SUPPLEMENTARY MATERIAL

Mapping Strategies to Assess and Increase the Credibility of Published Disproportionality Signals: A Meta-Research Study.

Running Title: Mapping strategies to assess credibility in disproportionality signals.

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Variables Group	Variables subcluster	Variable	Description	Accepted values
General Information	**Article details**	**ID**	Identification number for internal operative reference	integral (1-100)
		Title	Title of the article	character
		Brief	Whether the article was a brief or a full article	boolean (Y/N)
		PMID	PMID	integral
		Year	Year of publication	integral (1997-2019)
	Journal details	**Journal Title**	Name of the journal	factor
		Journal Category	category of the journal	factor (medical/pharmacological)
		Impact Factor	impact factor of the journal (2020)	numeric
	Study general design	**Medicinal Product Class**	Name of the drug class (if possible) investigated	factor
		Medicinal Products	Name of the individual drugs investigated	factor
		Adverse Events	Name of the adverse events investigated	factor
		Population	Population investigated with the main analysis	factor
Pharmacovigilance Analyses Robustness	**Database used**	**Database**	Name of the spontaneous reporting system used (acronym)	factor
		More than one database	Whether more than one spontaneous reporting system was used	boolean (Y/N)
	Disproportionality Analysis	**ROR**	Whether the Reporting Odds Ratio was calculated as a measure of disproportionality	boolean (Y/N)
		PRR	Whether the Proportional Reporting Ratio was calculated as a measure of disproportionality	boolean (Y/N)

		EBGM	Whether the Empirical Bayes Geometric Mean was calculated as a measure of disproportionality	boolean (Y/N)
		IC	Whether the Information Component was calculated as a measure of disproportionality	boolean (Y/N)
	Case-by-Case	**causality assessment**	whether a case-by-case causality assessment, using a causality score or searching for alternative explanations in each report, was performed	boolean (Y/N)
	Strength	**N° drugs**	number of drugs investigated	integer
		N° events	number of events investigated	integer
		Correction	whether a correction for multiple comparisons was performed	boolean (Y/N)
		Adjusted	whether an adjustment on one or more variables was performed	boolean (Y/N)
		Specifications	specifications about the kind of adjustment (e.g., sex, age) or the correction method (e.g., Benjamini-Hochberg, Bonferroni, Holm-Bonferroni)	factor
	Consistency	**Consistency**	Whether the disproportion was calculated on multiple subpopulations to see if it was consistent	boolean (Y/N)
		Subpopulation	Subpopulations on which the consistency was tested (e.g., sex, age, country, reporter type…)	factor
	ROR time-trend	**ROR time-trend**	Whether the evolution of the ROR was investigated	boolean (Y/N)
	Coherence	**MedDRA hierarchy**	whether an attempt to consider MedDRA preferred terms redundancy was performed using higher level of the MedDRA hierarchy (i.e.., HLT, HLGT, SOC)	boolean (Y/N)
		SMQ	whether an attempt to consider MedDRA preferred terms redundancy was performed using standardized meddra queries	boolean (Y/N)

		other query	whether an attempt to consider MedDRA preferred terms redundancy was performed using other non-standardized queries	boolean (Y/N)
	Specificity	**positive control**	whether a well-known association between a drug and an event was searched for to test the sensitivity of the disproportionality	boolean (Y/N)
		negative control	whether a well-known lack of association between a drug and an event was searched for to test the specificity of the disproportionality	boolean (Y/N)
	Time to onset	**time to onset**	whether the delay between drug administration and onset of the event was investigated	boolean (Y/N)
	Exclusion of bias	**exclusion of bias**	whether plausible biases were considered and accounted for in the analyses	boolean (Y/N)
		bias type	name of the biases considered	factor
	Biological gradient	**biological gradient**	whether the correlation between specified doses and the event was investigated	boolean (Y/N)
	Reversibility	**reversibility**	whether dechallenge and rechallenge rates were considered	boolean (Y/N)
Study Rationale	**Literature-based**	**Pre-clinical**	whether a study-rationale based on pre-clinical published results was specified in the introduction	boolean (Y/N)
		Case report	whether a study-rationale based on one or more case-reports was specified in the introduction	boolean (Y/N)
		Clinical Trial	whether a study-rationale based on clinical trials was specified in the introduction	boolean (Y/N)
		Observational	whether a study-rationale based on observational published results was specified in the introduction	boolean (Y/N)
		Pharmaco-vigilance	whether a study-rationale based on pharmacovigilance–on spontaneous reporting data– published results was specified in the introduction	boolean (Y/N)

	Methodological	**Methodological**	whether the rationale of the study is methodological (e.g., to test different disproportionality measures)	boolean (Y/N)
	Regulatory	**Regulatory**	whether the rationale of the study is regulatory (e.g., based on notoriety, novelty of the drug, risk management plans or warnings)	boolean (Y/N)
Literature support	**Passive support**	**Preclinical**	whether preclinical studies supporting the signal were considered in the discussion (and not in the introduction as a study rationale)	boolean (Y/N)
		Case-report	whether case-report supporting the signal were considered in the discussion (and not in the introduction as a study rationale)	boolean (Y/N)
		Clinical trials	whether clinical trials supporting the signal were considered in the discussion (and not in the introduction as a study rationale)	boolean (Y/N)
		Observational	whether observational studies supporting the signal were considered in the discussion (and not in the introduction as a study rationale)	boolean (Y/N)
		Pharmacovigilance	whether other pharmacovigilance (disproportionality) studies supporting the signal were considered in the discussion (and not in the introduction as a study rationale)	boolean (Y/N)
		Systematic Review	whether a previously published systematic review supporting the signal was considered in the discussion (and not in the introduction as a study rationale)	boolean (Y/N)
	Active literature elaboration	**Systematic Review**	whether the disproportionality was integrated with an active effort to perform a systematic review on the topic	boolean (Y/N)
New Clinical Data	**Case Report**	**Case Report**	whether the Disproportionality was proposed as an integration of a case-report	boolean (Y/N)
	Case series	**Case series**	whether the Disproportionality was proposed as an integration of a case-series	boolean (Y/N)

	Other observational	**Other observational**	whether the Disproportionality was proposed as an integration of another observational study (e.g., data from a registry)	boolean (Y/N)
Pharmacovigilance-Pharmacodynamic-Pharmacokynetic studies	**Literature support**	**Literature support**	whether the biological plausibility was discussed with data from the literature	boolean (Y/N)
	Pharmacodynamic	**Pharmacodynamic**	whether the Disproportionalities were correlated with a pharmacodynamic index (e.g., occupancy, IC50, pKi), or whether the individual cases were referred to a specific pharmacodynamic mechanism	
	Genetic	**Genetic data**	whether the Disproportionalities were correlated with a genetic index (presence of a mutation), or whether the individual cases were referred to a specific genetic mechanism	
	Pharmacokinetic	**Pharmacokinetic**	whether the Disproportionalities were correlated with a pharmacokinetic index (e.g., lipophilicity, Vd), or whether the individual cases were referred to a specific pharmacokinetic mechanism	boolean (Y/N)
	Index name	**Index name**	Name of the indexes used	Factor
Drug Utilization	**drug utilization**	**drug utilization**	whether the disproportionality was integrated with measures of drug utilization (e.g., number of prescriptions to calculate an estimate of risk)	boolean (Y/N)