Electronic Supplementary Materials 1: Additional information on methods

Title: Signals of adverse drug reactions communicated by pharmacovigilance stakeholders: a scoping review of the global literature

Submitted to Drug Safety by:

Daniele Sartori [1,2]* (daniele.sartori@who-umc.org), Jeffrey K Aronson [2], G Niklas Norén [1], Igho J Onakpoya [2]

1: Uppsala Monitoring Centre, Bredgränd 7B, 753 20, Uppsala, Sweden

2: Centre for Evidence-Based Medicine, Nuffield Department of Primary Care Health Sciences, University of Oxford, Woodstock Road, Oxford, OX2 6GG, United Kingdom

Stakeholders considered

We predefined seven stakeholder categories: (i) regulatory agencies/authorities (including national or regional pharmacovigilance centres and health agencies/ministries); (i) private non-governmental research organizations/foundations; (iii) academic departments/institutions; (iv) private pharmaceutical companies; (v) law firms; (vi) healthcare workers/hospitals; (vii) and patients. When multiple stakeholders co-authored a work, we matched the applicable category to that of the first author. Signals/SDRs from regulatory agencies were considered as authored by the regulatory agency that posted a given communication.

Specifics of VigiBase searches to retrieve reports to calculate the time to communication (TTC)

For each signal/SDRs, we coded medicinal product names (trade names or international non-proprietary names) to WHODrug (format B3/C3, March 2020) a standardized dictionary maintained by UMC. If only classes of medicinal products were used, we resorted to the Anatomical Therapeutic Chemical Classification. Where possible, adverse events were coded to the Medical Dictionary for Regulatory Activities (MedDRA, v. 23.0). DS had undertaken training in MedDRA coding prior to the start of the review. Coding to MedDRA was done at the Low Level Term, using the same MedDRA terms as indicated in studies. Where MedDRA coding required standardized MedDRA queries, we used the scope as indicated in the included studies; where no scope was specified, we defaulted to 'broad'. If studies used other terminologies than MedDRA (e.g.: COSTART, ICD, WHOART, READ codes etc.), we used the most applicable MedDRA term(s).

Using standardized drug and event names, we queried a frozen, deduplicated (see Norén, G.N., Orre, R., Bate, A. et al. Duplicate detection in adverse drug reaction surveillance. Data Min Knowl Disc 14, 305–328 (2007). https://doi.org/10.1007/s10618-006-0052-8), version of VigiBase (data lock point: 30/08/2020) for reports in which the medicinal product of each of the signals/SDRs was entered in VigiBase as 'suspected' or 'interacting'. 'Foreign reports' (i.e. reports sent to a country's national database from abroad) were excluded.

Notes and details on the calculation of the TTC

For each standardized drug-event or drug-drug event combination, we selected the 'first report' of ADR based on the earliest of two dates, entered in the E2B(R2) fields FirstDateDatabase (minimum values) or ReceiveDate (minimum values); the first, assigned by UMC, represents the first date in which a report of ADR was entered in VigiBase and is necessarily complete. The latter is the first date in which a report of ADR is received by a regional/national pharmacovigilance centre. By subtracting from the year of communication of a signal that of the first report in VigiBase, we calculated the TTC. This approach was similar to that of a previously published set of systematic reviews on withdrawals of marketing authorizations, but relied on unpublished, instead of peer-reviewed, reports of ADR.

The calculation of TTC could give rise to four scenarios: 1) TTC > 0 or 2) TTC = 0 or 3) TTC < 0 or 4) no TTC value. The first two indicate that reports in VigiBase for a given signal/SDR are available. The third suggests that while there are reports in VigiBase, they may have been entered in the database only after the year of communication of a signal. The last one suggests that there are no reports in VigiBase for a given medicinal product and event, as coded by DS.

Protocol amendments

Original protocol	**Amendment**	**Date of amendment**	**Affected aspect of study design**
Any SDR, or observational/interventional studies reporting findings described as “signal” to be considered eligible	Any SDR or observational/interventional studies reporting findings described as “signal” were eligible, provided they concerned previously undocumented SDRs	10/2020	Eligibility criteria
SDRs without a clear threshold for detection to be considered ineligible	Original authors were contacted to retrieve SDRs without a clear threshold for detection. SDRs for which we did not obtain a response were included in a separate analysis.	11/2020	Eligibility criteria
Systematic Reviews Data Repository (SRDR) to be used for data charting	Microsoft Excel used for data charting. All data in SRDR were migrated.	10/2020	Data charting
Pre-defined codebook (adapted iteratively) to code features of reports of ADRs	Codebook retained, but the codes were further grouped to the Bradford Hill viewpoints	02/2022	Data analysis
The date in which a report of ADR was entered in VigiBase, that of receipt at the national/regional pharmacovigilance centre and that of occurrence of ADR, whichever the lowest, to be used to calculate the time to signal (TTS)	Omission of the date of occurrence of ADR from the calculation of TTC.	03/2022	Data analysis

Use of OCEBM as tool to assign levels of evidence	OCEBM retained, however, sublevels were postulated	03/2022	Data analysis

Table 1. List of protocol amendments. SDR = signal of disproportionate reporting. ADR = adverse drug reaction

Rationales for amendments

Amendment to include only previously undocumented ADRs and criteria used to define them

We noted that several publications could have overestimated the median TTC. Our original protocol committed us to consider eligible any SDR, including, for example, those detected as part of methods development or evaluation – which are usually well-known – or the ones used as positive controls. As such, these SDRs may involve ADRs that were reported well before detection. We narrowed our eligibility criteria to publications concerning signals/SDRs of previously undocumented ADRs, as described in our Methods section.

Amendment to include SDRs without clear threshold for detection

During full texts review, we considered that omitting records without clear threshold for detection of SDRs could go against the purpose of a scoping review (i.e.: to comprehensively map the body of literature of a given topic). To ensure comprehensiveness then, we contacted original authors to clarify any unreported threshold. We requested additional information on the threshold of detection of SDRs for 48 records. We received clarification in 19 cases and no replies in the rest (in one we could not find the corresponding author's email).

Change of reference dates of reports of ADRs

Our published protocol prespecified a third date to calculate the TTC, that of onset of an ADR. Initial TTC calculations using this date were, for some cases, implausible, as the TTC values exceeded the time on market of some medicinal products – at times several year prior to phase I trials of a given medicinal product. To minimize such occurrences, we required reports to have valid (DD/MM/YYYY) dates of drug administration and ADR occurrence. Even with such constraints, we observed erroneous dates. Manual review of the reports leading to implausible TTC revealed possible reporting errors (e.g.: valid dates of administration preceding marketing date by a decade, such as a year reported as 2001 instead of 2010). Since we could not correct for these, we decided, conservatively, to use only the two dates described above as reference.

Change of charting form

As the review progressed, we recognised that the Systematic Review Data Repository (SRDR) was not expedient for charting SDRs. SRDR required outcomes to be prespecified for each record, which was time-consuming for SDRs that included dozens of outcomes of interest. Some aspects of disproportionality analysis could not be easily charted, such as changes to the 'background' (or 'denominator') used for comparison, which only applied to subsets of detected SDRs. Finally, standardization of drug names and ADRs was feasible in free-text fields, however, after export from SRDR (as csv files) all free-text data were entered in one structured field – requiring additional work. As such, we needed a data charting form that could adapt iteratively, so in 10/2020 we migrated the data on to a customised Excel sheet.

OCEBM and sublevels

When studies had no corresponding entry in the OCEBM tool, we created OCEBM sub-levels where possible. These applied to disproportionality analyses, meta-analyses whose included studies did not pre-specify the outcomes of interest, pooled randomized and non-randomized clinical trials (RCTs and non-RCTs), or studies with unclear randomization. We used the levels in the OCEBM tool and qualified them with symbols ("*", "#" etc.), as illustrated in the main text of this work (See table 2, footnotes). We deemed these changed necessary to provide a more granular overview of the evidence underpinning signals.

Coding of features of ADRs and grouping to Bradford Hill guidelines

We began coding according to a pre-defined codebook, which included the following entries: positive dechallenge, positive rechallenge, time to onset, dose-response relationship, site-specificity and population-specificity of ADR.

We considered grouping the codes of our codebook to the Bradford-Hill guidelines, given their almost universal recognition in pharmacovigilance. We iteratively added new entries to the codebook, as needed. These included "exclusion of competing causes", "sole suspected drug", "case ascertainment", "consistency", "coherence", "reported causality", "reporter type". We further merged site and population specificity into "specificity".

Coding of features of reports of ADRs

To provide descriptive statistics we grouped codes by Bradford Hill viewpoint. This was not always feasible, as reviewers could use features of reports that were not part of the original Bradford Hill's list.

Two of Bradford Hill's viewpoints, 'strength of association' and 'biological plausibility', were not considered. Within reports of ADRs, strength of association may be interpreted both as the values of disproportionality emerging from statistical screening of databases of reports of ADRs, or as the results of observational studies that aim at quantifying a risk of harm in a population following drug administration. We chose to omit the first, as the original paper by Bradford Hill focused on (dramatic) measures of risk, or measures with a denominator – as opposed to measures of disproportionality, which lack one. The second viewpoint was omitted in order to limit category errors, consistent with the decision to avoid using OCEBM level 5 (mechanistic evidence).

Below, we provide descriptions for each code and provide the Bradford Hill viewpoint we assigned.

Table 2. Codebook for the features of reports of ADRs and the Bradford Hill viewpoint we assigned to each.

Code	Description	Bradford Hill viewpoint
Positive dechallenge	Discontinuation of treatment, with subsequent event abatement.	Experimental evidence

Positive rechallenge	Reintroduction of treatment and reoccurrence of an event after positive dechallenge.	Experimental evidence
Time to onset	Time interval between the administration of a suspected medicinal product and the occurrence of an event, compatible with a drug-induced event.	Temporality
Dose-response relationship	Increases in seriousness/severity of an ADR, within the same patient or across a series of patients, together with increases in dose of the suspected medicinal product.	Biological gradient
Sole suspected drug	The medicinal product of interest is the only one available as 'suspected' in a report of ADR.	-
Exclusion of competing causes	Reports of ADRs contain sufficient evidence to rule out possible competing hypotheses – other than the suspected medicinal product – as causal agents. Such evidence may take the form of clinical narratives detailing differential diagnoses.	-
Case ascertainment	Reports of ADRs contain sufficient evidence to rule out possible miscoding of ADR terms, or misdiagnoses. In other words, the evidence suggests that the ADR terms match the clinical condition as it was reported. Such evidence may take the form of laboratory analyses or imaging procedures.	-
Consistency	Within a series of reports of ADR (i.e.: distinct, anecdotal within the same country, or across multiple countries) concerning the same drug and adverse event, there are similarities across e.g.: patient demographics, underlying disorders, concomitant drugs, co-reported ADRs, clinical course of course disease or event; more broadly, consistency refers to repeated observations of the same event in different patients, locations or times.	Consistency
Reported causality	Outcomes or values of internationally recognized, local or algorithmic probability scales (e.g. Naranjo, Karch-Lasagna etc.), as reported.	-

Reporter type	The professional or social background of a reporter, as pre-specified by reporting formats (e.g.: healthcare professional, patient, lawyer, journalist).	-
Coherence	The evidence available in the reports of ADRs is in keeping with the best available evidence on a given ADR.	Coherence