Drug Safety (2024) 47:585–599
https://doi.org/10.1007/s40264-024-01423-7

ORIGINAL RESEARCH ARTICLE

The REporting of A Disproportionality Analysis for DrUg Safety Signal Detection Using Individual Case Safety Reports in PharmacoVigilance (READUS-PV): Explanation and Elaboration

Michele Fusaroli[1] · Francesco Salvo[2,3] · Bernard Begaud[2] · Thamir M. AlShammari[4] · Andrew Bate[5,6] · Vera Battini[7] · Andreas Brueckner[8] · Gianmario Candore[9] · Carla Carnovale[7] · Salvatore Crisafulli[10] · Paola Maria Cutroneo[11] · Charles Dolladille[12,13] · Milou-Daniel Drici[14] · Jean-Luc Faillie[15] · Adam Goldman[16,17] · Manfred Hauben[18,19] · Maria Teresa Herdeiro[20] · Olivia Mahaux[5] · Katrin Manlik[9] · François Montastruc[21,22] · Yoshihiro Noguchi[23] · G. Niklas Norén[24] · Roberta Noseda[25] · Igho J. Onakpoya[26] · Antoine Pariente[2,3] · Elisabetta Poluzzi[1] · Myriam Salem[27] · Daniele Sartori[24,28] · Nhung T. H. Trinh[29] · Marco Tuccori[30] · Florence van Hunsel[31,32] · Eugène van Puijenbroek[31,32] · Emanuel Raschi[1] · Charles Khouri[33,34]

Accepted: 7 March 2024 / Published online: 7 May 2024

Abstract

In pharmacovigilance, disproportionality analyses based on individual case safety reports are widely used to detect safety signals. Unfortunately, publishing disproportionality analyses lacks specific guidelines, often leading to incomplete and ambiguous reporting, and carries the risk of incorrect conclusions when data are not placed in the correct context. The REporting of A Disproportionality analysis for drUg Safety signal detection using individual case safety reports in PharmacoVigilance (READUS-PV) statement was developed to address this issue by promoting transparent and comprehensive reporting of disproportionality studies. While the statement paper explains in greater detail the procedure followed to develop these guidelines, with this explanation paper we present the 14 items retained for READUS-PV guidelines, together with an in-depth explanation of their rationale and bullet points to illustrate their practical implementation. Our primary objective is to foster the adoption of the READUS-PV guidelines among authors, editors, peer reviewers, and readers of disproportionality analyses. Enhancing transparency, completeness, and accuracy of reporting, as well as proper interpretation of their results, READUS-PV guidelines will ultimately facilitate evidence-based decision making in pharmacovigilance.

Key Points

READUS-PV guidelines comprise 14 items for reporting disproportionality studies.

Their uptake will help enhance transparency, completeness, and accuracy, facilitating evidence-based decision making.

1 Background

Individual case safety report (ICSR) databases collect reports of suspected adverse drug reactions (ADRs) from both healthcare professionals and patients [1]. Disproportionality analyses, exploring ICSR databases to identify unexpected associations (in terms of nature or clinical presentation) between drugs and adverse events, when combined with a clinical review of the cases, provide valuable insight into emerging drug safety concerns, notably for ADRs that are unlikely to be fully captured by clinical trials [2–7]. Their apparent simplicity has led to a surge in the quantity of published disproportionality analyses [8], rising from 40 in 2017 to 180 in 2021 according to PubMed data [9] (presumably an underestimate because of the lack of standardization in reporting). This surge potentially overwhelms decision

Please also see the companion article available at https://doi.org/10.1007/s40264-024-01421-9.

Extended author information available on the last page of the article

makers and contributes to these results being disregarded due to the high ratio of noise to signal. Additionally, it may also directly influence patients and clinical practice [10]. Notwithstanding, almost 75% of the published studies present some type of *spin*, or distortion of study findings, which in disproportionality analysis may manifest as inadequate reporting, overstatement in the interpretation of the findings, or causal statements without taking into account underlying biases that may be sufficient to explain the association [11, 12]. This lack of proper reporting and interpretation in research is concerning, as it impedes the utilization and comprehension of research findings and contributes to research waste [13–15].

To address this issue, in an international effort, we developed the READUS-PV guidelines (**RE**porting of **A** **D**isproportionality analysis for dr**U**g **S**afety signal detection using ICSRs in **P**harmaco**V**igilance) [16]. Comprising 14 reporting recommendations (plus four for the abstract), these guidelines aim to (1) assist authors in the preparation of transparent, complete, and accurate articles; (2) allow self-assessment and replicability; (3) promote an adequate understanding of the results and their limitations; and (4) assist reviewers and editors in the evaluation of disproportionality analysis for publication.

READUS-PV is published as a set of two papers. In the development and statement paper, we outline the steps taken to build the checklist [17]. In this explanation and elaboration paper, aligning with the structure of EQUATOR Network guidelines [18] and using streamlined terminology (see Box 1 for a glossary of terms used), we substantiate the inclusion of each item and provide bullet points detailing each recommendation. Additional

Box 1 Glossary of terms

Term	Definition
Adverse event[a]	Any untoward (i.e., noxious and unintended) medical occurrence that develops in an individual exposed to a medicinal product. Possible conditions of exposure include appropriate medical use, medication errors, off-label use, overdose, misuse, abuse, and occupational exposure. The medical occurrence does not necessarily have a causal relationship with the exposure
Adverse drug reaction (ADR)[a]	Any adverse event characterized by an at least reasonable possibility that the medicinal product has caused the event
Causality assessment[a]	The process of evaluating and assigning a causal judgment to an observed association between a medicinal product and an adverse event, at the level of either individual ICSRs or case series. Causality assessment can rely on expert judgment/global introspection, structured guidelines and algorithms, or probabilistic approaches [19]
Drug	A drug is usually defined as any chemical substance that causes a change in an organism's physiology or psychology when consumed. To be consistent with pharmacovigilance terminology (e.g., drug-related problem, adverse drug reaction, drug-event combination) we adopted the use of the term drug, but these guidelines are valid for disproportionality analyses on any medicinal product used in the prevention, diagnosis or cure of diseases (e.g., vaccine, medical device, gene therapy, cell therapy, supplements)
Drug-event combination	The specific combination of medicinal product(s) and event(s) of interest
Individual case safety reports (ICSRs)[b]	Format and content for the reporting of one or several adverse events that occurred in a single individual at a specific point of time. It accommodates clinical phenotypes involving multiple events that may manifest sequentially over time
Pharmacovigilance[a]	The science and activities relating to the detection, assessment, understanding, and prevention of ADRs or any other drug-related problem
Case-by-case analysis	Analysis of each ICSR recording the drug-event combination to collect further information that is useful for the causality assessment
Safety signal[a]	Information that arises from one or multiple sources (including observations and experiments) that suggest a new potentially causal association or a new aspect of a known association between medicinal product(s) and adverse event(s). The information is judged to be sufficient to justify verificatory actions
ICSR database	A surveillance database that relies on ICSRs submitted by multiple stakeholders (healthcare providers, consumers, and pharmaceutical companies) because of spontaneous initiative or mandatory reasons)
Signal of disproportionate reporting (SDR)[a]	A statistical association between medicinal product(s) and event(s) identified by any disproportionality analysis within an ICSR database

CIOMS Council for International Organizations of Medical Sciences, *EMA* European Medicines Agency

[a]Definitions adapted from the CIOMS cumulative glossary, with a focus on pharmacovigilance (version 2.1)

[b]Definition adapted from the EMA definition of ICSR

sub-items were also proposed, which provide supplementary information that may enhance the completeness and usability of the study.

2 READUS-PV Recommendations

2.1 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 alarm or safety endorsement [20].

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.*

Explanation: Including 'disproportionality analysis' in the title facilitates identification by potential users, appropriate indexing in databases and screening for knowledge synthesis. This helps to provide a specific context for the analysis and informs the reader about the nature of the data under investigation. While alternative terms (e.g., 'case/non-case analysis') have also been used, consistent use of 'disproportionality analysis' going forward will reduce ambiguity and simplify the extraction for future meta-research and systematic reviews. Non-specific terms are not recommended because they do not optimally align to the study design and could result in misunderstandings.

Essential elements:

1. The study should be identified as a 'disproportionality analysis' in the title.
2. Avoid non-specific (e.g., 'data mining', 'real-world', 'pharmacovigilance', 'cross-sectional', or 'retrospective study') and misleading (e.g., increased risk) terms.
3. Identify the type of data in the title, specifying 'ICSRs' or other terms if appropriate (e.g., 'social media').
4. Clearly mention the name/acronym of the database(s) used (e.g., 'FDA Adverse Event Reporting System', 'Eudravigilance', 'VigiBase') in the title.

Additional elements:

1. Any other important quantitative analysis used in conjunction should be specified (e.g., 'pharmacovigilance/pharmacodynamic analysis' or 'a disproportionality analysis and systematic review').
2. When the study design is broader (e.g., hybrid design combining different data sources such as systematic review with meta-analysis and a disproportionality analysis) or the use of 'disproportionality analysis' in the title may be reductive, include the term at least among the keywords.

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

Explanation: The title should inform about the object(s) of the study. For example, a disproportionality analysis could explore (1) a specific drug-event combination (DEC); (2) the overall safety profile of a drug or its safety in a subgroup of users (e.g., looking at differences between sexes, or age groups); (3) the spectrum of potential iatrogenic determinants of a disease; and (4) methodological developments.

Essential elements:

1. Identify the research topic in the title, including the drug(s) and/or event(s) investigated.

Additional elements:

1. Consider mentioning the population investigated, for example when the analysis has been restricted to a specific therapeutic indication or to reports concerning pregnancy or children.

2.2 Introduction

Item 2. Background

In reporting a disproportionality analysis, it is crucial to provide the reader with a clear explanation of the scientific background and rationale for the study. This section sets the foundation for understanding the subsequent objectives, methods, and results, and helps the reader appreciate the significance and relevance of the study.

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.*

Explanation: The investigation of any research question should be preceded by the collection of evidence already accrued. The specific gap in knowledge should be identified based on limitations of previous studies, conflicting results, or unanswered needs.

Essential elements:

1. When a specific drug(s) is under study, describe their relevant features, including the active ingredient (preferably using the international nonproprietary name), therapeutic class, mechanism of action, pharmacodynamics, pharmacokinetics, indications, and target populations, as applicable.
2. When a specific adverse event(s) is under study, describe their relevant features, providing details about its nature,

clinical manifestations, severity, seriousness, and impact on the patient's quality of life.
3. Describe the research question under study, present evidence supporting it, and discuss known risk factors: previously identified pertinent signals (e.g., when investigating liver failure, present previous signals of increased transaminases for the same drug), and information retrieved from regulatory documents (e.g., Summary of Product Characteristics).
4. Highlight the specific gap in knowledge that necessitates further investigation, explaining why the current understanding is insufficient.

Additional elements:

1. Consider including further information on the drug(s), including brand names, formulations, administration routes, posology, dosing regimens, and duration of use.
2. Consider including information about the expected number of patients exposed, the average duration of exposure, and the background rate of the event(s), as they impact the number of ICSRs [21, 22].
3. Consider including information about the approval date and any relevant warning [23, 24].

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 prespecified hypothesis.*

Explanation: By specifying the rationale, the reader gains a clear understanding of the purpose and context of the analysis. Conception of a disproportionality analysis, excluding methodological studies, can usually be summarized as follows [25–27]: (1) reporting of signals emerging from agnostic/untargeted pharmacovigilance activities (e.g., emerging from routine analyses on the entire ICSR database without a prespecified hypothesis); (2) investigation of the overall safety profile of a specific drug (e.g., in case of conditional accelerated approval or a specific risk management plan [28]); (3) assessment of a prespecified evidence-based hypothesis (e.g., based on pharmacological plausibility, recent case report/series, or imbalances observed in clinical trials).

Essential elements:

1. Explain the rationale for performing the disproportionality analysis (see explanation).

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

Explanation: Regardless of the journal type, authors should carefully address the nature of spontaneous reporting data and the appropriateness of using disproportionality analysis to investigate the research question [29]. Notably, as with any study, the availability of already published pharmacoepidemiological and/or ICSR studies should be carefully considered before planning a disproportionality analysis, to avoid research waste and redundancies [25]. In particular, the question arises on the actual added value of a newer but similar analysis using the same ICSR database or datasets generating overlapping signals of disproportionate reporting (SDRs) [e.g., WHO VigiBase vs. US FDA Adverse Event Reporting System (FAERS)] [30]. Replication studies should be carefully justified as efforts to offer an additional novel complementary perspective, for instance by providing a case-by-case analysis or by accounting for previously unrecognized biases to assess the validity of a signal.

Essential elements:

1. Justify the ability of disproportionality analysis to fill the knowledge gap. If other studies addressing the same (or in good part similar) question are available, explain the actual added value of the current disproportionality analysis (e.g., a bias that has been previously neglected, new target population, different dosing regimen, new indication, accelerated approval, rare events, methodological limitations of previous studies).

Additional elements:

1. Consider concisely explaining, and providing appropriate reference for, the nature of ICSRs and disproportionality analyses.
2. In scientific journals not specialized in pharmacology and pharmacovigilance, consider more exhaustively explaining the nature of ICSRs and disproportionality analyses.

Item 3. Objectives

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

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

Explanation: An explicit and concise statement of the objective(s) will help readers understand the goal and assess whether the data and methods used adequately address it. Such statements may be written in the form of objectives or questions, including the event(s) and drug(s) under investigation, and the reference group used for comparison. Question formulation frameworks such as PICO (population, intervention, comparator, outcome) or PEO (population, exposure, outcome) could also help

in formulating the objective(s) [31, 32], in the lack of frameworks specific to disproportionality.

Essential elements:

1. Provide an explicit and concise statement of all primary and secondary objective(s) or question(s), logically progressing from the knowledge gap.
2. Clearly define the adverse event(s) and drug(s) under investigation.

Additional elements:

1. Specify when the disproportionality analysis has not been implemented to investigate reactions (drug-event association) but rather the co-occurrence of reactions (event-event association) [33], the influence of indication on ADRs (drug-indication-event association), or drug interactions (drug-drug-event associations) [34].

2.3 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').*

Explanation: As already explained for the title, the use of standardized terminology should be preferred to simplify study appraisal and reduce ambiguity.

Essential elements:

1. Identify the study as a 'disproportionality analysis'.
2. Specify the type of data used (e.g., ICSRs).

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.*

Explanation: The study design should be presented in a clear and structured manner, with appropriate justification for each operational choice, to facilitate critical assessment, replication, and interpretation of the study.

Essential elements:

1. Introduce the primary analysis with a clear reference to the study objectives.
2. Introduce sensitivity/secondary analyses as efforts to address potential sources of bias or uncertainty in the study, to check analysis assumptions, or to investigate effect modifiers or specific populations.
3. Specify whether a case-by-case causality assessment and/or a systematic review of the literature were conducted.

Additional elements:

1. For more complex study designs, consider including a flow diagram providing a clear overview of the design elements, such as data sources, population selection, exposure assessment, and stratifications.
2. In case a more complex study design is implemented, consider consulting other published checklists for the reporting (cfr. Table 3 in the Statement article).

Item 5. Data description, access, and preprocessing

Provide a well-referenced description of the database(s), including its extent and relevance to the research question.

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.*

Explanation: Information about the database content allows a correct interpretation of the results since disproportionality analysis is intrinsically based on comparing the ICSRs of interest with the underlying database. Given that reporting rate, drug utilization, and background rate may differ across countries, and due to masking bias (see later), the content of the database strongly affects the results.

Essential elements:

1. Specify the name of the database(s) used in the analysis.
2. Identify the database custodian [i.e., entity responsible for managing the databases)].
3. Describe the timespan and geographical coverage (catchment area).
4. Specify the type of medicinal products captured (e.g., drugs, vaccines, devices) or the number and class of drugs in the case of pharmaceutical companies' databases.
5. Identify the thesaurus, taxonomy, or ontologies used for coding drugs and events and the version. Commonly used ontologies include the Medical Dictionary for Regulatory Activities (MedDRA) terminology for events and the Anatomical Therapeutic Chemical (ATC) classification for drugs [35, 36].
6. Specify the size of the database (number of reports).

Additional elements:

1. Consider providing the rationale or justification for choosing a specific database(s). This may consider data

availability or quality, representativeness, or specific research objectives.
2. Consider providing information on data collection (e.g., possibility of a selection bias) and anonymization.
3. Consider describing quality measures applied to ensure integrity and reliability of data.

Item 5b. *Specify the extraction dates and describe and justify all choices used for data preprocessing, including any data transformation or exclusion, if appropriate.*

Explanation: Different operative choices in the preprocessing may lead to different results and affect their interpretation [37, 38]. These choices should be justified by referencing established guidelines or best practices in data preprocessing and addressing any potential biases or limitations introduced by the chosen methods [37, 39]. It may be sufficient to refer to a detailed preprocessing description available elsewhere, such as in a manuscript or on a website, but it is recommended to explain any preprocessing steps that significantly impacted the current investigation and to note any deviations from the original preprocessing algorithm.

Essential elements:

1. Specify the extraction/download date and the data access mechanism (e.g., online portal, data sharing agreement, dashboard, quarterly data). Provide a reference to the URL if available.
2. Specify any approval required to access the database (in accordance with the data availability statement).
3. Specify any restriction in place on access to data.
4. Describe the choices implemented in identifying and removing duplicate entries, handling missing or nullified data points, addressing incongruous or inconsistent data values, managing follow-up information for individual cases, and standardizing data elements (e.g., free-text drug names to active ingredients), or provide adequate reference.
5. Explain any data transformations performed to obtain variables not directly available in the dataset, such as doses, time-to-onset, or comorbidity (e.g., using drugs as a proxy), together with any underlying assumptions.
6. Describe any data exclusion.

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.*

Explanation: A comprehensive description of the study population, identifying and justifying any restrictions placed on the data, such as a specific period, age group, or geographical region [40–42], provides valuable information to assess the generalizability of the findings [43].

Essential elements:

1. Clearly describe the strategy implemented for any restriction to the study population for both primary and secondary analysis, when applicable.

Item 6b. *Describe the nature and the meaning of key variables assessed in the work.*

Explanation: Ensure that readers have a clear understanding of the key variables being assessed and how they relate to the research question, to simplify appraising the appropriateness of the analyses and of the interpretation of the results. For example, it is important to clarify which criteria were used to determine seriousness (e.g., death, hospitalization, life-threatening, disability).

Essential elements:

1. Describe the nature and meaning of key variables, such as whether they are continuous (e.g., age), binary (e.g., seriousness), or categorical (e.g., reporter qualification, or country).
2. Describe the management of key variables with missing values (e.g., sex unspecified).

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.*

Explanation: Ensure clarity in defining the objects of the study. The choices should be justified based on factors such as clinical relevance, data availability, pharmacological interactions, or specific research objectives [44, 45].

When grouping multiple drugs or events, the authors should refer to existing taxonomies (e.g., MedDRA or ATC [35, 36]), standardized MedDRA queries (SMQs), previous studies, knowledge engineering techniques, and justified and detailed expert opinions, or, alternatively, provide a clear clinical rationale [43, 46, 47].

Essential elements:

1. Specify and justify the assigned roles of drugs (suspect primary and secondary/concomitant/interacting).
2. Specify and justify the focus on active ingredients, trade names, or specific salts.
3. Specify and justify any groupings of drugs and/or adverse events, for primary, secondary and/or sensitivity analyses.

Additional elements:

1. Consider providing the list of free text mapped to the drug of interest.

Item 6d. *Describe any additional data source used, the type of data, and how they interact with ICSRs.*

Explanation: The refinement, validation, and prioritization of safety signals generated from disproportionality analysis often requires evidence from other data sources and methods [14]. Clinical trial reports, literature reviews, regulatory documents, and datasets of labeled ADRs may help assess expectedness [48]. Pharmacodynamic/pharmacokinetic, bioinformatic, and chemoinformatic data help explore pharmacological plausibility [49]. Healthcare and claims databases (other sources of real-world data) point to a possible alternative explanation and public health and clinical impact [50].

Essential elements:

1. Describe any additional data source and the type of data.
2. Describe how these data were linked to ICSRs and SDRs.

Item 7. Statistical methods

Describe all statistical methods, including those used to control 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.*

Explanation: Descriptive analysis can help to identify patterns and trends in the data and help identify and characterize both expected and unexpected confounders and effect modifiers. Geographical characterization helps exploring the impact of different pharmacovigilance systems, local warnings, and populational specificities.

Essential elements:

1. Present any descriptive analysis performed.

Additional elements:

1. Specify and justify any reference/comparator group.

Item 7b. *Describe the measure(s) selected for the disproportionality analysis, including any threshold used to identify SDRs. Explain the reason for this choice if applicable.*

Explanation: Although the choices of disproportionality measures, thresholds and algorithms for identifying SDRs have shown to impact their performances to detect known ADRs [6, 43, 51, 52], they are poorly reported in published articles [11]. Common measures used in 2D disproportionality analyses include the reporting odds ratio (ROR) [53], proportional reporting ratio (PRR) [54], information component (IC) [55], and the Empirical Bayes Geometric Mean [6, 51, 56, 57]. Measures used for investigating interactions (i.e. 3D) include Ω and INTSS (interaction signal score) [58, 59].

Essential elements:

1. State the disproportionality measure used, including its dimensionality (e.g., 2D or 3D).
2. Specify whether units are ICSRs or drug-event pairs (more than one per ICSR).
3. Specify and justify the comparator group (e.g., non-cases) [60].
4. Specify any ICSR and statistical threshold adopted for identifying an SDR.
5. Explain methods used for investigating drug interactions or other risk factors, if applicable.

Additional elements:

1. Consider explaining the disproportionality measure using a contingency table.

Item 7c. *Clearly describe any sensitivity analysis and any tool to control confounding, including any restriction, subgroup, stratification, adjustment, or interaction.*

Explanation: Sensitivity/secondary analyses aim to explore the robustness of the results to various assumptions and methodological choices made, and to control for confounding or effect modifiers, to the extent possible with ICSRs [3, 61].

An extensive description of the list of biases in the analysis of ICSR databases is beyond the scope of this guideline, and the reader should refer to previous reviews on this topic [1, 3, 62, 63].

Essential elements:

1. Describe and justify any sensitivity analysis.

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.*

Explanation: The synthesis of ICSR characteristics and the assessment of the causal role of drugs at the case-level [64–67] is a crucial task in validation and prioritization of SDRs and need to be described, taking into account dechallenge/rechallenge, concomitant drugs, time to onset, and, whenever available, medical history/comorbidities, narratives [64–67].

Essential elements:

1. Provide a clear description of the variables analyzed in the case-by-case analysis.

2. Describe any method used for causality assessment.

Item 7e. *Specify any statistical methods used for other data sources.*

Explanation: Because there is little evidence about approximation of risk estimates by disproportionality analyses [68, 69], any correlation with external data should be acknowledged as a merely theoretical investigation, for example, to explore pharmacological drug mechanisms [70, 71].

Essential elements:

1. Specify any statistical methods used for other data sources.

2.4 Results

Item 8. Description of reports

Describe in detail the ICSR selection process (i.e., the number of reports included and excluded at each step).

Item 8a. *Specify the number of ICSRs included at each stage, including reasons for exclusion.*

Explanation: Authors should report the number of ICSRs included at each stage of the study to simplify tracking and evaluate the sample size.

Essential elements:

1. Report the number of ICSRs and cases included at each stage of the study.
2. Report the reasons for exclusions (e.g., duplicates, incomplete ICSRs, exclusion criteria).

Additional elements:

1. Consider using a flow diagram [72].

Item 8b. *Provide key demographic and clinical characteristics of cases, comparing cases with any appropriate reference group if possible.*

Explanation: This item can help provide a better understanding of the population being studied and any potential confounders or susceptibility factors, such as age, sex, comorbidities, or concomitant drugs [42]. The appropriate reference group will depend on the specific research question and study design (e.g., the entire ICSR database vs. other reports recording the same medication).

Essential elements:

1. Present the results of the descriptive analysis.

Additional elements:

1. Consider presenting this information in a table.

Item 9. Results of disproportionality analyses

Describe in detail the results of disproportionality analyses.

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

Explanation: The reporting of all disproportionality results allows the readers to independently derive their interpretation from the results of the study. Providing, even in supplementary material, the figures of the contingency tables and the number of expected ICSRs may help readers to better understand the data underlying the calculations.

Essential elements:

1. Clearly present the results of the analysis, including point estimates, confidence intervals, and results of any sensitivity analyses. Provide the figures of the contingency tables.
2. Provide the number of expected ICSRs.

Item 10. Results of case-by-case analysis

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

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

Explanation: The analysis of cases included in the calculation of disproportionality estimates may help readers and decision makers to evaluate the validity of the results. These variables include the drug's suspected role, concomitants, alternative causes, underlying disease, time to onset, the outcome after dechallenge and/or rechallenge, dose and route, sex, age, and other events. The results emerging from the causality assessment should also be included in the presentation. The case-by-case analysis should provide a detailed synthesis of all, or a subset of, ICSRs prioritized using criteria or algorithms [73], which can help in identifying specific factors contributing to adverse events and assessing causality. Remember that an anonymization may be necessary to minimize the risk of re-identification of patients notably in rare diseases and/or drugs.

Essential elements:

1. Present the results of key features from the case-by-case analysis, quantifying missing values.
2. Present the results of the case-level causality assessment.

Additional elements:

1. Consider providing a list of ICSRs with all the variables assessed, in the form of a table.

2.5 Discussion

Item 11. Key results

It is wise 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 emerging safety signals.*

Explanation: By carefully discussing the characteristics of the ICSRs, key results, contextual evidence, and pharmacological plausibility, the authors can provide valuable insights into the validity of the safety signal(s) and the safety profile of the drug(s). All stakeholders should consider that the prevalent perspective in pharmacovigilance is that an SDR alone cannot prove causation and does not allow to calculate incidence or compare risks between drugs [12, 25, 74, 75]. Similarly, interpretation of a lack of statistically significant disproportionality (negative finding) as an absence of risk or of an inverse disproportionality signal (i.e., a lower-than-expected reporting) as a protective drug-related effect is discouraged [76]. In performing the aggregated causality assessment integrating existing and new evidence, the authors are referred to the Bradford Hill guidelines [77–80].

Essential elements:

1. Present key results distinguishing between expected reactions and emerging safety signals as applicable.
2. Contextualize results with existing knowledge, highlighting inconsistencies and new findings.
3. Contextualize results with pertinent information on the regulatory landscape, recent changes in prescribing patterns, and warnings.
4. Discuss pharmacological plausibility, considering mechanism of action, pharmacokinetics, and other relevant factors.
5. Negative results must also be presented and discussed, in the light of positive/negative control events for contextualization (e.g., establish basic assay sensitivity/specificity).

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.*

Explanation: External validity refers to how well the results of a study can be generalized to other populations and settings. ICSR databases, compared with clinical trials, are likely to be more representative of real-world scenarios, accounting for factors such as comorbidities, misuse, and comedications. However, if cases analyzed share a peculiar characteristic, for example overdose or misuse, the safety concerns identified may not be relevant to clinical settings.

Essential elements:

1. Discuss the generalizability of results, with reference to setting, catchment area, disease prevalence, drug utilization, population characteristics, unusual patterns of reporting (e.g., litigation-related or solicited reports).

Additional elements:

1. If applicable, consider discussing how different access to medication, diagnostic procedures, warnings, and regulatory actions may have resulted in different reporting rates among countries, and how they may have biased the results [81, 82].

Item 12b. *Discuss the potential relevance of results in clinical practice.*

Explanation: The proposed risk minimization measures should not only be based on the results and limitations of disproportionality analyses but also the validity of the safety signal(s) considering all sources of evidence. These proposals may include updates to drug labels, additional monitoring requirements, or restrictions on use in certain patient populations. It is important to carefully consider the potential benefits and risks. Providing recommendations based on disproportionality alone should be avoided.

Essential elements:

1. Propose relevant and balanced clinical/regulatory risk minimization strategies, if applicable.

Item 12c. *Propose further study designs, if applicable.*

Explanation: If the study identified a safety signal, propose further studies to refine, support, or refute the signal, quantify the risk, and identify risk factors. Healthcare databases are traditionally viewed as a complementary source of postmarketing real-world evidence and are suited for hypothesis testing.

Essential elements:

1. Propose specific study designs or additional data sources to further assess the safety signal(s).

Item 13. Limitations

Present general limitations of ICSR databases and specific limitations of the strategy implemented.

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

Explanation: It is crucial to discuss the limitations of the study to provide a balanced and appropriate interpretation of the findings. If multiple data sources were used, the limitations of each source and method should be discussed.

Disproportionality analysis alone can be one step towards identifying safety signals but cannot formally prove causation or measure incidence due to lack of details about patient exposure [3, 74], reporting biases [3, 82], and confounding biases. Efforts should be made to control for these factors through appropriate statistical methods or study design and to consider them as alternative explanations for the findings.

Finally, the adequacy of the database(s) and the information captured on key variables should be discussed in relation to the study objectives, including factors such as completeness, accuracy of coding, and consistency of reporting.

Essential elements:

1. Present general limitations of ICSR databases and disproportionality analyses.
2. Present specific limitations and efforts implemented to mitigate them.

2.6 Declarations

Item 14. Declarations

Provide clear and exhaustive declarations about data and software used, data and code availability, and conflicts of interest.

Item 14a. *Provide the source of funding/sponsorship and the role of the funders/sponsors for the present study and for any original study on which the present article is based.*

Explanation: This item helps readers assess the likelihood of potential conflicts of interest. It should also be disclosed whether the funder or sponsor has been involved in defining the question, collecting, and analyzing data, interpreting results, or approving the final report.

Essential elements:

1. Disclose sources of financial (e.g., salary) or non-financial (e.g., analytical service, access to commercial dataset) support, specifying relevant grant ID numbers for each funder. If no specific financial or non-financial support was received, this should be declared.
2. Explicitly report any interests (commercial, financial, or intellectual) that the funder/sponsor/author(s) may have in obtaining certain results.
3. Disclose any active involvement of the funder/sponsor (e.g., defining the question, collecting and analyzing the data, interpreting the results, or approving the final report). If funders or sponsors had no role in the study, this should be declared.

Item 14b. *Clearly identify potential commercial and intellectual conflicts of interest (e.g., link to any drug/event investigated, whether financial, legal action, or software used).*

Explanation: It is essential for authors to transparently disclose any potential commercial or intellectual conflicts of interest that might have influenced the study design, results, discussions, or conclusions. For instance, authors may have links to the drug or event under investigation, received financial compensation from companies involved in the study or related to its topic, or been engaged in legal actions involving the company or product being researched, or a competing product. Additionally, if authors used software or other tools developed or owned by a specific company, this could also influence the study's results and discussions.

Essential elements:

1. Disclose any of the authors' relationships or activities that readers could consider pertinent or that could have influenced the study.
2. If any authors had competing interests, report how they were managed.

Item 14c. *Declare any institutional approval needed or granted in the investigation.*

Explanation: Examples of such approvals may involve Ethics Committee or Institutional Review Boards (IRB), regulatory agencies, or data access committees. The manuscript should state the name of the approving body and the reference number or other identifying information.

Essential elements:

1. Declare any institutional approval.

Item 14d. *Include a statement on data availability, code availability (including the version of the statistical software used), and protocol registration.*

Explanation: By sharing data, analytic codes, and other materials, others can reuse the data, identify potential errors, attempt to replicate the findings, and gain a deeper understanding of the analysis beyond what is described in the Methods section [83]. Several publicly accessible repositories, such as Open Science Framework, Dryad, and Figshare, are available for hosting shared materials, and provide a URL/DOI. The clean dataset(s) used for analysis may be shared in a readily reusable format, such as a CSV file. For

code sharing, authors can provide the analytic code used in software with a command-line interface or detailed step-by-step descriptions for point-and-click software. Additionally, it is essential to mention the software used, along with its version number, in the Methods section, or a separate statement about the statistical analysis methods. If authors encounter barriers preventing them from sharing certain materials due to legal or licensing restrictions (e.g., commercial databases), they should make a clear declaration about it.

Essential elements:

1. Declare whether preprocessing data, postprocessing data, and code are available. Provide a URL or DOI.
2. Provide the URL or DOI to the protocol, if applicable.
3. Specify the software used and its version.

2.7 Abstract

Explanation: An abstract providing key information about the main objective(s), methods, results, and implications of the findings should help readers decide whether to access the full report. For some readers, the abstract may be all that they have access to. Therefore, results must be presented for all main outcomes for the main objective(s) regardless of the statistical significance, magnitude, or direction of effect. Terms presented in the abstract will be used to index the disproportionality analysis in bibliographic databases. Therefore, reporting keywords that accurately describe the question (such as population, drug, and event) is recommended. Of note, meta-epidemiological studies and several articles have highlighted the common misinterpretation (also called spin) of results from disproportionality analyses in published studies, notably in abstracts. Indeed, many disproportionality analyses intentionally or unintentionally overstate the strength of causal links, lack proper handling and discussion of biases, or over-extrapolate results to provide clinical recommendations, comparing drug safety profiles or claiming that a drug is well tolerated [12, 20, 25, 74, 75, 84]. We therefore encourage authors to appropriately present and interpret their findings in abstracts, which are often the only part of articles read and accessible to everyone.

Essential elements:

1. Report an abstract addressing each item in the READUS-PV for Abstracts checklist.

3 Conclusion

This explanation and elaboration paper justifies and details the selected reporting recommendations for disproportionality analysis. The adoption and editorial support of READUS-PV guidelines will have a positive impact on the reporting of disproportionality analyses conducted using ICSR databases. Increased transparency and accuracy resulting from improved reporting will benefit the research community, leading to enhanced evidence-based decision making and better patient care.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40264-024-01423-7.

Acknowledgements The authors would like to thank Alex Hlavaty for his help in designing and updating the www.readus-statement.org website. Emilio J. Sanz joined the consensus meeting and participated in the definition of the items.

Declarations

Funding Open access funding provided by Alma Mater Studiorum - Università di Bologna within the CRUI-CARE Agreement.

Conflicts of Interest Gianmario Candore and Katrin Malik are full-time employees at Bayer AG. Olivia Mahaux and Andrew Bate are full-time employees at GSK and own GSK restricted shares. Manfred Hauben was a full-time employee at Pfizer when the Delphi was conducted and owns stock/stock options in pharmaceutical companies that may manufacture/market drugs mentioned in this paper. Michele Fusaroli, Francesco Salvo, Bernard Begaud, Thamir M. AlShammari, Vera Battini, Andreas Brueckner, Carla Carnovale, Salvatore Crisafulli, Paola Maria Cutroneo, Charles Dolladille, Milou-Daniel Drici, Jean-Luc Faillie, Adam Goldman, Maria Teresa Herdeiro, François Montastruc, Yoshihiro Noguchi, G. Niklas Norén, Roberta Noseda, Igho J. Onakpoya, Antoine Pariente, Elisabetta Poluzzi, Myriam Salem, Daniele Sartori, Nhung T.H. Trinh, Marco Tuccori, Florence van Hunsel, Eugène van Puijenbroek, Emanuel Raschi, and Charles Khouri declare no conflicts of interest in relation to this research.

Ethics Approval The Research Ethics Committee of the University Hospital of Bordeaux has certified that the study does not need to be submitted to a Research Ethics Committee according to French regulation.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Availability of Data and Material Additional data have been made available in the supplementary material of the present paper and its companion article [17].

Code Availability Not applicable.

Protocol Registration This study was preregistered on the EQUATOR registry and the protocol was made available at: https://readus-statement.org/.

Author Contributions MF, CK, ER, and FS conceptualized and designed the study and developed the methodology. MF synthetized all answers at each step. MF wrote the original draft. All authors contributed to the interpretation of results and the review and editing of the draft. All the authors read and approved the final version.

Disclaimer Any opinions, findings, conclusions or recommendations expressed in this material are those of the authors and do not necessarily reflect the views of their organizations.

References

1. Raschi E, Moretti U, Salvo F, Pariente A, Antonazzo IC, Ponti FD, et al. Evolving Roles of Spontaneous Reporting Systems to Assess and Monitor Drug Safety. Pharmacovigilance. 2018. Available at: https://www.intechopen.com/online-first/evolving-roles-of-spontaneous-reporting-systems-to-assess-and-monitor-drug-safety
2. Croteau D, Pinnow E, Wu E, Muñoz M, Bulatao I, Dal Pan G. Sources of evidence triggering and supporting safety-related labeling changes: a 10-year longitudinal assessment of 22 new molecular entities approved in 2008 by the US food and drug administration. Drug Saf. 2022;45:169–80.
3. Faillie J-L. Case-non-case studies: principle, methods, bias and interpretation. Therapie. 2019;74:225–32.
4. Insani WN, Pacurariu AC, Mantel-Teeuwisse AK, Gross-Martirosyan L. Characteristics of drugs safety signals that predict safety related product information update. Pharmacoepidemiol Drug Saf. 2018;27:789–96.
5. Onakpoya IJ, Heneghan CJ, Aronson JK. Post-marketing withdrawal of 462 medicinal products because of adverse drug reactions: a systematic review of the world literature. BMC Med. 2016;14:10.
6. Pham M, Cheng F, Ramachandran K. A comparison study of algorithms to detect drug-adverse event associations: frequentist, bayesian, and machine-learning approaches. Drug Saf. 2019;42:743–50.
7. Tau N, Shochat T, Gafter-Gvili A, Tibau A, Amir E, Shepshelovich D. Association between data sources and US food and drug administration drug safety communications. JAMA Intern Med. 2019;179:1590–2.
8. Sartori D, Aronson JK, Norén GN, Onakpoya IJ. Signals of adverse drug reactions communicated by pharmacovigilance stakeholders: a scoping review of the global literature. Drug Saf. 2023;46:109–20.
9. Loke YK, Mattishent K, Navaneetharaja N. New adverse drug reaction signals from 2017 to 2021—genuine alerts or false alarms? Pharmacy. 2024;12:33.
10. Khouri C, Fusaroli M, Salvo F, Raschi E. Transparency and robustness of safety signals. BMJ. 2022;379: o2588.
11. Khouri C, Revol B, Lepelley M, Mouffak A, Bernardeau C, Salvo F, et al. A meta-epidemiological study found lack of transparency and poor reporting of disproportionality analyses for signal detection in pharmacovigilance databases. J Clin Epidemiol. 2021;139:191–8.
12. Mouffak A, Lepelley M, Revol B, Bernardeau C, Salvo F, Pariente A, et al. High prevalence of spin was found in pharmacovigilance studies using disproportionality analyses to detect safety signals: a meta-epidemiological study. J Clin Epidemiol. 2021;138:73–9.
13. Glasziou P, Altman DG, Bossuyt P, Boutron I, Clarke M, Julious S, et al. Reducing waste from incomplete or unusable reports of biomedical research. Lancet Lond Engl. 2014;383:267–76.
14. Boutron I, Ravaud P. Misrepresentation and distortion of research in biomedical literature. Proc Natl Acad Sci. 2018;115:2613–9.
15. Chalmers I, Glasziou P. Avoidable waste in the production and reporting of research evidence. Lancet Lond Engl. 2009;374:86–9.
16. READUS. READUS. [accessed 2024 Feb 28]. Available from: https://readus-statement.org/
17. Fusaroli M, Salvo F, Bégaud B, Alshammari TM, Bate A, Battini V, et al. The REporting of A Disproportionality analysis for drUg Safety signal detection using individual case safety reports in PharmacoVigilance (READUS-PV): development and statement. Drug Saf. https://doi.org/10.1007/s40264-024-01421-9.
18. Moher D, Schulz KF, Simera I, Altman DG. Guidance for Developers of Health Research Reporting Guidelines. PLOS Med. 2010;7: e1000217.
19. Bégaud B, Judith K J. Assessing causality from case reports. Textb Pharmacoepidemiol. 3rd ed. 2021. p. 246–56.
20. Moore N. Paper OK, title wrong. BMJ. 2011;342: d2732.
21. Orhon P, Robert M, Morand T, Cracowski J-L, Khouri C. Investigating the link between drug consumption and adverse events reporting in France. Fundam Clin Pharmacol. 2023;37:879–82.
22. Modgill V, Dormegny L, Lewis DJ. Reporting rates of adverse reactions to specialty care medicines exhibit a direct positive correlation with patient exposure: a lack of evidence for the Weber effect. Br J Clin Pharmacol. 2020;86:2393–403.
23. Pariente A, Daveluy A, Laribière-Bénard A, Miremont-Salame G, Begaud B, Moore N. Effect of date of drug marketing on disproportionality measures in pharmacovigilance: the example of suicide with SSRIs using data from the UK MHRA. Drug Saf. 2009;32:441–7.
24. Pariente A, Gregoire F, Fourrier-Reglat A, Haramburu F, Moore N. Impact of safety alerts on measures of disproportionality in spontaneous reporting databases: the notoriety bias. Drug Saf. 2007;30:891–8.
25. Raschi E, Salvo F, Khouri C. Conceiving, conducting, reporting, interpreting, and publishing disproportionality analyses: a call to action. Br J Clin Pharmacol. 2022;88:3535–6.
26. Montastruc J-L, Sommet A, Bagheri H, Lapeyre-Mestre M. Benefits and strengths of the disproportionality analysis for identification of adverse drug reactions in a pharmacovigilance database: commentary. Br J Clin Pharmacol. 2011;72:905–8.
27. de Boer A. When to publish measures of disproportionality derived from spontaneous reporting databases? Br J Clin Pharmacol. 2011;72:909–11.
28. Fusaroli M, Isgrò V, Cutroneo PM, Ferrajolo C, Cirillo V, Del Bufalo F, et al. Post-marketing surveillance of CAR-T-cell therapies: analysis of the FDA Adverse Event Reporting System (FAERS) database. Drug Saf. 2022. https://doi.org/10.1007/s40264-022-01194-z.
29. Fukazawa C, Hinomura Y, Kaneko M, Narukawa M. Significance of data mining in routine signal detection: analysis based on the safety signals identified by the FDA. Pharmacoepidemiol Drug Saf. 2018;27:1402–8.
30. Vogel U, van Stekelenborg J, Dreyfus B, Garg A, Habib M, Hosain R, et al. Investigating overlap in signals from EVDAS, FAERS, and VigiBase®. Drug Saf. 2020;43:351–62.
31. Stern C, Jordan Z, McArthur A. Developing the review question and inclusion criteria. AJN Am J Nurs. 2014;114:53.
32. Moola S, Munn Z, Sears K, Sfetcu R, Currie M, Lisy K, et al. Conducting systematic reviews of association (etiology): the Joanna Briggs Institute's approach. Int J Evid Based Healthc. 2015;13:163–9.
33. Fusaroli M, Raschi E, Gatti M, De Ponti F, Poluzzi E. Development of a network-based signal detection tool: the COVID-19

adversome in the FDA adverse event reporting system. Front Pharmacol. 2021;12:3542.
34. Noguchi Y, Tachi T, Teramachi H. Review of statistical methodologies for detecting drug–drug interactions using spontaneous reporting systems. Front Pharmacol. 2019. https://doi.org/10.3389/fphar.2019.01319.
35. Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). Drug Saf. 1999;20:109–17.
36. WHO Collaborating Centre for Drug Statistics Methodology, Guidelines for ATC classification and DDD assignment, 2023. Oslo, 2022.
37. Giunchi V, Fusaroli M, Hauben M, Raschi E, Poluzzi E. Challenges and opportunities in accessing and analysing FAERS data: a call towards a collaborative approach. Drug Saf. 2023. https://doi.org/10.1007/s40264-023-01345-w.
38. Fusaroli M, Giunchi V, Battini V, Puligheddu S, Khouri C, Carnovale C, et al. Standardization of drug names in the FDA Adverse Event reporting system: the DiAna dictionary. medRxiv. 2023. https://doi.org/10.1101/2023.06.07.23291076v1.
39. Norén GN, Orre R, Bate A, Edwards IR. Duplicate detection in adverse drug reaction surveillance. Data Min Knowl Discov. 2007;14:305–28.
40. Mahaux O, Powell G, Haguinet F, Sobczak P, Saini N, Barry A, et al. Identifying safety subgroups at risk: assessing the agreement between statistical alerting and patient subgroup risk. Drug Saf. 2023;46:601–14.
41. Seabroke S, Candore G, Juhlin K, Quarcoo N, Wisniewski A, Arani R, et al. Performance of stratified and subgrouped disproportionality analyses in spontaneous databases. Drug Saf. 2016;39:355–64.
42. Sandberg L, Taavola H, Aoki Y, Chandler R, Norén GN. Risk factor considerations in statistical signal detection: using subgroup disproportionality to uncover risk groups for adverse drug reactions in VigiBase. Drug Saf. 2020;43:999–1009.
43. Wisniewski AFZ, Bate A, Bousquet C, Brueckner A, Candore G, Juhlin K, et al. Good signal detection practices: evidence from IMI PROTECT. Drug Saf. 2016;39:469–90.
44. Reich CG, Ryan PB, Schuemie MJ. Alternative outcome definitions and their effect on the performance of methods for observational outcome studies. Drug Saf. 2013;36:181–93.
45. Pearson RK, Hauben M, Goldsmith DI, Gould AL, Madigan D, O'Hara DJ, et al. Influence of the MedDRA® hierarchy on pharmacovigilance data mining results. Int J Med Inf. 2009;78:e97-103.
46. Souvignet J, Declerck G, Trombert B, Rodrigues JM, Jaulent M-C, Bousquet C. Evaluation of automated term groupings for detecting anaphylactic shock signals for drugs. AMIA Annu Symp Proc AMIA Symp. 2012;2012:882–90.
47. Standardised MedDRA Queries | MedDRA. Available at: https://www.meddra.org/standardised-meddra-queries
48. Fusaroli M, Salvo F, Bernardeau C, Idris M, Dolladille C, Pariente A, et al. Mapping strategies to assess and increase the validity of published disproportionality signals: a meta-research study. Drug Saf. 2023. https://doi.org/10.1007/s40264-023-01329-w.
49. Nguyen TTH, Pariente A, Montastruc J-L, Lapeyre-Mestre M, Rousseau V, Rascol O, et al. An original pharmacoepidemiological-pharmacodynamic method: application to antipsychotic-induced movement disorders. Br J Clin Pharmacol. 2017;83:612–22.
50. Gauffin O, Brand JS, Vidlin SH, Sartori D, Asikainen S, Català M, et al. Supporting pharmacovigilance signal validation and prioritization with analyses of routinely collected health data: lessons learned from an EHDEN network study. Drug Saf. 2023. https://doi.org/10.1007/s40264-023-01353-w.
51. Harpaz R, DuMouchel W, LePendu P, Bauer-Mehren A, Ryan P, Shah NH. Performance of pharmacovigilance signal-detection algorithms for the FDA adverse event reporting system. Clin Pharmacol Ther. 2013;93:539–46.
52. Ding Y, Markatou M, Ball R. An evaluation of statistical approaches to postmarketing surveillance. Stat Med. 2020;39:845–74.
53. Van Puijenbroek EP, Van Grootheest K, Diemont WL, Leufkens HGM, Egberts ACG. Determinants of signal selection in a spontaneous reporting system for adverse drug reactions. Br J Clin Pharmacol. 2001;52:579–86.
54. Evans SJ, Waller PC, Davis S. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. Pharmacoepidemiol Drug Saf. 2001;10:483–6.
55. Bate A, Lindquist M, Edwards IR, Olsson S, Orre R, Lansner A, et al. A Bayesian neural network method for adverse drug reaction signal generation. Eur J Clin Pharmacol. 1998;54:315–21.
56. DuMouchel W. Bayesian data mining in large frequency tables, with an application to the FDA spontaneous reporting system. Am Stat. 1999;53:177–90.
57. Candore G, Juhlin K, Manlik K, Thakrar B, Quarcoo N, Seabroke S, et al. Comparison of statistical signal detection methods within and across spontaneous reporting databases. Drug Saf. 2015;38:577–87.
58. Martin D, Menschik D, Bryant-Genevier M, Ball R. Data mining for prospective early detection of safety signals in the vaccine adverse event reporting system (VAERS): a case study of febrile seizures after a 2010–2011 seasonal influenza virus vaccine. Drug Saf. 2013;36:547–56.
59. Norén GN, Sundberg R, Bate A, Edwards IR. A statistical methodology for drug–drug interaction surveillance. Stat Med. 2008;27:3057–70.
60. Gravel CA, Douros A. Considerations on the use of different comparators in pharmacovigilance: a methodological review. Br J Clin Pharmacol. 2023;89:2671–6.
61. Khouri C, Nguyen T, Revol B, Lepelley M, Pariente A, Roustit M, et al. Leveraging the variability of pharmacovigilance disproportionality analyses to improve signal detection performances. Front Pharmacol. 2021. https://doi.org/10.3389/fphar.2021.668765.
62. Raschi E, Poluzzi E, Salvo F, Pariente A, De Ponti F, Marchesini G, et al. Pharmacovigilance of sodium-glucose co-transporter-2 inhibitors: What a clinician should know on disproportionality analysis of spontaneous reporting systems. Nutr Metab Cardiovasc Dis NMCD. 2018;28:533–42.
63. Cutroneo PM, Sartori D, Tuccori M, Crisafulli S, Battini V, Carnovale C, et al. Conducting and interpreting disproportionality analyses derived from spontaneous reporting systems. Front Drug Saf Regul. 2023. https://doi.org/10.3389/fdsfr.2023.1323057.
64. Hill AB. The environment and disease: association or causation? Proc R Soc Med. 1965;58:295–300.
65. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30:239–45.
66. Behera SK, Das S, Xavier AS, Velupula S, Sandhiya S. Comparison of different methods for causality assessment of adverse drug reactions. Int J Clin Pharm. 2018;40:903–10.
67. WHO – Uppsala Monitoring Centre. The use of the WHO-UMC system for standardized case causality assessment. 2018 [last accessed 2024 Feb 28]. Available from: http://www.who-umc.org/Graphics/24734.pdf
68. Khouri C, Petit C, Tod M, Lepelley M, Revol B, Roustit M, et al. Adverse drug reaction risks obtained from meta-analyses and pharmacovigilance disproportionality analyses are correlated in most cases. J Clin Epidemiol. 2021. Available from: https://www.jclinepi.com/article/S0895-4356(21)00026-3/abstract

69. Maciá-Martínez M-A, de Abajo FJ, Roberts G, Slattery J, Thakrar B, Wisniewski AFZ. An empirical approach to explore the relationship between measures of disproportionate reporting and relative risks from analytical studies. Drug Saf. 2016;39:29–43.
70. De Bruin ML, Pettersson M, Meyboom RHB, Hoes AW, Leufkens HGM. Anti-HERG activity and the risk of drug-induced arrhythmias and sudden death. Eur Heart J. 2005;26:590–7.
71. Fusaroli M, Giunchi V, Battini V, Gringeri M, Rimondini R, Menchetti M, et al. Exploring the underlying mechanisms of drug-induced impulse control disorders: a pharmacovigilance-pharmacodynamic study. Psychiatry Clin Neurosci. 2023;77:160–7.
72. Gatto NM, Wang SV, Murk W, Mattox P, Brookhart MA, Bate A, et al. Visualizations throughout pharmacoepidemiology study planning, implementation, and reporting. Pharmacoepidemiol Drug Saf. 2022;31:1140–52.
73. Lieber T, Gosselt HR, Kools PC, Kruijssen OC, Van Lierop SNC, Härmark L, et al. Natural language processing for automated triage and prioritization of individual case safety reports for case-by-case assessment. Front Drug Saf Regul. 2023. https://doi.org/10.3389/fdsfr.2023.1120135.
74. Khouri C, Fusaroli M, Salvo F, Raschi E. Interpretation of pharmacovigilance disproportionality analyses. Clin Pharmacol Ther. 2023. https://doi.org/10.1002/cpt.2951.
75. Cortes B, Jambon-Barbara C, Cracowski J-L, Khouri C. Validity, relevance and interpretation of pharmacovigilance disproportionality analyses. Bone. 2023;170: 116685.
76. Raschi E, Salvo F, La Placa M, Poluzzi E, De Ponti F. Reduced reporting of neuropsychiatric adverse events with tumor necrosis factor alpha inhibitors for hidradenitis suppurativa: caution before concluding for risk reduction. J Eur Acad Dermatol Venereol. 2020;34:e430–1.
77. Shakir SAW, Layton D. Causal association in pharmacovigilance and pharmacoepidemiology: thoughts on the application of the Austin Bradford-Hill criteria. Drug Saf. 2002;25:467–71.
78. Perrio M, Voss S, Shakir SAW. Application of the bradford hill criteria to assess the causality of cisapride-induced arrhythmia: a model for assessing causal association in pharmacovigilance. Drug Saf. 2007;30:333–46.
79. Fusaroli M, Raschi E, Giunchi V, Menchetti M, Rimondini Giorgini R, De Ponti F, et al. Impulse control disorders by dopamine partial agonists: a pharmacovigilance-pharmacodynamic assessment through the FDA adverse event reporting system. Int J Neuropsychopharmacol. 2022;25:727–36.
80. Sultana J, Hurtado I, Bejarano-Quisoboni D, Giorgianni F, Huybrechts KF, Lu Z, et al. Antipsychotic utilization patterns among patients with schizophrenic disorder: a cross-national analysis in four countries. Eur J Clin Pharmacol. 2019;75:1005–15.
81. Bailey C, Peddie D, Wickham ME, Badke K, Small SS, Doyle-Waters MM, et al. Adverse drug event reporting systems: a systematic review. Br J Clin Pharmacol. 2016;82:17–29.
82. García-Abeijon P, Costa C, Taracido M, Herdeiro MT, Torre C, Figueiras A. Factors associated with underreporting of adverse drug reactions by health care professionals: a systematic review update. Drug Saf. 2023;46:625–36.
83. Mansmann U, Locher C, Prasser F, Weissgerber T, Sax U, Posch M, et al. Implementing clinical trial data sharing requires training a new generation of biomedical researchers. Nat Med. 2023;29:298–301.
84. Hauben M, Patadia V, Gerrits C, Walsh L, Reich L. Data mining in pharmacovigilance: the need for a balanced perspective. Drug Saf. 2005;28:835–42.

Authors and Affiliations

Michele Fusaroli[1] · Francesco Salvo[2,3] · Bernard Begaud[2] · Thamir M. AlShammari[4] · Andrew Bate[5,6] · Vera Battini[7] · Andreas Brueckner[8] · Gianmario Candore[9] · Carla Carnovale[7] · Salvatore Crisafulli[10] · Paola Maria Cutroneo[11] · Charles Dolladille[12,13] · Milou-Daniel Drici[14] · Jean-Luc Faillie[15] · Adam Goldman[16,17] · Manfred Hauben[18,19] · Maria Teresa Herdeiro[20] · Olivia Mahaux[5] · Katrin Manlik[9] · François Montastruc[21,22] · Yoshihiro Noguchi[23] · G. Niklas Norén[24] · Roberta Noseda[25] · Igho J. Onakpoya[26] · Antoine Pariente[2,3] · Elisabetta Poluzzi[1] · Myriam Salem[27] · Daniele Sartori[24,28] · Nhung T. H. Trinh[29] · Marco Tuccori[30] · Florence van Hunsel[31,32] · Eugène van Puijenbroek[31,32] · Emanuel Raschi[1] · Charles Khouri[33,34]

✉ Michele Fusaroli
michele.fusaroli2@unibo.it

✉ Francesco Salvo
francesco.salvo@u-bordeaux.fr

Emanuel Raschi
emanuel.raschi@unibo.it

[1] Department of Medical and Surgical Sciences, Alma Mater Studiorum, University of Bologna, Bologna, Italy

[2] Université de Bordeaux, INSERM, BPH, Team AHeaD, U1219, 33000 Bordeaux, France

[3] Service de Pharmacologie Médicale, CHU de Bordeaux, INSERM, U1219, 33000 Bordeaux, France

[4] College of Pharmacy, Almaarefa University, Riyadh, Saudi Arabia

[5] Global Safety, GSK, Brentford, UK

[6] Department of Non-Communicable Epidemiology, London School of Hygiene and Tropical Medicine, London, UK

[7] Pharmacovigilance and Clinical Research, International Centre for Pesticides and Health Risk Prevention, Department of Biomedical and Clinical Sciences (DIBIC), ASST Fatebenefratelli-Sacco University Hospital, Università degli Studi di Milano, Milan, Italy

[8] Novartis Pharma AG, Basel, Switzerland

[9] Medical Affairs and Pharmacovigilance, Bayer AG, Berlin, Germany

[10] Department of Medicine, University of Verona, Verona, Italy

[11] Unit of Clinical Pharmacology, Sicily Pharmacovigilance Regional Centre, University Hospital of Messina, Messina, Italy

[12] UNICAEN, EA4650 SEILIRM, CHU de Caen Normandie, Normandie University, Caen, France

[13] Department of Pharmacology, CHU de Caen Normandie, Caen, France

[14] Department of Clinical Pharmacology, Université Côte d'Azur Medical Center, Nice, France

[15] Desbrest Institute of Epidemiology and Public Health, Department of Medical Pharmacology and Toxicology, INSERM, Univ Montpellier, Regional Pharmacovigilance Centre, CHU Montpellier, Montpellier, France

[16] Department of Internal Medicine, Sheba Medical Center, Ramat-Gan, Israel

[17] Department of Epidemiology and Preventive Medicine, School of Public Health, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

[18] Pfizer Inc, New York, NY, USA

[19] Present Address: Department of Family and Community Medicine, New York Medical College, Valhalla, New York, USA

[20] Department of Medical Sciences, IBIMED-Institute of Biomedicine, University of Aveiro, 3810-193 Aveiro, Portugal

[21] Department of Medical and Clinical Pharmacology, Centre of PharmacoVigilance and Pharmacoepidemiology, Faculty of Medicine, Toulouse University Hospital (CHU), Toulouse, France

[22] CIC 1436, Team PEPSS (Pharmacologie En Population cohorteS et biobanqueS), Toulouse University Hospital, Toulouse, France

[23] Laboratory of Clinical Pharmacy, Gifu Pharmaceutical University, Gifu, Japan

[24] Uppsala Monitoring Centre, Uppsala, Sweden

[25] Institute of Pharmacological Sciences of Southern Switzerland, Division of Clinical Pharmacology and Toxicology, Ente Ospedaliero Cantonale, Lugano, Switzerland

[26] Department for Continuing Education, University of Oxford, Oxford, UK

[27] Health Canada, Ottawa, ON, Canada

[28] Centre for Evidence-Based Medicine, Nuffield, Department of Primary Care Health Sciences, University of Oxford, Oxford, UK

[29] PharmacoEpidemiology and Drug Safety Research Group, Department of Pharmacy, University of Oslo, Oslo, Norway

[30] Tuscany Regional Centre, Unit of Adverse Drug Reaction Monitoring, University Hospital of Pisa, Pisa, Italy

[31] Netherlands Pharmacovigilance Centre Lareb, 's-Hertogenbosch, The Netherlands

[32] PharmacoTherapy, Epidemiology and Economics, University of Groningen, Groningen Research Institute of Pharmacy, Groningen, The Netherlands

[33] Pharmacovigilance Department, Université Grenoble Alpes, Grenoble Alpes University Hospital, Grenoble, France

[34] UMR 1300-HP2 Laboratory, Université Grenoble Alpes, INSERM, Grenoble Alpes University, Grenoble, France