

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

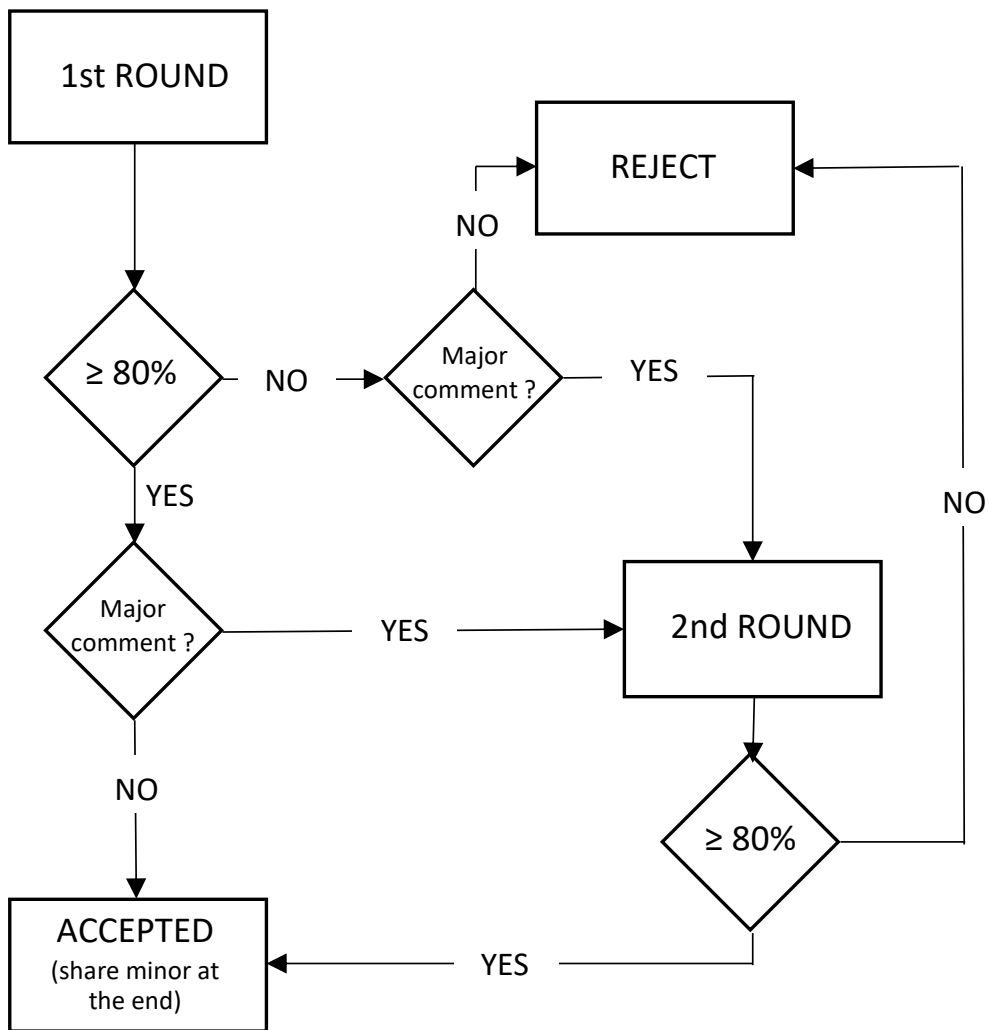
Supplementary Material Drug Safety

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Supplementary Figure 1. Decision rules for selecting items in the online Delphi process.



Supplementary Table 1. The READUS-PV checklist

Section and topic	Item #	Checklist item	Location where item is reported
Title			
	1a	<i>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.</i>	
	1b	<i>Report the name of adverse event(s) and/or drug(s) under study, when applicable.</i>	
Introduction			
Background	2a	<i>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.</i>	
	2b	<i>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.</i>	
	2c	<i>Explain why ICSR databases and disproportionality analysis are suitable to fill the knowledge gap.</i>	
Objectives	3	<i>State specific objectives, identifying the adverse event(s), the drug(s), and the reference group, including any pre-specified hypothesis, if applicable.</i>	
Methods			
Study design	4a	<i>Identify the study (i.e., “disproportionality analysis”) and the type of data used (e.g., “individual case safety reports”).</i>	
	4b	<i>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.</i>	
Data description, access, and pre-processing	5a	<i>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.</i>	
	5b	<i>Specify the extraction dates and describe and justify all choices used for data pre-processing, including any data transformation or exclusion, if appropriate.</i>	
Variables definition	6a	<i>Describe the study population, including any restriction.</i>	
	6b	<i>Describe the nature and the meaning of key variables assessed in the work.</i>	
	6c	<i>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.</i>	
	6d	<i>Describe any additional data source used, the type of data, and how they interact with ICSRs.</i>	
Statistical methods	7a	<i>Present any descriptive analysis performed, specifying variables investigated, statistical tests, and significance thresholds.</i>	
	7b	<i>Describe 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.</i>	
	7c	<i>Clearly describe any sensitivity analysis and any tool to control confounding, including any restriction, subgroup, stratification, adjustment, or interaction.</i>	
	7d	<i>Specify the variables and methods used for the case-by-case analysis, including any algorithm or criteria used to assess causality, if performed.</i>	
	7e	<i>Specify any statistical methods used for other data sources.</i>	
Results			
Participants	8a	<i>Specify the number of individual case safety reports included at each stage, including reasons for exclusion.</i>	
	8b	<i>Provide key demographic and clinical characteristics of cases, if possible comparing cases with any appropriate reference group.</i>	
Disproportionality analysis	9	<i>Present all results including confidence intervals. Present also results of sensitivity analyses, if performed.</i>	

Case-by-case analysis	10	Present the case-by-case analysis of key variables. Present the causality assessment, if applicable.	
Discussion			
Key results	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.	
External validity	12a	Discuss the external validity of the results to the general population.	
	12b	Discuss the potential relevance of results in clinical practice	
	12c	Propose further study designs if applicable	
Limitations	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.	
Declarations			
	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.	
	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).	
	14c	Declare any institutional approval needed or granted in the investigation.	
	14d	Include a statement on data availability, code availability (including the version of the statistical software used), and protocol registration.	

Supplementary Table 2. The READUS-PV checklist for abstracts

Section and topic	Item #	Checklist item	Location where item is reported
Background	1a	State the aim/rationale for performing the study.	
	1b	Specify the adverse event(s) and/or the drug(s) under study, when applicable.	
	1c	Specify the specific population or setting, when applicable.	
Methods	2a	Identify the study as a “disproportionality analysis” and specify the type of data used.	
	2b	Specify the name of the database(s) used and the type of access.	
	2c	Specify the timeframe and geographical region, when applicable.	
	2d	Specify the disproportionality measure(s) used and their statistical significance threshold(s).	
	2e	Specify if a case-by-case analysis is performed.	
Results	3	Report main findings including their precision (e.g., 95% confidence intervals), together with a short summary of the case-by-case analysis.	
Conclusion	4a	Clearly report key conclusions.	
	4b	Acknowledge that the disproportionality analysis is a hypothesis generating or refinement approach.	
	4c	State the implications and clinical relevance of the findings.	

Supplementary Table 3. Items proposed by participants through the open text survey and deemed not suited for the reporting guideline or excluded during the DELPHI process.

Reason	Item
Guideline for conducting (and not reporting) disproportionality analysis	Be careful in creating subsets where the number of reports is small.
	Prefer to integrate frequentist and Bayesian
	If the analysis investigates a class of drugs or a cluster of events, sub-analyses should be scheduled to identify possible leading drugs or events for the signal of disproportion.
	For the granularity of events, 'Preferred Terms' (PT) should be preferred, otherwise justify
	For the granularity of drugs, whenever possible, the International Non-proprietary Name of the drugs should be preferred.
	For adjustment/stratification, do not set more covariates than necessary (only variables that are thought to impact the results in a consistent way) since patient information obtained from the spontaneous reporting system is limited and subgroups may be too small.
	Subgroup analyses may be preferred, when compared to stratified analysis, as they seem to show a better performance.
	a minimum of 500 for national and 5000 reports for international databases is recommended to limit the number of false-positive associations
	In case of negative disproportionality analysis, it could be interesting to estimate how many additional cases would be needed to turn the disproportionality significant.
	Use appropriate strategies to test for statistical significance in descriptive analyses
	Always descriptive against the most appropriate reference group
	Explore issues of extrapolations (when there is only a limited overlap between the characteristics of the exposed population and the characteristics of the comparator). Adjustments of the disproportionality measure should be performed using at least those variables for which a significant difference has been observed.
	Give both unadjusted and adjusted disproportionalities
	Quantitative data should be completed by case-by-case information: authors should try to obtain a precise imputability analysis (Naranjo scale, WHO score) for at least some of the queried reports for instance by retrieving more information from their national database. To define new potential safety signals and partly exclude other potential risk factors. If applicable, dechallenge and rechallenge analysis could reinforce drug-event association. Analysing time to event onset could provide meaningful clinical knowledge. possible alternative causative agents distribution
	Ambiguous
	Include negative results, if applicable
<80% Agreement	Objectives : <ul style="list-style-type: none"> • Specify granularity of events and drugs and its rationale (e.g., same mechanism, pathogenesis)
	Methods: <ul style="list-style-type: none"> • Provide a general description of the data collection process. • Describe the structure and available fields • Describe the access extent (e.g., public, pharmacovigilance center, aggregated data, narratives). • Provide each definition as the presence in a specific field(s) of a standardized or free-text term(s). • Clearly state how the time window(s) during which an individual was considered exposed to the drug(s) was/were defined (e.g. as time gap between drug end date and drug start date) • Show contingency tables, relevant mathematical formulas, and any hyperparameters • Describe and justify minimum sample size and statistical power for rare events, small databases, subgroups, if applicable.
	Results : <ul style="list-style-type: none"> • Specify when the first and last cases were found • Specify the median number of reports per year • Report combinations of medical products and events not exceeding the pre-specified threshold(s) • Report whether each statistical signal was previously documented and the source

	<p>Discussion :</p> <ul style="list-style-type: none"> • Discuss how database and healthcare have changed over time of study • Provide a script/code availability statement • Share the script/code used • Provide the exact query for medical products and adverse events, comparison and confounders.
	<p>Abstract :</p> <ul style="list-style-type: none"> • Introduce previous evidence from published and unpublished documents • Specify terminologies or dictionaries used • Complement main findings with corresponding expected counts • Integrate with a comprehensive clinical assessment of individual reports, including coherence, if applicable • Discuss main aspects of internal and external validity • Propose future directions.
<p>Proposed after Delphi</p>	<ul style="list-style-type: none"> • Declaration item concerning role and participation of authors. • Declaration item concerning patient and public involvement.