SMQ "acute central respiratory depression" in its narrow form (see Supplementary Material). **Additional Data Sources:** To explore the pharmacological basis of the event, we integrated pharmacosurveillance and pharmacodynamic data. We interpolated intraclass disproportionality results with Homo Sapiens affinity data (pKi) from the ChEMBL database.

Item 7. Statistical methods

Describe all statistical methods, including those used to control for confounding, selective reporting, and other biases specific to disproportionality analyses, and provide rationale.

Item 7a. *Present any descriptive analysis performed, specifying variables investigated, statistical tests, and significance thresholds.*
Item 7b. *Describe and justify the measure(s) selected for the disproportionality analysis including any threshold used to identify signals of disproportionate reporting. Explain the reason for this choice if applicable*
Item 7c. *Clearly describe any sensitivity analysis and any tool to control for confounding, including any restriction, subgroup, stratification, adjustment, or interaction.*
Item 7d. *Specify the variables and methods used for the case-by-case analysis, including any algorithm or criteria used to assess causality, if performed.*
Item 7e. *Specify any statistical methods used for other data sources.*

Box 10: Example of item 7a, 7b, 7c, 7d, 7e of READUS-PV checklist
Descriptive analysis: The characteristics of cases and non-cases exposed to X were described using mean and standard deviation for continuous variables, while numbers and rates for categorical variables. The median and interquartile range was used to describe the time-to-onset of the event(s) of interest, and cumulative distribution of time-to-onset was also presented. Chi-square tests were employed to assess the association between categorical variables. A significance threshold of $p < 0.05$ was used to determine statistical significance. **Disproportionality analysis:** The Proportional Reporting Ratio (PRR) was used as the primary disproportionality measure, and calculated as follows: ([number of reports related to event X and drug Y]/[total number of reports related to drug X])/([number of reports related to event X and other drugs]/[total number of reports related to other drugs]). Only drug-event pairs reported in at least three cases were selected, and they were considered as SDR only if their lower limit of the

95% confidence interval (95% CI) exceeded 1. The analysis was report-based, counting each report only once independently of the number of events or drugs reported.
Sensitivity Analysis: A sensitivity analysis and a subgroup analysis were conducted. The sensitivity analysis was conducted in a smaller dataset, that included all ICSRs collected in the database was used; it was composed by all ICSR collected up to the day in which dear doctor letter was sent to all the GPs a restriction of use for the Drug X was published. Different time periods (e.g., 1 year, 5 years) were considered to explore variations in reporting trends. The subgroup analysis concerned stratification of by age groups: under 65 years and ≥65 years old. Multivariate regression models were utilized to control for potential confounding. Variables such as age, gender, and concomitant medication usage were included in the models to adjust for their influence on adverse event reporting patterns.
Case-by-Case Analysis: The Naranjo algorithm was used to assess causality. This algorithm assigns scores based on specific criteria, helping evaluate the likelihood of a drug-event association ranging from definite, probable, possible, to doubtful. Only ICSR considered as probably or possibly related to the drug X, applying the Naranjo Algorithm, were first selected. Thereafter, only ICSR with a high grade of diagnostic certainty (*i.e.*, Level 1 or 2 of Brighton Case definition) were finally included in the case-bay case assessment, which included: health status, medical history, drug used, indication, dosage and administration route, the duration of therapy, time to onset and concomitant therapies at the time of the event.
Statistical Methods for Other Data Sources: A logistic regression was used to assess the predictability of the ROR of hypertension for each drug based on drug affinity on a set of receptors (…).

Results

Item 8. Participants

Describe in detail the ICSRs selection process; beside text, consider the use of a flow diagram.

Item 8a. *Specify the number of individual case safety reports included at each stage, including reasons for exclusion.*
Item 8b. *Provide key demographic and clinical characteristics of cases, if possible comparing cases with any appropriate reference group.*

Example of item 8a and 8b of READUS-PV checklist

Among the 500,000 reports recorded in the database during the study period, 25,000 reports related to a vaccine, 5,000 duplicate cases and 500 aberrant cases (e.g., ICSR with event occurrence before the use of any of suspected drugs) were excluded. Thus, 465,500 reports were included in the present analysis. Among them, 5,500 were considered as cases (750 exposed to the drug X), and 460,000 (4.600 exposed to the drug X) were considered as non-cases (see Figure 1 for more details).

Elderly and women were more represented in cases than in non-cases, while the majority of ICSRs were observed in female patients. Seventy percent (70%) of ICSR were reported in the United States of America while healthcare professionals were the most frequent reporter category (66.6% of ICSRs).
Regarding the seriousness criteria, other medically important conditions and hospitalization were the most frequent reported criteria, 35.7% and 22.2%, respectively. In 70.6% of ICSRs Drug X was the only drug reported. Concomitant medication and Fatal outcomes were reported sparsely (0.8% and 0.5%, respectively; see Table X for more details).

Item 9. Results of disproportionality analyses

Describe in detail the results of disproportionality analyses.

Item 9. *Present all results including confidence intervals. Present also results of sensitivity analyses, if performed.*

Box 12: Example of item 9 of READUS-PV checklist

Drug X was associated with a higher risk of reporting of event Y (ROR 1.2 [95%CI 1.1; 1.3]). ROR results were also higher than in sensitivity analysis concerning serious event only (1.4 [1.3; 1.5]). After the stratification for age, ROR was revealed higher than expected only in elderly (ROR ≥75 years: 1.9 [1.7-2.0]), while no differences were detected for younger patients (0.9 [0.7;1.4]; see Figure X).

Item 10. Results of case-by-case analysis

Describe in detail the results of the case-by-case, including the variables investigated.

Item 10. *Present the case-by-case analysis of key variables. Present the causality assessment, if applicable.*

Box 13: Example of item 10 of READUS-PV checklist
In the case-by-case analysis, three distinct cases were thoroughly examined to assess adverse events related to medications. In the first case, a 65-year-old male patient experienced severe hypokalemia within 48 hours of initiating Drug X at a dosage of 20mg orally daily. No concomitant medications were reported, and alternative causes were ruled out, leading to a definite association (Naranjo score: 9). The second case involved a 72-year-old female with a history of heart disease, taking 40mg of Drug Y and 10mg of Drug Z orally daily. Symptoms occurring a week after initiating the medications improved upon discontinuation of Drug Z, indicating a probable association (Naranjo score: 7). The third case, a 55-year-old male on 30mg of Drug X orally daily, experienced an adverse event within 24 hours of administration. While no concomitant medications were reported, the association was deemed possible (Naranjo score: 5). These analyses provide valuable insights into the detailed variables, timelines, and causality assessments, aiding in a comprehensive understanding of the adverse events studied.

Discussion

Item 11. Key results

It is good practice to begin the discussion with a short summary of the key results with reference to study objectives. This section will help readers assess whether the subsequent interpretation and implications offered by the authors are supported by the findings.

Item 11. *Discuss key results with reference to study objectives and contextualize them within the current literature and other consulted sources. Clearly discriminate between expected reactions and potential safety signals.*

Box 14: Example of item 11 of READUS-PV checklist
Summary of Key Results: The disproportionality analysis aimed to investigate adverse events associated with Drug X and Drug Y. Our findings indicated a statistically significant disproportionality for severe hypokalemia in patients taking Drug X, with a strong association observed (Naranjo score: 9). Conversely, while Drug Y was suspected in some cases, the analysis revealed no significant disproportionality, indicating a lack of robust evidence for a causal link. **Contextualization:** Contextualizing these results within the existing literature, our findings align with prior studies highlighting the potential risk of hypokalemia associated with Drug X, corroborating the existing safety concerns. The lack of significant disproportionality for Drug Y contrasts with certain case reports, emphasizing the complexity of adverse event assessments and the need for comprehensive analysis. Pharmacologically, Drug X's mechanism of action involving electrolyte imbalances substantiates the observed hypokalemia, providing mechanistic plausibility to our findings.

Item 12. External validity

Discuss the external validity of the study results.

Item 12a. *Discuss the external validity of the results to the general population.*
Item 12b. *Discuss the potential relevance of results in clinical practice.*
Item 12c. *Propose further study designs, if applicable.*

Example of item 12a, 12b, 12c of READUS-PV checklist
External Validity: ICSR databases offer a unique lens into drug-related adverse events, capturing a diverse range of patient demographics, comorbidities, and complex medication regimens, which often align more closely with the complexities

encountered in clinical practice than controlled clinical trials. However, it's essential to discern specific patient characteristics within our dataset. In our case, even if the drug showed indeed an association with the event, the case-by-case analysis identified a common pattern of misuse at higher-than-expected doses. This signal might therefore not be directly applicable to the broader patient population. Nonetheless, it highlights the potential for misuse of this drug and the possible existence of an unknown toxicity.

Transferability to Clinical Practice: Regarding the transferability of our results to clinical practice, we propose a nuanced approach to risk minimization strategies. Because our study identifies potential safety signals, we advocate for a balanced perspective, emphasizing the importance of evidence-based decision-making. Clinical recommendations cannot be derived solely from disproportionality analyses. Instead, a comprehensive evaluation, incorporating various forms of evidence and clinical expertise, should guide any implementation of risk mitigation strategies. If the signal was to be confirmed, a change to the SmPC, integrating the toxicity section, would also be appropriate.

Proposal for Further Study Designs: This disproportionality signal deserves further investigation to confirm or refuse the association. This may be achieved by specifically designing analytical observational research such as cohort studies not only to corroborate the signal, but also to assess risk estimates, and identify drug- and patient-related risk factors (not sufficiently captured by spontaneous reports). This may ultimately support decision-making process by regulators, and policy makers for proper and timely signal management.

Item 13. Limitations

Present general limitations of SRSs and specific limitations of the strategy implemented.

Item 13. *Present general limitations, making clear that disproportionality analysis alone cannot prove causation or measure incidence, and specific limitations, including confounding and reporting bias and efforts to mitigate them.*

Example of item 13 of READUS-PV checklist

_We acknowledge limitations of this study, which are inherent to the nature of spontaneous reporting systems (under-reporting and possible selective reporting) as well as specifically related to the study design. Because of its hypothesis-generating nature, disproportionality analysis cannot be used to infer a causal relationship, but rather to highlight a potential association requiring corroboration by a hypothesis-testing study design (e.g., analytical observational research). Given the lack of a denominator, namely subjects actually exposed to the drug(s), and the expected under-reporting phenomenon, disproportionality measures and their magnitude cannot quantify the real risk in clinical practice but can only inform about an increased risk of adverse event reporting and not of adverse event occurrence. Consequently, incidence cannot be calculated. Moreover, verification of events through clinical features, including laboratory and instrumental tests, comorbidities and adjustment of therapeutic regimens is limited due to missing data and no access to narratives [if applicable]. Moreover, the lack of disproportionality should not be automatically interpreted as a safety endorsement, since disproportionality measures are interdependent and methodological choices in selecting the comparator may have a substantial impact. Moreover, several factors may result in selective reporting and relevant ability to detect disproportionality, including known and largely reported drug-event combinations (the so-called competition bias); the setting, pattern, and extent of use (which are related to the marketing life and evolving guidelines), as well as the attitude of clinicians toward reporting. All these aspects may explain why XXX was not associated with significant disproportionality notwithstanding the non-negligible number of reports. Moreover, it must be taken into account that XXX have been approved for the treatment of advanced disease, after the failure of previous lines of treatment. Therefore, channeling bias cannot be ruled out.

However, major confounders and key reporting biases have been taken into account during study design and relevant minimization strategies have been performed. Indeed, we performed a sensitivity analysis setting the active comparison to the indication for the drug, reducing the risk of spurious associations generated by the indication bias. Furthermore, removing the reports recording the masking drug YYY, we reduced the impact of competition bias on the drug-event combination of interest.