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

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**SUBJECT AREAS**
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**KEYWORDS**
Signal, adverse event, adverse drug reaction, ADR, scoping review, protocol, signal detection, pharmacovigilance
Abstract

**Background:** Signals of adverse drug reactions are the basis of some regulatory risk-minimization actions in pharmacovigilance, such as changes to the section of undesirable effects in Summaries of Products Characteristics (SmPCs). Reviews of the evidence of signals have highlighted that these are mostly supported by reports of adverse drug reactions or multiple types of evidence, but have so far been limited to specific medicinal products, time intervals, groups of adverse drug reactions and specific countries. The time that elapses between a report of a suspected adverse drug reaction and the communication of a signal has not been systematically investigated. Furthermore, difficulties in causally linking medicinal products to adverse events have been highlighted, but the elements of reports of suspected ADRs that authors used to support putative causal relationships have been rarely characterized.

**Methods:** We plan a scoping review to chart the evidence underpinning signals in pharmacovigilance and the time that it takes to communicate a signal. We shall retrieve records from electronic databases, without language or publication restrictions; we shall apply backward and forward citation to adjust for variations in database indexing. We shall also hand-search the websites of 35 regulatory agencies/authorities, restricted publications from Uppsala Monitoring Centre, and drug bulletins in the list of International Society of Drug Bulletins. If websites do not report signals, signals will be requested from the competent stakeholder. We shall use the Oxford Centre for Evidence-Based Medicine Levels of Evidence to chart and summarize evidence. We shall use VigiBase, the World Health Organization’s Global Individual Case Safety Report database, to determine the date of reporting for reports of adverse drug reactions. Plots, or pictograms (if appropriate), will be used to represent the time from the first report of a suspected adverse drug reaction to a signal.

**Discussion:** We expect that the findings from this exploratory investigation will be useful in better understanding global patterns of similarities or differences in regulatory decision-making in terms of evidence and timing of communications, and in identifying relevant research questions for future systematic reviews.

**Scoping review registration:** osf.io/jtv38
Background
A systematic review of definitions, later adopted by the Council for International Organizations of Medical Sciences, defined signal as “information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, which would command regulatory, societal or clinical attention, and is judged to be of sufficient likelihood to justify verificatory and, when necessary, remedial actions” [1, 2]. Based on this definition, a signal can be supported by diverse levels of evidence, ranging from one or more reports of suspected adverse drug reactions (ADRs) to observational studies and randomized clinical trials [3–5]. On the other hand, signals of disproportionate reporting, a subtype of signal [1], can be highlighted solely by statistical associations resulting from ratios of observed versus expected numbers of reports (i.e. disproportionality) [6]. Different stakeholders can detect signals – including regulatory agencies, academia, independent research organizations, or patients and their health carers – and avail themselves of several channels to disseminate them, such as peer-reviewed articles, abstracts, drug bulletins, websites, and restricted publications. Minutes of meetings of committees can also document discussions relating to signals [7]. Comparative assessments of signals discussed at the Pharmacovigilance Risk Assessment Committee have suggested that reports of ADRs often supported signals, but that support from multiple sources of evidence increased the likelihood of a regulatory action (e.g. changes to Summaries of Product Characteristics) [8, 9]. Similar investigations carried out in the USA have highlighted the same finding [10]. Regulatory actions, however, appear to be inconsistent across international settings; discrepancies in communications of the same risks of drug-induced harms in healthcare systems have been recorded, and it has been suggested that they may be better understood by characterizing the strength of the underpinning evidence [11, 12].

An important component of detection of signals of ADRs is clinical judgment of the data. The Bradford-Hill viewpoints or guidelines [13] and other structured methods of causality assessment [14] have typically guided clinical judgments in pharmacovigilance, but their intrinsic subjectivity has
yielded low interrater agreement across independent assessors [15]. Though some methods have higher interrater agreement than others, there appears to be no consensus on which ought to be the gold standard [16]; consequently, regulators’ clinical judgments on features of reports of ADRs have occasionally been criticized by healthcare workers or their professional associations [17–20]. It has been reported that the difficulties in assessing causality result in delays in the withdrawal of medicinal products from the market when fatal adverse events are attributed to their use [21]. Furthermore, the time intervals before signals of ADRs and follow-up with regulatory actions are determined by availability of information about the ADRs at medicinal product launch; in fact, these intervals were shorter when ADRs were present in a sample of the Food and Drug Administration’s ‘drug label’ at launch (e.g. severe liver injury with telithromycin or suicidal behaviour with varenicline), but longer when ADRs were absent [22]. Other accounts report that it may take 2–12 years for drug-induced harms to be communicated to healthcare workers after marketing authorization of a medicinal product [23–26]. These studies have computed the difference between dates of communication of signals and launch dates to measure the time-to-signal, while databases of reports of ADRs, such as VigiBase, the World Health Organization’s (WHO’s) global individual case safety reports database, could estimate this interval and account for unpublished records. Ultimately, signals are spread across a gamut of channels of dissemination and may be supported by one or more levels of evidence, or solely by statistical associations. Investigations supporting evidence and delays in the time-to-signal have been limited to specific countries, time intervals, medicinal products or adverse effects. The types of subjective judgments that are applied to features of reports of ADRs to detect signals also remain scarcely characterized. Given these premises, systematic investigations are warranted.

Methods/design

The questions this review will address are: 1) What levels of evidence support signals of adverse drug reactions communicated by drug regulatory authorities or other pharmacovigilance stakeholders? 2) What are the similarities and differences between the levels of evidence supporting signals from different stakeholders? 3) Have the levels of evidence changed over time? 4) What is the interval
between a signal and the first report of the corresponding suspected adverse drug reaction? 5) Has this interval shortened or increased over the years? 6) In the case of signals supported by reports of adverse drug reactions, what elements of the reports have led authors to signal suspected drug-related harms?

The aims of this scoping review are: (a) to provide an evidence synthesis for decision-making at a regulatory level; (b) to collate signals currently in different platforms; (c) to produce an overview of the types and levels of evidence of studies supporting signals; (d) to highlight any differences or similarities in assessment of the evidence used to support signals, with a particular focus on reports of ADRs; (e) to better understand the delays before signals are detected and to clarify whether they have changed over time.

Pharmacovigilance, as defined by the European Union directive 2001/83/EC [27]; regulation 2004/726/EC [28]; Good Vigilance Practices – Module IX [7]; International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use efficacy guidelines E2A to E2F [29], will serve as references to contextualize pharmacovigilance in a global landscape.

**Searches**

We shall search MEDLINE (via PubMed, 1946 - present), EMBASE (1974 - present), PsycINFO (1806 - present), Web of Science (indexes SCI-EXPANDED, CPCI-S, 1945 - present) for signals published by organizations involved in pharmacovigilance and/or independent research groups (e.g. regional pharmacovigilance centres or academia), and pharmaceutical companies. We shall use Web of Science to perform backward and forward citation screenings; if we are unable to use Web of Science, we shall use Google Scholar.

We shall search the English language websites of regulatory authorities or organizations involved in the WHO Programme for International Drug Monitoring through the websites’ search engines, to identify communicated signals and among minutes of meetings, expanding the list of countries compiled by Onakpoya et al. [21] where possible. If signals are not publicly available in a country, we shall forward requests to the competent authority. If the evidence used to support available signals is not publicly available, we shall issue freedom of information requests (where regulated) for
Assessment Reports or equivalent documents.

We shall hand-search the Uppsala Monitoring Centre’s SIGNAL Document, the WHO Pharmaceuticals Newsletter, the Full List of WHO Medical Product Alerts, the WHO Drug Information, Australian Prescriber, Prescrire International, and other drug bulletins available in English via the International Society of Drug Bulletins’ index for relevant records.

We shall query Google Scholar in incognito browser tabs. We shall evaluate the results as long as two consecutive pages of results yield at least one useful article.

We shall also search OpenGrey and GreyNet International.

We shall use VigiBase [30], to obtain additional information on the year in which suspected ADRs were first reported.

The data lock point for the retrieval of all records is 6 August 2019.

Additional file 1 – Search strategy details the complete search strategy for electronic databases (adapted to PubMed) and for grey literature.

**Inclusion Criteria**

Peer-reviewed papers and government or agency reports and working papers concerning one or more medicinal products for human use [31] and one or more adverse events, effects, or reactions [32] that are statistically associated by disproportionality analysis [33-35], or

(a) with the primary aim of detecting, assessing, or reviewing one or more signals, as defined by [1];
(b) that explicitly mention the successful detection of a signal or whose results constitute a signal;
(c) that have been indexed or discussed as signals, e.g. in tables of contents or minutes of meetings.

Documents in languages other than English will be included if the review team can translate them into English. Requests for translations will be issued to the publishing stakeholder if the review team cannot translate.

**Exclusion Criteria**

(a) Abstracts or papers for which the full text is unavailable.
(b) Documents that claim that the evidence does not support a signal or that no signal was detected.
(c) Signals that are communicated in the same or similar form or substance more than once by the
same stakeholder (only the first signal in chronological order will be considered, if no new information appears in subsequent reports).

(d) Non-English documents and websites for which a translation is unavailable.

**Primary Outcome(s)**

Evidence level assessment and comparison of evidence sources used to support signals.

**Secondary Outcome(s)**

Elements of reports of suspected ADRs that authors used to support putative causal relationships between drugs and adverse reactions in signals.

**Data retrieval**

All retrieved records will be imported into EndNote™ X8.2. We shall deduplicate records manually, based on list of authors, titles, abstracts, journal, paging.

Two reviewers will independently search the titles and abstracts to determine eligibility. Any disagreements will be resolved through discussion. If a consensus cannot be reached, a third reviewer will arbitrate.

**Data extraction, selection, and coding**

We shall extract data from eligible studies and documents with the aid of forms provided online by the Systematic Review Data Repository and adapted to scoping reviews. Studies will be screened by title and abstract, and then by full text, against the inclusion and exclusion criteria. Data to be extracted are: publication year, type of evidence used to support signals, definition of signal used in a study or signal communication, year of the case report of the suspected ADR that was first transmitted to VigiBase and that relates to the same medicinal product and ADR in a considered signal, country of origin/communication of a signal, stakeholder, design, eligibility criteria, population involved, setting, brandname of the medicinal product (where available), corresponding active pharmaceutical ingredient(s), formulation, considered ADR(s), and possible confounding factors.

Medicinal products will be coded to substance level, using the WHO Drug Dictionaries (latest version available at the start of the review), and adverse events at the Low-Level Term level of the hierarchy in the Medical Dictionary for Regulatory Activities® (MedDRA) (latest version available at the start of
the review), where possible (e.g. signals of increased mortality or serious adverse events cannot be
coded to MedDRA).

One reviewer will independently extract and code the data, and a second will independently cross
validate the findings. Any disagreements will be resolved through consensus. If no consensus is
reached a third reviewer will arbitrate.

**Stakeholder(s)**

We consider “stakeholders” to be healthcare practitioners and patients, national and international
regulatory agencies or authorities, national and regional pharmacovigilance centres, non-
governmental organizations, research institutions, and academia.

**Calculation of the time-to-signal**

The date on which an ADR occurred, as stated in reports of ADRs entered in VigiBase will be used to
calculate the time-to-signal, by accounting for the date on which the signal relating to the same
combination of medicinal product and adverse effect was communicated. If the date of occurrence of
the ADR is unavailable, we shall use the first date in which the report was entered in VigiBase instead.

**Strategy for data synthesis and dissemination of results**

We shall summarize findings narratively by level of evidence (documented using the Oxford Centre
for Evidence-Based Medicine levels of evidence); stakeholder; signal subtypes (e.g. signals of
disproportionate reporting).

Descriptive statistics, where appropriate, will accompany summaries of findings, and be applied to
quantify the proportions of elements in spontaneous case reports associated with signals.

We shall also present the time-to-signal, and changes in evidence sources over time and across
stakeholders, in timeline plots and pictures (if appropriate).

We shall report this scoping review according to the Preferred Reporting Items for Systematic Reviews
and Meta-Analyses (PRISMA) extension for Scoping Reviews [36].

**Discussion**

To the best of the authors’ knowledge, this would be the first study to systematically chart the
evidence in support of signals and draw international comparisons of its levels using a standardized
framework. The time from the first report of an ADR to the communication of a related signal will also be quantified and compared across different healthcare settings, accounting for unpublished reports of ADRs available in VigiBase – the largest database of this kind.

The accepted pharmacovigilance definition of “signal” is nowadays used in a broader context than its early formulation from the mid-60s. That merely alluded to rates of reporting of adverse effects across different groups of patients that would exceed a predefined threshold and, in turn, “be made a signal to the computer to invoke a secondary program” to produce a desired output [37] (our emphasis). Since its inception, the definition has been applied inconsistently or ambiguously [38]; moreover, there are no guidelines for reporting signals in publications, which complicates the retrieval of relevant publications. As such, the assistance of a medical librarian became indispensable in the design and adaptation to selected databases in search strategies, which were iteratively developed in line with published literature on search strategies for adverse effects [39, 40] to increase the relevance of the records retrieved. It is, however, beyond the scope of this review to evaluate the trade-off of specificity and sensitivity of the search strategy. The retrieval of data from electronic databases has revealed over 8600 unique publications, including abstracts and publications, without language restrictions. This number is likely to increase when the grey literature has been fully retrieved. Without prespecified constraints on adverse effects, medicinal products, or study designs, the retrieved dataset is bound to display heterogeneity of methods and endpoints. At early stages of this review we anticipated a large number of records, with varying methods and endpoints; so, we opted for a narrative-driven data synthesis (charting).

A challenge in this study has been to identify appropriate inclusion criteria; in principle, the presence or absence of a signal could be judged for each retrieved study – notwithstanding their numbers. However, in light of the breadth of levels of evidence that support signals, such judgments would have to be extended to the whole of the published and unpublished scientific literature, to preserve logical consistency. Given the added subjectivity introduced in this process, we saw fit to ground eligibility criteria on the explicit mention of successful detection of a signal or on the use of methods unequivocally applied in signal detection (disproportionality analysis). Similarly, the decision to
contact regulatory agencies to retrieve unavailable signals reflects the position that there are
different channels of communications (such as direct healthcare communications or notices posted on
agency websites) for signals [8] and that inaccurate expressions have been used to refer to them
[38]. Previous characterizations of the evidence underpinning “initial safety signals” [41] have
cocussed, for example, solely on Drug Safety Communications published by the US Food and Drug
Administration [42]. These postings concern “important drug safety issue(s)” with “potential to alter
the benefit-risk analysis for a drug in such a way as to affect decisions about prescribing or taking the
drug” [43]. The agency’s website, however, also lists “potential signals of serious risks” [44], that is
cocerns “about an excess of adverse events compared to what would be expected to be associated
with a product’s use” [45]. This indicates that resorting to a pre-established set of webpages may
result in omission of relevant records and may misrepresent the activities of those regulatory
agencies who refer to “signal” using different expressions.

Abbreviations
ADR(s): Adverse drug reaction(s)
MedDRA: Medical Dictionary for Regulatory Activities®
WHO: World Health Organization

Declarations
Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Availability of data and materials
The data extraction form with the extracted data will be made public via osf.io. The full URL will be
made available once the scoping review is published. Data used to calculate the time-to-signal will
also be made available, since it will be included in the extraction form; the dates of onset of an ADR,
or dates of reporting to VigiBase, will be available on request to the corresponding author.

Competing interests
JKA has written papers on adverse drug reactions in peer-reviewed journals and has received royalties
from textbooks that he has edited or co-edited; he has often acted as an expert witness in cases
involving adverse drug reactions, including opioids, most often in Coroners’ courts. DS has authored signals published on drug bulletins, as abstracts or posters and received funding for doctoral studies from Uppsala Monitoring Centre. Part of the material expected to be reviewed has been published in peer-reviewed journals, drug bulletins and abstracts or posters by other researchers presently or formerly belonging to this foundation. IJO has no competing interests

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**Authors’ contributions**

DS designed the study, with input from IJO and JKA.

NR substantially aided DS in the design of the search strategy and its adaptation to multiple databases.

This manuscript was written by DS, IJO, and JKA.

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IJO is an MD, with an MSc and DPhil in Evidence-Based Health Care from the University of Oxford, Oxford, UK.

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