WP5 - Literature review on signal management

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1. Background and rationale of literature review

There are many published articles addressing various scientific aspects of signal management which could provide additional information to further enrich and support the development of guidance for signal management as foreseen in SCOPE Work package 5 on signal management. The main aim of this review was to identify those publications with potential useful tools and ideas relevant in the European regulatory setting, especially at a national level.

The aim was to highlight in particular those publications that serve to further develop a Best Practice Guidance (BPG) as an outcome of the signal management work package and to provide further scientific context to our work. This review is a tailored review with special attention to the practical regulatory applicability. Therefore this review does not provide a meta-analysis or a comprehensive review of all literature in this area.

In addition to the legal requirements and guidance, Especially the CIOMS Working Group, Practical aspects of signal detection in pharmacovigilance (1) remains a cornerstone document and is addressing multiple topics, many of them still current and relevant. We will not describe this extensive document here, but we have undoubtedly taken into consideration through this project.

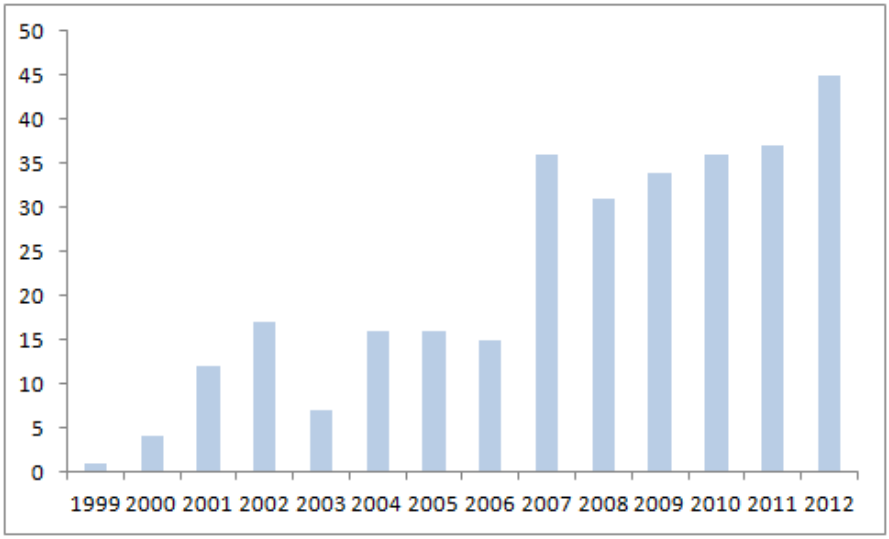
Other thorough background overviews of the area have previously been published (2–4) and the intention is not to repeat the work but to further build on the already constructed knowledge base. This document is meant only as primary guidance. For a more detailed discussion of each topic the interested reader should refer to the relevant referenced publications.

2. Methodology of literature search

A literature search to identify publications in English, detailing signal management methodologies was performed without time constraints. The majority of the papers reviewed were published in the last 15 years.

Search algorithm (Medline Ovid):”Product Surveillance, Postmarketing"[Mesh] AND signal[tiab].

Fig. 1 Articles distribution over time in Medline*



**Years 2013 and 2014 are missing due to delay in indexing articles*

After running the above mentioned query, 363 publications were retrieved from the database and after first selection a total of 64 articles were considered for inclusion. References cited in the papers retrieved were used to locate further articles and the collection was also supplemented with publications suggested by pharmacovigilance experts participating in SCOPE and with some other results from more specific searches in relation to particular topics (see Annex 1-Additional specific queries).

Finally, a total of 78 papers were included in the review (see Table 1). Research which was conducted in a regulatory environment, using data and/or tools from national competent authorities are marked with an * in the bibliography.

Table 1 Number of citations included in the review

Topics	Number of relevant citations retained from the initial search	Citations added after references checks, suggestions from reviewers or other specific searches
Topic 1-Signal detection	42	4
Topic 2 and 3- Signal validation, prioritization and assessment	18	5
Topic 4- Reports of special interest	4	5

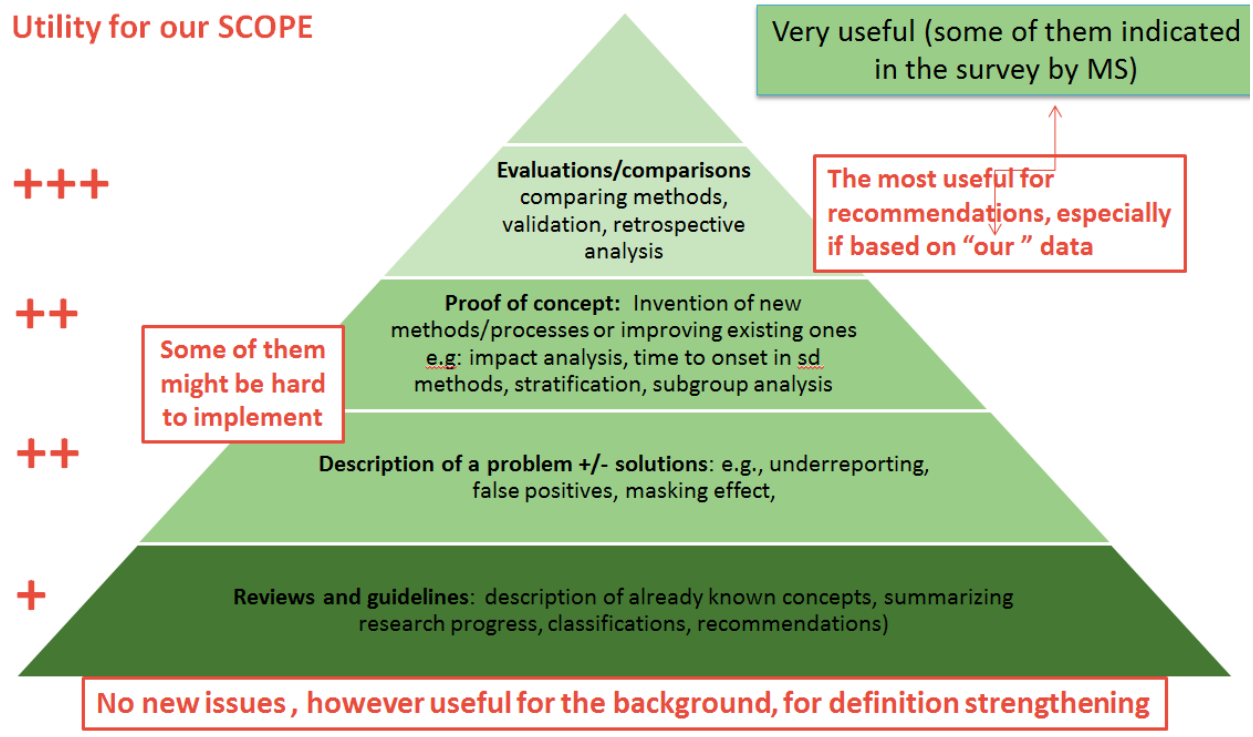
3. Classification of articles and summary of findings

Selected articles were classified according to their main theme and the utility for the objective and focus (see **Fig. 2**) of SCOPE Work package 5. The most relevant literature findings are discussed below.

A non-even distribution across subtopics was observed with a majority (62%) of articles referring to signal detection, some (28%) to signal validation, prioritization and assessment and a minority (10%) covering reports of special interest.

Signal validation, prioritization and assessment were reviewed together as these terms are sometimes defined and used differently by scientific community compared to the way they are described in the EU legislation and the regulatory guidance. The difference between validation and assessment sometimes is perceived as artificial and mainly for administrative purposes.

Fig.2 Classification of relevant articles according to the main topic and utility in the context of the SCOPE project



3.1 Signal detection topic

After selection, we found 46 articles articles relevant for signal detection. The available studies mainly addressed the following ideas:

- **Publications comparing various statistical methods**

Many studies aimed to compare various statistical detection methods in order to decide which one has the best performance. In general, consensus is reached that there are no significant differences between Bayesian and frequentist approaches and that it is possible to achieve comparable performance with any method, particularly if they are being used as binary classifiers. Instead, the way methods are implemented in a specific database and decisions around that seem to be more important than the method itself, therefore a method should be chosen based on both convenience and ease of implementation. This finding was also supported by recent research within PROTECT project (5).

With regards to time to detection, the identified information is contradictory, some researchers (6) found that quantitative methods tested (PRR, GPS, URN) are slower compared to traditional (qualitative manual) screening, with PRR having the shortest time lag ~1.5 months (and also non-significant) while Alvarez et al (7) found a mean time gain for PRR compared to qualitative review of 2.5 years.

In the scientific community there is an agreement that disproportionality methods alone are not sufficient to detect all safety issues and in order to detect as many safety signals as possible a combination of the quantitative and qualitative methods is preferable.

- **Publications on limitations and challenges of the currently used methods**

Articles in this category highlight one or several challenges or limitations of currently employed signal detection methods and either described them or tried to estimate their impact while sometimes also offer solutions for improvement.

Challenges in using the disproportionality methods for signal detection as listed in the literature, are briefly mentioned below:

- The burden of false positives signals: The majority of signals represent noise, because the reported ADR terms are often associated with the treatment indications, co-morbidities, protopathic bias, channeling bias and other artifacts or are already labeled (4). Methods generating many false positives increase the workload.
- False positive signals induced by co-prescriptions: when a signal with a drug frequently co-prescribed with a second drug known to cause a specific ADR is falsely detected as a signal for that drug. Avillach et al (8) present an automated method to decrease the number of false-positive signals generated by co-prescription of drugs known to be associated with a particular event.
- False negatives: Absence of disproportionality in spite of a true association between a drug and an ADR can cause a false negative result.
- Lack of exposure information: Due to lack of exposure information, risk ratios of specific events cannot be computed. Reporting rates vary as function of notoriety, surveillance and market size effect and they are not always a reliable estimate.
- Competition bias/masking: drug-event combinations with a high case count can potentially lead to that a new drug that causes this event may not stand out quantitatively is masked (9). For example because rhabdomyolysis is very frequently reported in association with statins, if

another drug is also reported in relation to it, the number of reports needs to be very high in order for that signal to stand out.

- Problems associated with multiple testing (statistical noise): an inherent problem in screening a large number of associations is that multiple tests are performed and increase the chance of false positive findings (10).
- Under-reporting: low reporting rate (and absence of disproportionality of reporting) does not guarantee absence of a causal relationship between a drug and an event.
- Media bias: Is considered that increased media attention can lead to false positive signals. On the other hand, it can also have beneficial effects as stimulating the reporting by creating awareness. High media attention also affects prioritization (11).

- **Articles on fine tuning: adjusting the methods and implementation decisions**

Articles in this category provide information on adjusting the current methods in order to improve performance. Various approaches are available: choice of threshold and precision estimate, decision to look only at suspect drugs or all drugs, count based on cases or combinations, exclusions of some well-known strong associations, the level of aggregation at which the data mining is performed, filtering and prioritization in an early phase, including some more variables in the calculation of the statistical score etc.

Grundmark et al (12) explored a way of improving signal detection by standardizing the background data, namely restricting to a certain therapeutic group. Albeit just a pilot study at the moment, this approach showed promising results and would be rather easy to implement in the current systems.

A few articles (13,14) tried to investigate the impact of terminology grouping on signal generation. The results showed that mining at higher levels of the hierarchy (as HLTs or SMQs) do not seem to improve signal detection but rather small groups of effective synonyms in the MedDRA PT level should be combined. This latter approach can improve signal detection performance (14).

While thresholds have been proposed for disproportionality methods, these are dataset-specific and have been chosen on the basis of empirical testing and pre-defined range of sensitivity and specificity, which can be highly database-dependent, therefore universally valid thresholds or other implementation decisions are impossible to recommend (5).

- **Publications on other sources of signals and novel mining methods**

Some recent studies use data from multiple sources (e.g., literature, electronic healthcare records, prescription event monitoring systems, structure–activity relationship) in order to enrich current systems in use. A new range of methods are being developed and investigated which may potentially supplement the traditional methods, for searching in these non-traditional data sources. These are all still in very early phase of development and are currently not routinely implemented in most of the organizations.

A review of novel data mining approaches for signal detection, including sources as: biomedical literature, chemical and biological information sources, and patient-generated data in health related web forums was performed by Harpaz et al (15). Newer approaches often aim the facilitation of identification of multivariate associations representing complex safety phenomena such as drug-drug interactions, syndromic events, or class effects.

Utilization of electronic health care records for drug safety signal detection has been explored recently by several groups (16–18).

In addition, some researchers focus on automatic text mining or literature searches (19) or on molecular structure similarity (19) to improve signal screening.

Data mining of social media data is also under investigation with regards to its potential for safety surveillance (20,21).

3.2 Signal validation, prioritization and assessment

Twenty three articles referred to signal validation, prioritization and assessment.

Decisions related to signal validation are usually complex and involve some degree of subjectivity, as they are based on a combination of qualitative clinical, epidemiological, pharmacological and regulatory criteria without much possibility of quantitative comparisons. The challenge is to identify which signals are likely to be true new signals, medically important and warrant priority for further investigation. Apart from the already mentioned CIOMS VIII report (1), there are no specific regulations, guidelines or standards that provide an objective basis for these decisions, however a pattern of variables which are most commonly taken into consideration in this decision making process can be deduced from the publications.

Signal prioritization

The identified publications attempt to construct frameworks for signal prioritization and validation and to support decision making in this area. However there still seems to be a lack of research in this topic.

Different tools to prioritize signals are mentioned the literature:

- FDA drafted a guidance in March 2012 about prioritization. Although it has not been definitively accepted or published as far as we know, it addresses factors to be used to prioritize a newly identified safety signal. It is recommended to estimate the hazard posed by a safety issue based on three variables: (1) the relative seriousness of the issue; (2) the estimated size of the population exposed to the risk of the drug; and (3) the suspected frequency of harm to patients exposed to the drug. The combination of factors 2 and 3 provides an estimate of population risk; the combination of factors 1 and 3 provides an estimate of personal risk to the patient.
- Signal impact analysis is another method to prioritize signals and was described by Waller et al (22). This method take into account the strength of evidence and potential public health impact

and constructing four priority scales. The components of strength of evidence are: PRR score, strength/weaknesses of case reports (overall quality) and biological plausibility. The components of public health scores: the number of cases, the seriousness of the reaction and the reporting rate. Public health score might underestimate its importance when the issue is relevant only to a subset of the population. This tool was also validated in a regulatory setting.

- A Regulatory Pharmacovigilance Prioritization System (RPPS) described by Seabroke et al added two dimensions to the previously used signal impact analysis tool: agency regulatory obligations and public perceptions. The RPPS tool was aimed to be used in signal management.
- A multi criteria decision analysis (MCDA) framework is a comparable approach developed by Levitan et al (23), the difference being that it has been developed in a Marketing Authorisation Holder setting.
- A triage logic was developed by Stahl et al. (24). It is an algorithm for filtering associations taking into account positive rechallenge, rapid reporting increase, new drugs, serious reactions, multinational reporting, while focusing on DMEs.
- VigiRank (25) is a data-driven screening algorithm for emerging drug safety signals that accounts for report quality and content. The variables considered for inclusion capture different aspects of strength of evidence, including quality and clinical content of individual reports, as well as trends in time and geographic spread.

Another type of prioritization, event based prioritization is mainly based on the lists of events of special interest, selected according to pre-defined criteria (e.g., designated medical event (DME) and important medical events (IME) lists. Hochberg et al. (6) hypothesize based on their results that the potential value of data mining as an adjunct to qualitative methods is higher when only serious ADRs classified as DME are considered. Alvarez et al. (7) also mention that the IME list could fulfill a role in reducing the overall workload of signal detection without missing important clinical signals.

Harpaz et al. (26) tried to combine signals from spontaneous reports and electronic health records for improving the positive predictive value of signal detection methods and therefore helping in prioritizing a list of ranked signals.

Last but not least, Coloma et al (27) published an interesting prioritization exercise, albeit in electronic healthcare records, considering public health importance, novelty and biologic plausibility and with the aid of a semi-automatic tool.

Signal validation and assessment

The processes of signal validation and assessment are often referred as signal evaluation, signal investigation or signal analysis, illustrating that the terminology used in the published literature is very diverse. The most thorough description of this step in the published literature is mainly found in international guidelines and reports such as EMA and FDA guidelines and CIOMS reports. Other published literature that could be relevant in a regulatory setting as well as research in this area is sparse. It is a relevant area for more research.

A publication from Segec et al(28) about Strategy in Regulatory Decision Making for Management of Progressive Multifocal Leukoencephalopathy (PML) (28)(Segec et al., 2015)is a good example of high level knowledge sharing within the EU-network. A tool for regulatory decision for management of PML was developed and piloted, and authors found, that the methodology developed for PML was a rational approach to consider available evidence and could improve regulatory decision making. Others are encouraged to use and modify this methodology on other particular topics.

3.3 Reports of special interest

Nine articles relevant for reports of special interest were found. Five of them are about signal detection for vaccines (29–33) , two with signal detection in paediatric populations (34,35) and two on medication errors (36,37). There is a CIOMS guidance specially dedicated to vaccines (31) as due to of their special utilization pattern (intended for prevention in large cohorts of healthy individuals), vaccines pose some interesting challenges to traditional signal detection approaches.

Albeit limited research was published in this area, there are several international working groups working in this field and an expansion of the current knowledge is expected in the next few years. Here we mention: GRiP (Global Research initiative in paediatrics) (38), ADVANCE (Accelerated development of vaccine benefit-risk collaboration in Europe) (39).

Pharmacovigilance guidance including guidance on signal management in product- or population-specific areas is available at the EMA website. A module is developed for vaccines and biological medicinal products (module I) (40), and two modules are planned on Pregnancy and breast-feeding (module III) and Geriatric population (module IV). For the reactions of special interest, it was previously shown that not all events are equally detectable, sometimes due to the way ADRs are reported. Some of them might be more effectively monitored by using other data sources (41), and focusing on previously constructed lists of important medical events is more efficient (see point 3.2 regarding event based prioritization).

In the context of Medication Errors, WHO the publication- Reporting and learning systems for medication errors: the role of pharmacovigilance centres, (42) describes a tool (the P Method) to detect preventable ADRs in national pharmacovigilance databases. To detect medication errors from spontaneous reports, this method explores 20 risk factors in relation to health-care professional practice, patient behavior and drug quality to assess preventability of ADRs.

More research regarding stratification and sub-grouping in general will be soon available as part of PROTECT project.

4. Main findings and conclusions

There is a relatively large amount of research available regarding signal management, most of it focused on signal detection, however in recent years, publications addressing other steps of signal management, as validation, prioritization and assessment, have also appeared. Signal validation, prioritization and

assessment are less well explored scientifically and we encourage and recommend further scientific work in this areas in order to improve quality and consistency of decision making in the context of managing signals. For the reports of special interest, two areas were mainly addressed by scientific groups: screening related to vaccines and in pediatric population.

Interesting and relevant research in this area is ongoing within PROTECT project and we will integrate their results and recommendations in our project outcomes as possible and appropriate.

We identified useful findings that could potentially be interesting and helpful in signal detection (e.g, adjusting implementation decisions for detection methods, adopting prioritization and validation frameworks), though some of the methods are not yet sufficiently validated and an added value to the current systems is not guaranteed (e.g. the usefulness of screening EHR data). Based on the reviewed literature, no significant changes to the current way of signal management within the EU-network is suggested, however some adjustments and modifications can benefit the current systems. These will be addressed as applicable in the Best Practice Guidance that will be developed as a deliverable of SCOPE WP5. In addition, the scientific literature will be used to fine tune the definitions and concepts used in signal management in the EU PhV environment/network, which sometimes can lead to confusion.

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6. Bibliography organized per topics of interest

*Research which was conducted in a regulatory environment, using data and/or tools from national competent authorities are marked with an * in the bibliography.*

Signal detection

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Annex 1 Additional queries

PubMed verbatim search terms:

Adverse Drug Reaction Reporting Systems/statistics & numerical data*

Drug-Related Side Effects and Adverse Reactions*

Product Surveillance, Postmarketing/statistics & numerical data*

Drug safety

Signal AND Assessment

Signal AND Management

Signal AND Evaluation

ADR OR AE

Spontaneous report/reporting

Signal AND Analysis

Signal AND Strengthening

Signal AND confirmation

Signal AND Recommendation for action (or outcome)

PubMed MeSH Terms

Adverse Drug Reaction Reporting Systems

Drug-Related Side Effects and Adverse Reactions

Humans

Product Surveillance, Postmarketing/methods*

Pharmacovigilance