The **RE**porting of **A D**isproportionality analysis for dr**U**g **S**afety signal detection using spontaneously reported adverse events in **P**harmaco**V**igilance (**READUS-PV**)

Draft version

Title

The title should be clear and exhaustive.

1. Identify the analysis as a "disproportionality analysis" and make explicit the type of data.
2. Report the name of adverse event(s) and/or medicinal product(s) under study, when applicable.

Background

Explain the scientific background and rationale for the study.

3. Describe the medicinal product(s) and its utilization and/or the nature of the adverse event(s) and its frequency. Describe the safety issue under investigation, its plausible pathogenesis, and the specific gap in knowledge.
4. 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-specifiied hypothesis.
5. Explain –or provide appropriate reference about–the nature of pharmacovigilance data and the principles of disproportionality studies. Clarify why they are suitable to fill the knowledge gap.

Objectives

Specify aims so that they logically follow the research question(s).

6. State specific objectives, expliciting the adverse event(s), the medicinal product(s), and the reference group, including any pre-specified hypothesis, if applicable.

Methods

Study design

Present key elements of study design early in the paper.

7. Identify the study (i.e., "disproportionality analysis") and the type of data used (e.g., "spontaneous reports").
8. Provide an outline of primary and sensitivity analyses performed, including complementary designs such as case-by-case and review of the literature.

Data description, access, and pre-processing

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

9. Specify the name of the database(s), the database(s) custodian, and the coverage. Specify the type/number of medicinal products included within the database, and the ontologies used for coding medicinal products and events.
10. 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.

Variables definition

Clearly define all events, medicinal exposures, potential confounders, and effect modifiers investigated.

11. Describe the features of variables assessed in the work: provide details on their nature and their meaning.
12. Specify and justify any hierarchical grouping of drugs or events. For drugs, specify and justify whether active ingredients/trade names/salts were considered and/or the selected role.
13. In case additional data sources were used, provide a description of the sources, which type of data were used for this study and how they interact with spontaneous reporting data.

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.

14. Present any descriptive analysis performed, specifying variables investigated, statistical tests, significance thresholds.
15. Describe the measure selected for the disproportionality analysis, including any threshold used to identify signals of disproportionate reporting. Specify whether units in the disproportionality referred to an individual patient/report or to an individual drug-event pair.
16. Clearly describe any sensitivity analysis and any tool to control for confounding, including any restriction, subgroup, stratification, adjustment or interaction.
17. Specify the variables and methods used for the analysis of individual cases, including any algorithm or criteria used to assess causality, if performed.
18. Specify any statistical methods used for non pharmacovigilance data sources.

Results

Participants

Describe in detail the reports selection, as text and/or as a study flow diagram.

19. Specify number of reports and cases included at each stage, including reasons for exclusion
20. Provide key demographic and clinical characteristics of cases, if possible comparing cases with any appropriate reference group.

Disproportionality analysis

Describe in detail the results of disproportionality analyses, including the less important information in a supplementary material.

21. Present all results (point estimates and confidence intervals), including sensitivity analyses, if applicable.

Case-by-case review

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

22. Present the case-by-case review on key features. Present the causality assessment, if applicable

Discussion

Key results

Summarize key results with reference to study objectives.

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

External validity

Discuss the external validity of the study results.

24. Discuss the external validity compared to trial settings and other spontaneous reporting databases. In particular, discuss how the results are influenced by, and generalize to, the exposed populations in specific geographic areas, if relevant.
25. Discuss transferability of results in clinical practice.
26. Propose further study designs to refine the signal or quantify risk, if applicable

Limitations

Give a cautious overall interpretation of results considering objectives, data and method limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.

27. 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

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

28. Provide the source of funding and the role of the funders for the present study and for any original study on which the present article is based.
29. Clearly identify potential commercial and intellectual conflicts of interest (e.g., link to any medicinal product/event investigated, whether financial, or legal action, and software used).
30. Declare any institutional approval needed or granted in the investigation.
31. Specify statistical software (version).
32. Include a statement on data availability, code availability and protocol registration.

Abstract

Provide an informative and balanced summary of background, objectives, methods, key findings, and conclusions.

Background

1. State the rationale for performing the study
2. Specify the adverse event(s) and/or the medical product(s) under study, when applicable
3. Specify the specific population or setting, when applicable

Methods

4. Identify the study as a “disproportionality analysis” and specify the type of data used
5. Specify the name of the database(s) used and the type of access
6. Specify the timeframe and geographical region, when applicable
7. Specify the disproportionality measure(s) used and their statistical significance threshold(s)
8. Specify if a case-by-case assessment is performed

Results

9. Report main findings in terms of estimates and their precision (e.g., 95% confidence intervals), together with a short summary of the case-by-case review, with particular regard for causality and expectedness.

Conclusion

10. Clearly report key conclusions
11. Mention that the disproportionality analysis cannot conclude on a definite causal link
12. State the implications and clinical relevance of the findings