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Screening for adverse reactions in EudraVigilance

Table of contents

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1. Introduction

When a pharmaceutical product is first authorised for use in clinical practice the information regarding its use is usually only that obtained from the programme of clinical trials supporting the marketing authorisation application. While these trials will have demonstrated a positive benefit-risk under carefully monitored conditions, adverse reactions that are rare, only emerge after prolonged exposure, or affect types of patients under-represented in clinical trials may remain undetected. To identify such reactions an elaborate system of post-authorisation surveillance is conducted by pharmaceutical companies, regulators and the World Health Organisation.

Many sources of data are used to detect adverse drug reactions (ADRs) but one kind of data collection in particular, the collection of individual case safety reports (ICSR) concerning suspected ADRs in people exposed to medicines, is specifically performed for this purpose. The data processing system for ICSRs used by the EU regulatory network is called EudraVigilance (EV) and includes a management system for reporting and evaluating suspected ADRs of medicinal products marketed in the European Economic Area (EEA). The first version was launched in December 2001.

When EV was first set up, direct access to the data was limited to regulatory authorities. At the current time (2016) plans are under way to extend routine access to Marketing Authorisation Holders (MAH) and the Uppsala Monitoring Centre. Moreover, access is granted in various forms to research groups and the public. Hence, there is increased interest in how the processes of signal detection are performed in EV.

Regulatory guidance is provided concerning signal detection in spontaneous report data in the Annex to Good Pharmacovigilance Practice Module IX. The purpose of this guidance is to give a more discursive account of the potential uses of EV in screening for ADRs and to clarify the changes implemented and the rationale behind them based on evidence from recent research activities, including the IMI PROTECT project (http://www.imi-protect.eu/). Thus, this guidance should be viewed as a scientific discussion, not as providing regulatory requirements. This guidance also updates and supersedes the previous guideline on the use of statistical signal detection in EV (EMEA/106464/2006 rev. 1)

The focus of the document is, where possible, on evidence based recommendations; therefore the structure followed throughout is to provide results of studies or empirical evidence first and then detail how these have been translated in recommendations and actual implementation in EV. A section is dedicated to each of the populations for which specific methods are implemented: total population, paediatric and geriatric. In each section the approach is first to discuss the more classical disproportionality methods that are the starting points of most of the signal detection systems and then alternative rule-based methods using clinical information. Finally, a simple approach is proposed to integrate the disproportionality and alternative methods efficiently. After the different populations are described, a section is dedicated to other approaches that can potentially influence the decision of the pharmacovigilance experts to further investigate a drug-event combination (DEC).

When the screening methods identify a DEC for further investigation, it can be evaluated in a number of ways that will be discussed in section 5. Only after such evaluation can a DEC be considered as a signal related to the safety of the medicinal products. It should also be noted that, when a signal has been identified from other sources of evidence, the absence of a positive screening result in EV does not refute the signal.

Two tools are used in EV for signal detection. The electronic Reaction Monitoring Report (eRMR) is a standard report that provides summarised signal detection data from EV. The EudraVigilance Data Analysis System (EVDAS), which operates on the EudraVigilance Data Warehouse, is used in

conjunction with the eRMR to enhance signal detection[1]. It contains many predefined tables and graph formats for report presentation and has a variety of functions useful in the later stage of the signal management activities. The eRMR and the reports providing statistical information in EVDAS incorporate many of the principles discussed in this guidance; hence, this discussion gives some insights into the thinking behind them and the methods are discussed in relation to these electronic tools when appropriate. However, these tools and their use are described in separate user manuals (User Manual of the electronic Reaction Monitoring Report and EVDAS User Manual[2]).

This report is aimed at all those using EV for signal detection and in particular those with an interest in understanding the logic behind the eRMR, interpreting its outputs and, possibly, contributing to future development of the system. This may include those involved in signal detection and evaluation activities, pharmacovigilance scientists and programmers or statisticians involved in setting up signal detection systems. A basic level of understanding of statistical signal detection is assumed, introductory notions of the concepts developed in this guidance can be found in Almenoff 2005 and Bate 2009.

In order to maintain the performance of a signal detection system it should be run using clearly defined signal detection rules. Each of these rules should be characterised by tests run within the dataset to which they are applied. Of course, any new process of signal detection added subsequently in EV will be formally tested to investigate its impact on the overall performance of the system and afterwards this guidance will be updated.

2. Scope

This guidance concerns methods of routine signal detection as used on EV data together with the elements for their interpretation and their potential advantages and limitations in the frame of pharmacovigilance. It also addresses the evidence behind the methods, how to use them efficiently and the areas of uncertainty that require resolution before firm recommendations can be made. The recommended methods were selected and tested by the European Medicines Agency (EMA) in consultation with experts from National Competent Authorities (NCAs) and subsequently provided to all NCAs. Most of the methods implemented are also available, from 2017, to MAHs; when a specific recommendation applies only to the EU regulatory network it is noted.

Alongside the routine signal detection in EV based on statistical methods, a number of other criteria are used to indicate when a DEC requires further investigation. This guidance also describes these criteria and, when available, the evidence supporting them.

Some areas will not be addressed, most particularly signal detection based only on clinical review. This is often the preferred method when few reports have been received for a product. Also, the guidance focus is on signal detection activities, not on signal validation or evaluation for which more extensive data review and analysis are required.

Finally, this guidance is not intended as a review of quantitative methods in pharmacovigilance in general as such theoretical discussions are available elsewhere (Bate 2009, Gould 2015).

A common observation (Hauben 2005), and one also confirmed in IMI PROTECT (Wisniewski 2016), is that the absolute performance of a signal detection method may vary between ADR databases and it should be noted that any information regarding performance of the methods described in this guideline

[1] For the EU regulatory network, the eRMR is provided both as a separate tool and in EVDAS; in the latter, however, the full spectrum of functionalities is not available. For MAH, the eRMR is only provided through EVDAS.
[2] The user manuals are available on EMA website under the EudraVigilance training section from Janaury 2017.

relates only to their use in EV unless otherwise stated and cannot be assumed to translate to other databases.

3. An integrated approach to signal detection

Disproportionality methods used in EV have been demonstrated to detect about 50% of ADRs before other, currently used methods of signal detection (Alvarez 2010). However, substantial numbers of adverse reactions cannot be detected by these statistical methods or can be detected earlier by alternative methods. Hence, any comprehensive and efficient routine signal detection system will seek to integrate a number of different methods to prioritise DECs for further evaluation.

An example of a commonly used alternative method is prioritising specific AEs which are both clinically important and commonly associated with exposure to drugs (e.g. Stevens Johnson Syndrome, SJS) so that even a single report with a new drug should prompt further investigation. In addition, quantitative assessments of concomitant variables, e.g. reporter assessments of the likelihood of causality, may also have a role in signal detection. Other statistical rules based on spontaneous reports may also be considered as useful supplements to disproportionality. Typically, such rules may look for increases in the reporting rate for a particular adverse event even when no disproportionality exists. The creation of methods that take into account other information besides disproportionality statistics is a matter for ongoing research. Some simple methods are described in the second part of this guidance and evaluated within the EV signal detection environment.

3.1. Considerations related to performance

Even when only one carefully characterised method of signal detection is used a major challenge is to reliably assess its performance. When a signal detection system is constructed using several different methods then these parameters should ideally be established for each method in competition with the other methods. In addition, if this performance is to be maintained in a working pharmacovigilance system, each method must be carefully standardised so that a set of rules or criteria are consistently applied. This includes not just the statistical methods, which lend themselves to standardisation, but also non-statistical methods.

To evaluate and compare the performance of the methods used it is necessary to specify what properties define an effective signal detection system and then to set up experiments to measure the extent to which these properties are achieved. In PROTECT (Candore 2015) the properties considered were:

- Sensitivity: the probability that a known ADR would be detected;
- Positive predictive value (PPV or precision): the probability that a DEC highlighted for review identifies an ADR;
- Time to detection of known ADRs.

The element of time is introduced since a DEC highlighted for review at an earlier time point may allow earlier action to reduce the risk to patients.

The probability that a DEC not corresponding to an ADR would not be highlighted (specificity) was not estimated partly because the heterogeneous nature of MedDRA terms makes the concept of a non-ADR somewhat arbitrary and partly because levels of evidence of non-association vary across DECs and those with high levels of evidence are likely to form an atypical set (Slattery 2016). The positive predictive value was instead preferred for its useful role as an indicator of the effort expended per

signal detected[3] which is an important consideration in designing an efficient signal detection system. Hence, it was a natural choice of performance parameter.

The target performance that should be aimed for in a signal detection system is likely to differ between different user groups. In particular, it will depend on the signal evaluation resources available but, in allocating these, it must be borne in mind that these resources must be shared between assessment of the DECs highlighted for review and other methods of signal detection. The effort which is put into each method should ideally reflect the likelihood of finding an ADR and may also need to consider the likely clinical impact of the signal.

How a reference database to establish the performance of a signal detection system should be constructed is a matter for debate but certain rules are clear. The set of ADRs for the products used to assess the performance of a signal detection method should be moderately comprehensive and the subject of a reasonable level of consensus. When comparing two different detection methods the same set of products and ADRs should be used. When assessing the performance for a particular setting – e.g. across a company's portfolio of products, it is best to mirror the conditions in which the method is routinely used as closely as possible. For the performance statistics described above, no set of 'non ADRs' is required and this somewhat eases the construction of the database as it is usually simpler to identify ADRs than products and events that are reliably known to be unrelated.

The reference standard used to classify a signal as true positive or a false positive/unknown for the results shown in this guidance is based mainly on the reference used in PROTECT. This includes the EMA database[4] that maps section 4.8 of the summary of product characteristics (SPC) for centrally authorised products (CAP) to MedDRA preferred terms (PT)[5] and a set of non-CAPs product for which a dedicated mapping exercise was carried out.

The performance of SDAs can be analysed over all MedDRA preferred terms or on a subset that reflects more closely the concerns of pharmacovigilance experts. The second alternative is chosen when showing all empirical results in this guidance as it reflects the real world pharmacovigilance process. Therefore, all performances shown were evaluated using only known ADRs that are also Important Medical Event (IME[6]) reactions identified in MedDRA[7].

4. Screening for adverse reactions in the total population

4.1. Disproportionality methods

4.1.1. Components of the statistical signal detection system based on disproportionality methods

Spontaneous reports are sent to EV only when a patient experiences an adverse event that may have been caused by a medicine. Two facts that can be inferred from this reporting process is that examination of the dataset will not give direct information about the numbers of patients taking the medicine who do not experience an adverse event or the numbers of patients having the clinical event who are not taking a medicine. A consequence of this is that relative association measures at

[3] More precisely the reciprocal of the PPV will reflect workload.
[4] The database is available at the bottom of this webpage http://www.imi-protect.eu/adverseDrugReactions.shtml.
[5] For the CAPs it was also possible to identify which adverse drug reactions had been added to the SPC after the marketing authorisation was granted: these data were used to check the robustness of the results provided.
[6] The IME list was created to facilitate both the classification of suspected adverse reactions and the pharmacovigilance data analysis activities of stakeholders in the EU. Its development is co-ordinated by the EudraVigilance Expert Working Group: https://eudravigilance.ema.europa.eu/human/textforIME.asp
[7] Results based on the whole set of MedDRA reactions were evaluated as well: these results do not change any practical recommendation.

population level (e.g., relative risks or odds) of clinical events for patients taking a medicine compared with those not taking the medicine cannot be calculated. Instead, signal detection relies on disproportionality measures which are relative proportions conditional on reporting to the database. The functional form of these measures is identical to that of the population measures restricted to the persons in the database but the values calculated cannot be directly transformed into measures of clinical relevance or impact.

Disproportionality statistics take the form of a ratio of the observed proportion of spontaneous ICSRs with a medicinal product that include a specific adverse event to the proportion that would be expected if no association existed between the product and the event. The calculation of the expected value is based on ICSRs that do not contain the specific product and it is assumed that these ICSRs contain a diverse selection of products most of which will not be associated with the adverse event. Hence, these ICSRs reflect the background incidence of the event in patients receiving any medicine.

There are a number of different ways to calculate such statistics and this choice is the first step involved in designing a statistical signal detection system. Secondly a set of rules, based on the observed value of the disproportionality statistic and, usually, also on other statistics (e.g. number of reports received), is adopted to indicate when a given drug-event combination (DEC) should be highlighted for further inspection. When this occurs it is often referred to as a signal of disproportionate reporting (SDR). When introducing the concept of an SDR it is conventional to note that these statistical criteria alone do not usually constitute a 'signal' in the pharmacovigilance context[8]. This is to emphasise that results from such statistical approaches may merely reflect a disproportionality of reporting, which could be a result of numerous non-causal factors such as confounding, reporting artefacts, different coding practices or combination of the above. In other words, this statistical association may reflect, but does not imply, a causal relationship between the exposure to the medicine and the occurrence of the adverse event.

Most disproportionality measures are designed so that they would be expected to rise if a causal relationship exists between a medicine and an adverse event. Thus, the thresholds might incorporate the disproportionality measure using a simple threshold criterion. It declares an SDR (if no other rules are involved) only if the measure rises above this threshold. Such simple rules have drawbacks and more complex conditions are usually applied but this illustrates the concept.

Lastly, the third step involved in designing a statistical signal detection system is the decision whether the calculations and the set of rules are based across the whole database or adjusted using subgrouping variables.

The combination of a disproportionality measure (what was referred above as the first step in designing a statistical signal detection system), its corresponding set of rules (second step) and where these are applied (third step) is referred to as a signal detection algorithm (SDA). An example of an SDA is the Reporting Odds Ratio (ROR) with thresholds on both the number of reports and the lower bound of the 95% confidence interval of the ROR calculated on the whole database. In this example, i) the disproportionality measure chosen is the ROR, ii) the set of rules are the thresholds on both the count and the statistics itself and iii) no subgroup or stratification is used. Based on this SDA, an SDR is declared only when both conditions on the thresholds are met on the whole database.

4.1.2. Selection of a disproportionality method

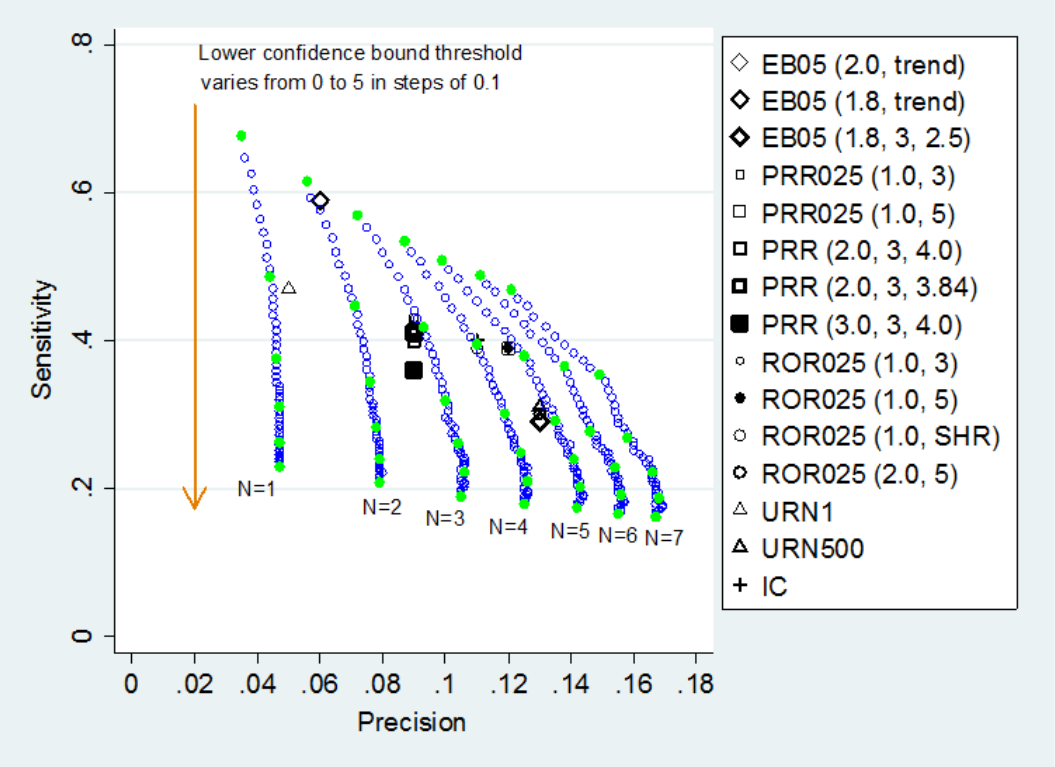
A number of disproportionality measures have been proposed for signal detection purposes and the performance of many of them (all based on two-by-two contingency tables) have been evaluated

[8] This concern led the CIOMS VIII report to re-designate SDR as 'statistic of disproportionate reporting' but we do not follow this suggestion as it is not technically a statistic.

within the PROTECT project in conjunction with a range of rules to define an SDR and on several reporting databases including EV (Candore 2015). The disproportionality statistics evaluated were the Proportional Reporting Ratio (PRR), the Reporting Odds Ratio (ROR), the Information Component (IC), the Empirical Bayes Geometric Mean (EBGM) and the Urn model; the set of rules to define an SDR often being based on a lower confidence bound for the statistic and a minimum number of reports, but in a few instances included also time trend and thresholds on the disproportionality statistics value itself (see table 4 in the Appendix for more details on the methods used). The databases included formed a diverse set, encompassing regulatory (EV and UK Sentinel), research (VigiBase) and industry (Sapphire, Argus, OCEANS and ARISg). However, databases of very small size were not included.

A notable result from PROTECT and previous studies (Van Puijenbroek 2002) is that the choice of disproportionality statistic is not an important or limiting factor in determining the performance of a signal detection method. The performance obtained using any given disproportionality statistic is largely determined by the set of thresholds chosen to define a SDR. This is illustrated in Figure 1 which displays the range of achievable performance in term of sensitivity and PPV by the ROR method in EV over a range of thresholds based on i) the lower bound of the 95% confidence interval and ii) the number of reports.

Figure 1. Envelope of sensitivity and positive predictive value achievable with different thresholds for the ROR in EV[9]



The performance of all the methods tested in PROTECT could be approximated by appropriate choice of thresholds for the ROR. In addition to PPV and sensitivity, the time to detection, calculated as average number of months from first report received for a product to the first time an SDR occurred, was also roughly the same, in fact tending to be slightly shorter with the ROR method.

[9] Data from PROTECT Work Package 3 project, details on the methods used in Appendix, table 4. Values in green represent unit thresholds on the 95% lower confidence bound (e.g. 0, 1, 2, 3, 4 and 5).

Disproportionality statistics differ in the amount of time and computer resources needed for calculation, the amount of effort and expertise needed to modify them when required, and how easily they can be communicated to non-statisticians. Hence, a conclusion of this work is that the choice of statistic, within the set evaluated in PROTECT, should be made on the basis of convenience.

Implemented recommendation in EudraVigilance

The PRR, which is a very simple calculation, has previously been implemented as the signal detection method in EV. However, the fact that the ROR is an equally simple method, gives the same performance as the PRR, but also forms the basis of more complex statistical models makes it the best choice for future development of the EV system (eRMR and EVDAS) where flexible analytical methods to adjust for confounding and explore alternative models for signal detection will assume ever greater importance.

4.1.3. Thresholds defining SDRs in EudraVigilance

As seen, a set of rules applied to the summary statistics calculated for each DEC is defined such that SDRs are considered to occur only if each statistic reaches or exceeds its corresponding threshold. Too low a threshold will result in large, and potentially unmanageable, numbers of SDRs to investigate. This will also reduce the resources available for assessment of each SDR. Too high a threshold will result in delay or even failure to identify important ADRs. Thus the choice of thresholds is fundamental to the success of a signal detection system.

Thresholds for a disproportionality method are often based on two separate indicators, one reflecting the disproportionality statistic itself and another based on the number of reports received. For the former, in practice, rather than the point estimate, a formal lower confidence bound is often used (e.g. ROR025 reflecting the lower bound of the 95% confidence interval). Although this is calculated using the same formula as the confidence bound used in inference it should not be viewed in this light. The rationale for its use is simply that when the statistic is based on few reports it falls further below the point estimate and makes an SDR less likely. Hence it is an intuitive way of incorporating the degree of confidence we have about the reliability of the data to support an SDR into the process. Within PROTECT it has also been shown that a threshold based on the lower confidence bound performed better than a threshold with an additional criteria based on the absolute value of the disproportionality statistic itself (Candore 2015).

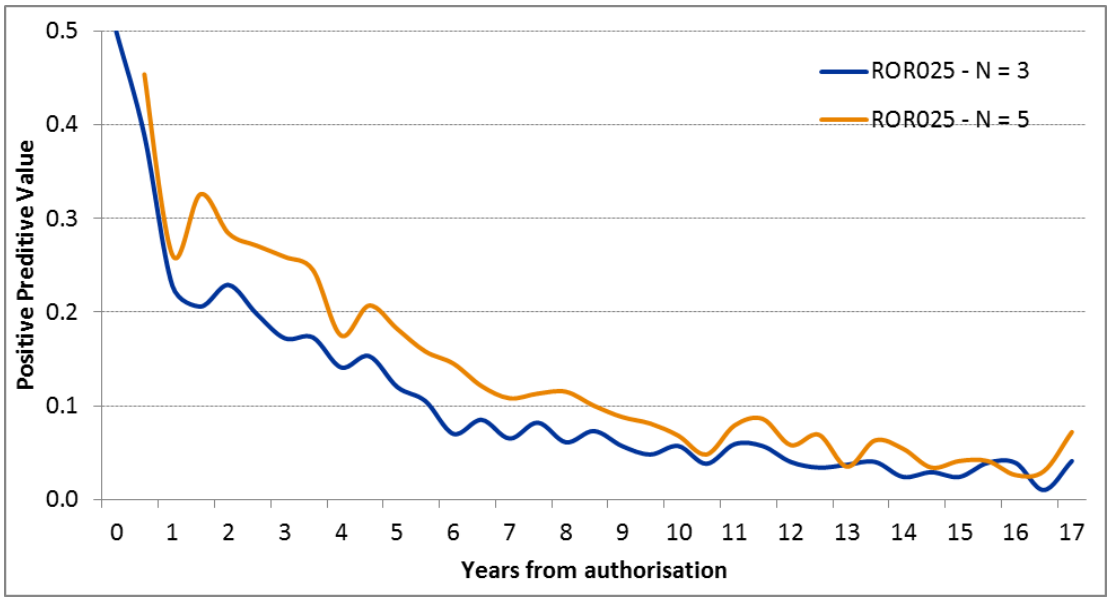
The ranges of sensitivity and precision that can be obtained by altering the thresholds for the lower confidence bound of the PRR and for the number of reports of a DEC have been investigated in EV. Early work (Slattery 2013) showed that raising the threshold for PRR025 (the lower confidence bound) above 1 could result in appreciable loss of sensitivity with limited reduction of false positive signals. In the light of later work (Maciá-Martínez 2016) this is understandable. This work showed that a correlation exists between the value of a disproportionality statistic and the relative risk of an adverse reaction estimated in epidemiological studies, therefore setting any threshold on the disproportionality statistic above 1 might lead to missing an adverse reaction for which the risk ratio is not great enough.

By contrast, increases in the threshold for the numbers of reports of a DEC produced fewer false positives with little loss of either sensitivity or time gained for investigation of adverse events. A threshold of five compared to a threshold of three gave a reduction of 25% in false positive signals in return for a loss of 12% in ADRs detected early and an increase of the median time to SDR by only one month.

Later, results from PROTECT (based on ROR and PRR) confirmed the benefits of raising the threshold for the count instead of the threshold for the lower confidence bound. In this study a threshold of five compared to a threshold of three produced a fall of only 9% in true positives, a delay in the median time to generate an SDR of eight months and a reduction of 35% in false positives. Results between the studies are slightly different because the reference standard varied and the earlier work was probably more reflective of the real objectives of pharmacovigilance since it included only ADRs unknown at the time of the SDR.

Results from PROTECT (Candore 2015) also show that the proportion of SDRs that turn out to be ADRs (positive predictive value) decreases over the lifetime of the product. Figure 2 shows this pattern for the ROR with two different thresholds on the number of reports defining the SDRs of 3 and 5.

Figure 2. Change in positive predictive value with time from authorisation using the ROR025 in EV[10]



The reduction in PPV over time was mirrored in all methods tested and in all datasets and it appears more marked during the first years after marketing authorisation. Thus there appears to be a fall in return from statistical signal detection with time on the market; hence it might be more efficient to vary the amount of effort invested in signal detection over the life-cycle of the product. This seems to suggest that newly authorised products could initially be monitored efficiently and with high precision using a lower case count threshold. Moreover, when a product has just been authorised it will take some time to generate the minimum number of reports needed, therefore having a lower threshold on the number of cases should help detecting safety concerns earlier, whereas later in the life cycle of a substance it seems sensible to raise the case count threshold.

It is worth remarking that, while the above work suggests that lower thresholds should apply particularly to newly authorised products, it may be that some older products evoke particular concerns which suggest greater vigilance is warranted and this is easily accomplished by retaining them in the group that is monitored more 'intensively'. Generally, however, the majority of products with a lower threshold on the number of report will be newly authorised products.

In conjunction with lower thresholds to detect safety concerns earlier for products for which the safety profile is less known, a higher frequency of review than products with a more established safety profile may be considered. The frequency to choose will depend on current uncertainty about the safety of the

[10] Data from PROTECT Work Package 3 project, details on the methods used in Appendix, table 4.

products, as reflected, for example, in the risk management plan, on the rate of accrual of new reports and also on the resources available for monitoring.

In conclusion, while there is some level of evidence on using the lower bound confidence interval of the disproportionality statistics with a value of 1 as a threshold, there is no universally applicable rule to define the exact number of reports for the lower and higher thresholds and the frequency of monitoring, although it is clear that some products warrant more vigilant signal detection. In addition to what is considered an adequate level of performance (sensitivity, PPV and time to SDR) and marginal improvements in performance obtained by modifying the thresholds, elements such as the amount of resources available for signal evaluation and current knowledge of the product need to be taken into account.

Implemented recommendation in EudraVigilance

The following criteria are applied in the EV system (eRMR and EVDAS) to define an SDR:

- The lower bound of the 95% confidence interval greater than one;
- The number of individual cases greater than or equal to

  3 for active substances contained in medicinal products included in the additional monitoring list in accordance with REG Art 23 (see GVP Module X), unless the sole reason for inclusion on the list is the request of a post-authorisation safety study (PASS);

  5 for the other active substances;
- The event belongs to the IME list.

4.1.4. Subgroup analyses and stratification

Spontaneous ADR reporting systems cover a range of very diverse products aimed at diverse conditions and used across a broad range of patient populations. For example, vaccines are given to healthy subjects, especially children and therefore only a very high level of safety is likely to be acceptable. Also, ICSR reporting patterns vary over time and between different geographical regions. The simplest statistical signal detection algorithms disregard this diversity and give equal weight to information from all products, conditions and patients.

Ignoring the diversity and potential confounding factors within the dataset may result in signals either being masked or false associations being flagged as potential signals. Stratification is generally used in epidemiology to reduce bias due to confounding, when a third variable is associated both with the drug exposure and the event of interest, and may also be of benefit in signal detection algorithms. Information from various covariates may be used in different ways to enrich/supplement statistical signal detection processes. Two strategies may be considered:

1. Subgrouping: *different measures* of disproportionality are estimated, one within each of a number of subgroups defined by the covariates. An SDR is considered to exist if the conditions for an SDR are met within any subgroup.
2. Stratification[11]: *a single measure* of disproportionality is estimated by a weighted average across all the subgroups, using standard methods. An SDR is considered to exist if the conditions are met when using this adjusted measure.

[11] This terminology is used inconsistently in the literature. We have adopted what appears to be the original meaning of stratification as operating within but combining across subgroups based on, for example, usage such as 'stratified sampling'.

A few studies have investigated the impact of stratification and subgroups analysis on SDAs (Hopstadius 2008, Woo 2008, Evans 2008). This has also been investigated within the PROTECT project (Seabroke 2016) on several databases (including EV) and with several disproportionality methods (ROR, IC and EBGM).

In PROTECT both the strategies described above were tested. Variables under investigation were: age; gender; time period (when the cases were reported); vaccines versus the other drugs; seriousness (considering two scenarios, seriousness based on CIOMS criteria[12] and seriousness if any reaction in the case is an IME); reporter qualification (splitting patient and health care professional reports); report source (excluding litigation cases), country and region where the report originated (see table 5 in the Appendix for more details).

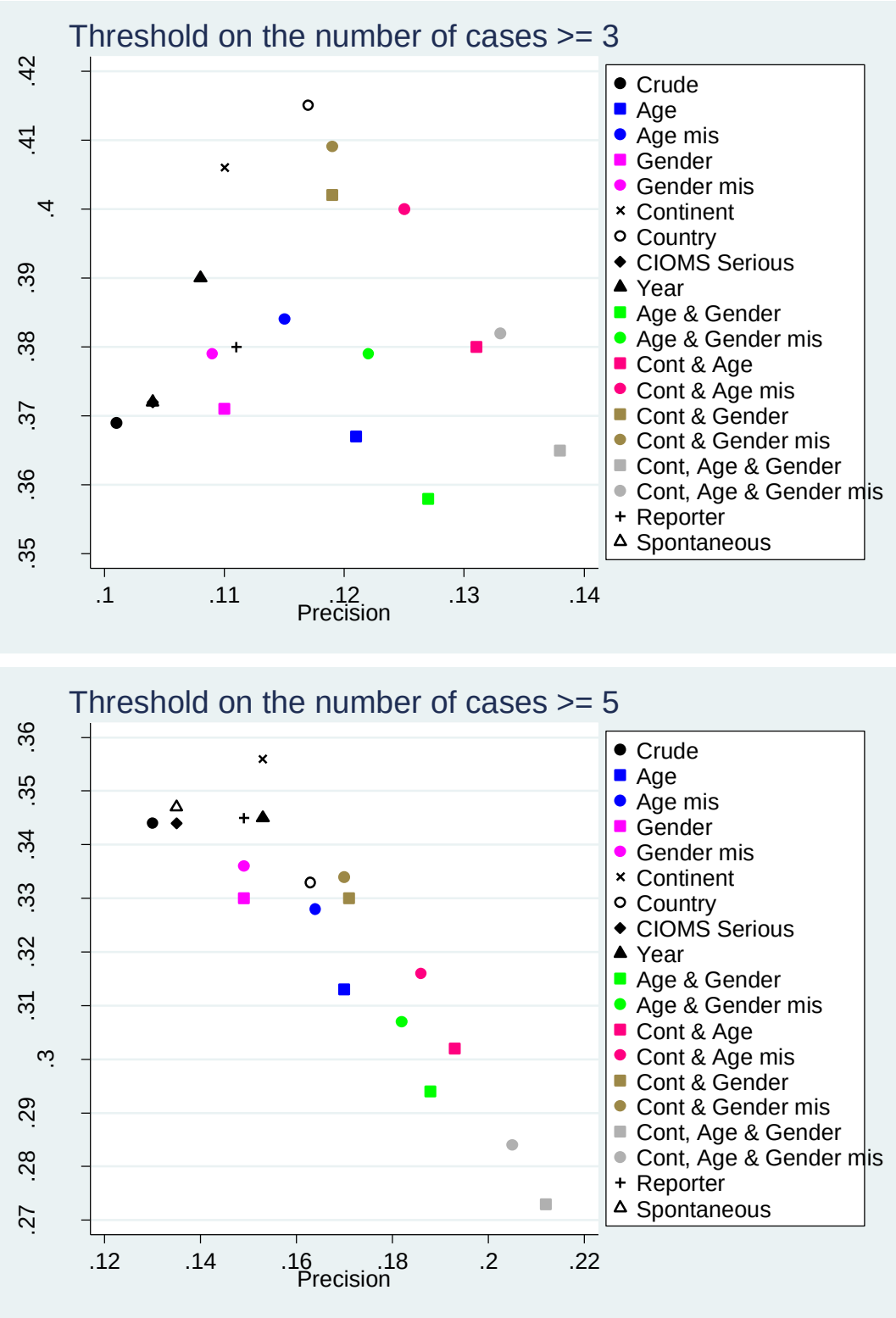
A notable finding of PROTECT work was that subgroup analyses for all variables evaluated consistently performed better than stratified/adjusted analyses in all databases; the results and following discussion focus therefore only on the subgrouping. Moreover, in EV subgroup analyses consistently showed benefits in both precision and sensitivity over crude[13] analyses for some variables (figure 3).

Two additional findings related to EV can also be seen in figure 3. First, the effect of subgrouping differed depending on the threshold applied to the count of reports, either 3 or 5. Using a threshold of 3 within each subgroup, appreciable improvements in both sensitivity and precision could be achieved, while smaller improvements could be achieved with a threshold of 5 and these could be accomplished with fewer variables. For instance, using a threshold of 3 the geographical groupings increased sensitivity, addition of age (point labelled 'Cont & age mis' in figure 3, see table 5 in the Appendix for more details on the labels used) increased PPV whilst sacrificing some of the added sensitivity but still gave an improvement in both measures compared to ungrouped (crude) analysis. While the same grouping variables used with a threshold of 5 increased PPV but reduced sensitivity compared to the crude analysis.

The second finding was that the inclusion of litigation cases did not improve the performance with both thresholds on the counts (3 and 5 reports) and, in fact, made it slightly worse (see points labelled as 'Crude' and 'Spontaneous', the former including litigation cases, the latter excluding them, in figure 3): this result helps in providing some empirical evidence that in EV such reports should be excluded during disproportionality analysis (but still used as a subsidiary information in signal validation). This recommendation accords with general principles of analysis that the data should be collected using a homogeneous procedure. It also eliminates the concern that litigation cases – which tend to increase the chances of a specific adverse event being reported for a specific drug – could mask the same effect with other products.

[12] This variable was studied only in EV.
[13] Crude analysis is the analysis performed on the whole dataset without any subgrouping or stratification.

Figure 3. Sensitivity and positive predictive value using subgroup analysis with the ROR025 in EV[14]



[14] Data from PROTECT project, details on the variables used for the subgroup in Appendix, table 5. The 'mis' in the variable names denote that missing data has been included as a separate category in the subgroups for that specific variable; the '&' denotes that two or more covariates have been combined. In the top graph, the subgrouping by 'Spontaneous' and 'CIOMS Serious' overlap at (0.104, 0.372).

Figure 3 also suggests there may be some value in sub-grouping for variables such as patient reporting and non-serious reporting, that are the main changes in reporting rules to EV with the new legislation. Both subgroup calculations (point labelled respectively as 'CIOMS - Serious' and as 'Reporter' in figure 3) are associated with some improvement in performance but not as marked as for other variables. An increase in the proportion of non-serious reports in EV is expected as a result of the 2010 pharmacovigilance legislation[15] and this might impact the patient reporting as well; a further investigation on the performance of these sub-groupings might then be useful.

The above discussion is by no means an exhaustive description of potential improvements to signal detection based on grouping variables. Some research has suggested that restricting signal detection to within therapeutic areas may have advantages (Grundmark 2014) and restriction to within classes of products, most commonly vaccines, has also been studied (Seabroke 2016, De Bie 2012).

When deciding which subgroup analysis to recommend, other considerations than changes in sensitivity and PPV (as shown in figure 3) should be considered:

- Overall workload: when limited resources are available it is important to also consider any change in the number of DECs highlighted for review with the methods proposed; this is not explicit from sensitivity and PPV (see table 1 for an example);
- Visualisation / ease of understanding: the subgroup results should be easy to present in a signal detection system, this will also facilitate communication of their usage and meaning to the signal evaluators;
- Time to detection of known ADRs: variation in time to detection was not studied for different subgroup sizes in PROTECT but it is credible to assume that having too many small groups might require more time to reach the threshold on the number of reports and therefore the time to an SDR.

Table 1. Difference in the number of true and false positives between the crude and the subgroup analysis recommended on EV when using the ROR025

Criteria	Threshold	TP	FP	Delta % TP	Delta % FP	Delta % SDR
Crude	N = 3	1,863	16,658			
Subgroup on reporting region and excluding litigation cases	N = 3	2,050	16,646	10.0%	-0.0%	0.0%
Crude	N = 5	1,737	11,584			
Subgroup on reporting region and excluding litigation cases	N = 5	1,796	9,965	3.3%	-13.9%	-11.7%

TP = True Positive; FP = False Positive; SDR = Signal of Disproportionate Reporting

Implemented recommendation in EudraVigilance

The following criteria are applied in the EV system (eRMR and EVDAS) to define an SDR:

- The exclusion of litigation cases (these cases are still used during signal evaluation)
- The use of subgrouping by geographical region of reporting.

[15] Until July 2012 senders were obliged to send to EV only serious reports. However, non-serious reports from a number of organisations who were sending them were also accepted. After the new pharmacovigilance legislation was implemented a transitional period has been put in place to enable all the stakeholders to adapt to the change in EV business rules. This transitional period is foreseen to end mid 2017 (pending the successful outcome of audit of the new EV system) and only after the transitional period ends shall all non-serious reports be sent.

4.1.5. Some operational choices

As per standard pharmacovigilance practices, the following default settings are used in EV for routine signal detection (eRMR) and signal evaluation (EVDAS) when calculating the ROR:

- *Type of reports*: default setting uses 'Spontaneous cases', 'Other' and 'Not available to sender (unknown)' as Report Type (E2B C.1.3) and exclude litigation cases as Primary Source Qualification (E2B C.2.r.4). 'Other' and 'Not available to sender (unknown)' are included based on the assumption that they mostly contain spontaneous cases;
- *Cases or adverse events*: the computations are based on the count of individual cases received, thus a given ICSR may contribute only to one cell of the table used for the ROR calculation even if the safety report includes either multiple products or multiple events (see Appendix 13.1 for more details). This approach has been chosen to keep the independence between the variables used to compute the ROR so that its variance will not be underestimated;
- *Drug characterisation*: the value of the ROR is computed taking into account the medicinal products reported as 'suspect' or 'interacting' (in the context of a drug-drug interaction). For specific ad hoc analyses e.g. drug-drug interactions, the concomitant medication can be added to the calculation;
- *Level of hierarchy for adverse event*: the MedDRA hierarchy is implemented in EV and the Preferred Term is used for routine signal detection. For specific ad hoc analyses other levels or groupings may be useful;
- *Level of hierarchy for drug*: for routine signal detection the value of the ROR is computed at the active substance level. Some grouping of active substances (e.g. by salts or route of administration) is also performed. On occasion, for instance for vaccines, ROR for routine signal detection is calculated at the medicinal product level (i.e. brand name). For specific ad hoc analyses other levels or groupings may be useful.

4.2. Alternatives to SDR based on clinical information

The statistical signalling methods use only a limited part of the information contained in ICSRs and various attempts have been made to augment signal detection using other features of the reports (Caster 2014). These attempts have two different, and sometimes contrasting, aims: to improve safety (not missing events that might hide causal relationship or important events for the patients) and, possibly, to gain efficiency.

Two types of additional information are routinely employed in EV signal detection. The first of these is a subgroup of MedDRA terms based on expert opinion and the second is information from the ICSRs regarding the survival of the patient. These are more formally described below:

- *Designated medical events (DME)*: some types of adverse event are known to arise in a high proportion of cases in causal association with medicinal products. Hence even a single report in conjunction with a medicinal product for which it has not previously been observed may arouse suspicion. A list of such adverse events, complemented by important and serious events that should not be missed, is created and maintained by the EMA[16]. The list is also occasionally reviewed and revised in the light of empirical assessment of signal detection performance and emerging clinical opinion;

16 http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000587.jsp&mid=WC0b01ac0580727d1b

- *Fatal events*: reports in which the patient died following an adverse event classified as an IME are also of concern given the possibility that the death may have occurred directly as a result of the adverse event. Whilst this does not increase the likelihood that the adverse event is causally related to the medicinal products, such reports are given special attention because they may impact the patient and the public health importance should they later prove to be related.

4.2.1. Characterisation of additional methods

The same reference database compiled for the evaluation of signal detection methods in the IMI PROTECT project can also be used to examine the performance of the additional clinical measures, either in absolute terms or viewed as supplementary to the statistical signal detection method.

Table 2. Performance of disproportionality and additional methods in EV

Criteria	True positive	False positive	Sensitivity	PPV
ROR025 (N=3)*	2,050	16,646	40.6%	11.0%
ROR025 (N=5)*	1,796	9,965	35.6%	15.3%
DME (2012 definition)	1,172	8,702	23.2%**	11.9%
DME (2015 definition)	967	6,739	19.2%**	12.5%
DME (2016 definition)	963	5,295	19.1%**	15.4%
Fatal (IME)	2,064	36,313	40.9%	5.4%

* SDR calculated as recommended in section 4.1 with threshold on the lower bound of the 95% c.i., number of reports, using geographical regions subgroups and excluding litigation cases

** The sensitivity of the DME is limited by the size of the list itself since only reactions belonging to the list can be detected

The SDRs in table 2 were calculated using the methods recommended in the first part of this guidance (section 4.1). A threshold on the count of 3 cases returns roughly one ADR for every 9 SDRs. Increasing the threshold on the count to 5 improves this to about one ADR per 7 SDRs, at the cost of some sensitivity.

Overall the performance of the DME criterion appears similar to SDRs – about 1 ADR for every 7 reports fulfilling the criterion. However, it should be recalled that the SDR can detect any ADR involving an IME and hence has wider applicability than DMEs. This makes it a more flexible and powerful technique although it is clear that some known problem areas should always be investigated before an SDR arises. The precision varies widely between DMEs and each revision of the list had as a consequence an improvement of the performance.

Table 3. Performance of additional methods as complement to the SDR in EV

Criteria	True positive	False positive	Sensitivity	PPV
DME (2012 definition) - with no SDR (N=3)	971	7,718	19.2%	11.2%
DME (2012 definition) - with no SDR (N=5)	973	7,993	19.3%	10.9%
DME (2015 definition) - with no SDR (N=3)	796	5,981	15.8%	11.7%
DME (2015 definition) - with no SDR (N=5)	806	6,217	16.0%	11.5%
DME (2016 definition) - with no SDR (N=3)	793	4,707	15.7%	14.4%
DME (2016 definition) - with no SDR (N=5)	803	4,869	15.9%	14.2%
Fatal (IME) - with no SDR (N=3)	600	25,793	11.9%	2.3%
Fatal (IME) - with no SDR (N=5)	700	28,793	13.9%	2.4%

To examine how these additional criteria perform as supplement to the statistical methods, table 3 shows the performance on DECs without an SDR.

For DME, performance remain very similar. Moreover review of the confirmed signals in 2013 showed that a quarter was related to DME PTs; of these, 53% did not yet have an SDR confirming the utility of using the DME as a complement to the statistical criteria.

The decision to highlight fatal outcome only against IMEs, rather than against all adverse events listed on the ICSR, was based initially on the view that non-IMEs were unlikely to contribute to the fatality. It was also found empirically to increase efficiency. In EV, more than 90% of fatal cases are reported with at least one IME and focusing only on fatal IME reduces the number of DECs with a fatal event by 70%[17]. Even with this improvement, the criterion based on fatalities only returns one ADR for around twenty reports investigated, and this is closer to one in forty when excluding DECs with an SDR; further research may be warranted to find ways of obtaining better precision.

Implemented recommendation in EudraVigilance

In the EV signal detection system (eRMR), both DMEs and IME fatal reports are used routinely as an addition to SDR methods because of their additional value to augment signal detection, improving safety (both) and efficiency (DMEs).

4.3. Conclusions on screening methods for the general population

As shown, there is some value in using both the statistical and clinical based methods presented to achieve a more comprehensive and efficient routine signal detection system. There are different ways in which the two can be combined, ranging from probabilistic (Caster 2014) to simpler rule based methods.

In EV the choice made is to highlight a DEC for review if any of the statistical and clinical based conditions is satisfied. The information about the three methods is combined and visualised in one single variable in order for the signal detection expert to identify the DECs for further investigation using just one variable and not three simultaneously.

In case two or more methods simultaneously trigger a DEC to be highlighted, a prioritisation rule is applied to show only one method as a trigger, with the method to be prioritised determined on consideration of both efficiency and safety (not missing potential important events). The DME list, created with the aim to serve as safety net and with an overall performance similar to the SDRs, seemed a good candidate to be prioritised; while SDRs were a good candidate to follow given their better performance compared to the fatal events and the vast amount of research demonstrating their utility.

The three methods are also visualised separately to allow the signal detection reviewer to see how each of them contribute to a DEC being highlighted for review.

[17] The reason lies in the fact that a fatal case with more than one event reported, will be highlighted in the eRMR multiple times according to the number of the medicinal products and events reported. For example, a fatal report with one medicinal product and 5 events, one IME and 4 non-IME, will lead to 5 DECs highlighted in the eRMR. Focusing only on IME will reduce the number of DEC highlighted to 1.

Implemented recommendation in EudraVigilance*

In the EV signal detection system (eRMR), a DEC is highlighted for review if any of the condition of the statistical (SDR) or clinical based (DME and fatal) method is satisfied.

The methods are combined to present the signal detection reviewer with a summary information in a single value; when two or more methods simultaneously trigger a DEC to be highlighted, the following prioritisation is applied:

1. DME
2. IME SDR
3. IME fatal cases

The result of each of the three methods is also visualised separately.

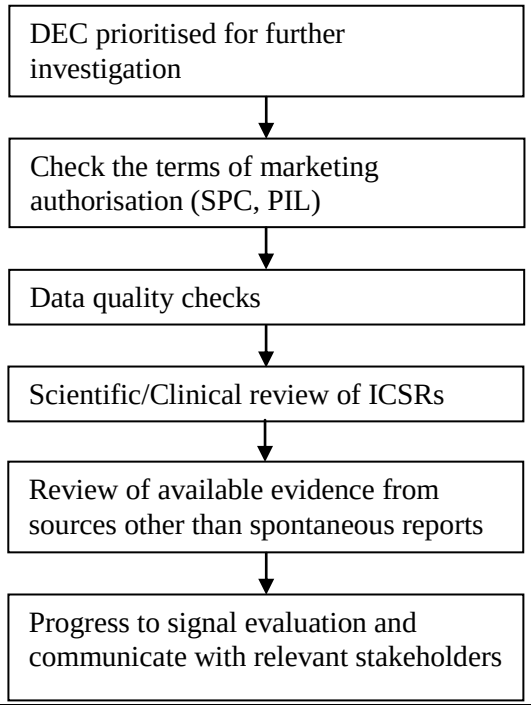
* This feature is an option requested by the European Regulatory Network and has not been implemented in the eRMR version for industry

5. Interpretation of screening results based on spontaneous report data

The purpose of screening spontaneous report databases is to focus the attention of signal detection experts to DECs for which further investigation of the possibility of a causal relationship appears to be merited. This is true whether the method involves statistical algorithms, rules based on specific aspects of the data, or unconstrained inspection of the ICSR data by a pharmacovigilance expert. The identification by these methods of a DEC for further evaluation is only a preliminary step in a process and should not be seen as reliable evidence of an ADR.

The further steps in assessing whether a DEC should be treated as a signal are described below and shown schematically in the diagram (figure 4). The assessment may end at any step if evidence emerges to show that the case for a signal is not supported.

Figure 4. Steps in assessing a DEC



A preliminary step is to check the terms of the marketing authorisation regarding the DEC under investigation. In particular, the summary of product characteristics (SPC) and the Package Information Leaflet (PIL) should be checked to determine if the DEC is already a known ADR and, if so, if questions remain regarding its frequency and severity.

5.1. Review of ICSRs

The next validation step applied to DECs identified by the screening processes is a detailed review of all the information contained in the ICSRs. When reviewing SDRs the nature of the entire database as a background for the disproportionality statistic may also be considered. The following elements may be relevant to this review:

- The medical terminologies which have been used in the reports populating the database;
- Whether the reported events are best represented by a single medical code or require a group of codes;
- The quality of the ICSRs (e.g. miscoding, duplicate reports, missing and erroneous data);
- The geographical area and time period covered by the database;
- Differences in coding practices between countries and reporting regions;
- The type of medicinal product included in the database;
- The likely drug exposure in the population covered by the reporting system;
- Changes in reporting rules and practices since database creation/drug addiction;
- Under-, over- and mis-reporting;
- The source of ICSRs (e.g. all unsolicited reports).

In EV, some of these elements might be less relevant, e.g. - type of medicinal products included, while other might be more important given its international character e.g. - different coding practices between reporting countries.

Having understood all the coding of the suspected ADR related in the spontaneous reports, it should be considered if the reports appear to support a causal relationship between the product and the adverse event. Examples include that the event should occur in a credible temporal relationship to the exposure to the product, events may ease upon withdrawal of a medicine and recur upon re-exposure. However, these factors should be regarded with caution since they may also have influenced the decision to send the ICSR. Hence the ICSRs in EV are likely to be a subset of adverse events selected on the basis of a possibly spurious appearance of causality. Nonetheless, review of these features still has an important role. In particular, the absence of any consistency in the temporal relationships may suggest that the observed events are not an ADR.

5.2. Review of other evidence

Even at the initial stage of signal detection, evidence concerning a DEC may be available from sources other than EV. If substantial doubt remains after the initial validation concerning whether the DEC should be classified as a signal it may be appropriate to review these sources. However, if a clear signal has been identified then all these sources will be reviewed at the stage of signal evaluation – not covered by this document.

Sources of data that may be reviewed are the marketing authorisation application, the risk management plan, periodic safety update reports (PSUR), data on suspected unexpected serious adverse reactions (SUSARs), post-authorisation commitments and published reports of studies. These sources may help to identify the existence of known class effects or increased susceptibility among certain patient subgroups. Information in PSURs may include estimates of population exposure and cumulative safety data aimed at ongoing evaluation of the risks and benefits of medicines, randomised clinical trials (RCTs), observational studies, other relevant data sources and meta-analyses. It should be noted that, although non-spontaneous reports to EV collect information from clinical studies, imbalances in adverse events between treatment groups in a clinical trial may be seen as indicative of a potential ADR when viewed by a clinical assessor in the context of other study information that is not reported to EV. Hence appropriate review of relevant studies may add substantially to evaluation of reported SUSARs.

6. Methods aimed at specific patient populations

When ICSR databases are sufficiently large, some classes of patients may be identified that merit separate attention in signal detection due to known or suspected systematic differences in their responses to medicines. Two such groups that can be differentiated in most databases are based on age: paediatrics and geriatric patients.

A note of caution in designing such subgroup analyses is that too fine divisions of the data may result in lack of power to detect signals. Thus it may be best to use quite large subgroups and to monitor specific patient populations in parallel with analyses of the total dataset.

The methods of analysis performed on subgroups in EV mirror those for the entire database; therefore both statistical and clinical based methods are introduced following the same structure applied in the first part of the guidance. Separate validation is not presented because reference datasets of subgroup specific ADRs are currently unavailable. Hence the strength of evidence for signal detection in subgroups is somewhat lower than for the entire dataset but a prospective pilot in real-word signal detection has confirmed a relatively low workload and the utility of applying the methodologies proposed in these subgroups. In addition, results of the pilot have been useful in refining the methods proposed.

6.1. Paediatric population

Often a single paediatric group is chosen below a selected age threshold. Although childhood is a period of rapid change and no threshold is likely to define a homogenous group, this succeeds in defining a population with marked developmental, physiological and psychological differences from adults.

The paediatric group is defined in the EV system including all patients with an age up to and including 17 years old.

6.1.1. Disproportionality methods

Statistical disproportionality tools can be applied to ICSRs relating to the use of medicines in children to increase the ability to detect signals in the paediatric population from spontaneous ICSR databases.

In line with the general population, the disproportionality method proposed is the ROR and the thresholds used to define an SDR are also based on its 95% confidence interval and on the number of individual cases. However, the lower number of ICSRs usually received for the paediatric population

compared to the rest would advocate the use of a lower threshold for the count and the avoidance of further subgrouping within this population in order to preserve the power.

Another difference from the use in the total population is the use of within-group disproportionality statistics: only disproportionalities that are significantly higher than those in the non-paediatric group should be highlighted for additional consideration (Blake 2015). The rationale for this choice is to try avoiding to consider for further review disproportionalities already highlighted in the overall population focusing on disproportionalities that are more pronounced in the paediatric group.

Implemented recommendation in EudraVigilance

In the EV signal detection system (eRMR), for the paediatric population within-group disproportionality is used defined as follow:

Relative Paed ROR = ROR_{Paed} / ROR_{Rest}

An SDR is defined when all of the following criteria are applied:

- The lower bound of the 95% confidence interval of the ROR_{Paed} is greater than one;
- The lower bound of the 95% confidence interval of the Relative Paed ROR is greater than one;
- The number of individual cases in the paediatric population is greater than or equal to

  2 for active substances contained in medicinal products included in the additional monitoring list in accordance with REG Art 23 (see GVP Module X), unless the sole reason for inclusion on the list is the request of a post-authorisation safety study (PASS);

  3 for the other active substances;
- The event belongs to the IME list.

6.1.2. Clinical based methods

An additional way to focus on paediatric safety issues can be with the aid of a list of adverse events clinically relevant in the children population.

This list of targeted medical events (TMEs) is similar in purpose to the DME for the general population and shares some of its principles even if adapted to the paediatric population. It therefore contains adverse events that are known to be causally associated with medicinal products and to have more serious outcomes in children than adults. To identify the terms in the TME, the reactions most commonly associated with fatal or life threatening cases in children served as a starting point based on the assumption that these events are not expected in children. Terms that are already present in the DME list should be excluded to avoid duplication during the screening.

Implemented recommendation in EudraVigilance*

In the EV signal detection system (eRMR), TME are also used to focus on paediatric safety issues.

* This feature is an option requested by the European Regulatory Network and has not been implemented in the eRMR version for industry

6.1.3. Conclusions

The statistical and clinical based methods are combined following the same approach as in the overall population, both in term of prioritisation and having a separate visualisation.

Implemented recommendation in EudraVigilance*

In the EV signal detection system (eRMR), ICSRs from the paediatric population are clearly identified. A DEC is highlighted for review if any of the condition of the statistical (SDR) and clinical based (TME) method is satisfied.

The methods are combined to present the signal detection reviewer a summary information in one single value; when both methods simultaneously trigger a DEC to be highlighted, the TME value is prioritised.

* This feature is an option requested by the European Regulatory Network and has not been implemented in the eRMR version for industry

6.2. Geriatric population

Specific signal detection measures aimed at older recipients of medicines are a reasonable precaution given the high frequency of simultaneous use of multiple medicines and the possibility of impaired physiological elimination mechanisms.

The age threshold at which such measures should be implemented has not been clearly established. Although the proportion of patients for whom suspected adverse reactions are reported increases with age, some research has suggested that this can be explained by more common use of medicines (Begaud 2002). Thus it may be better to choose a threshold based on increased exposure rather than possible increased susceptibility.

The geriatric group is defined in the EV system including all patients with an age greater than and including 65 years old.

6.2.1. Disproportionality methods

Statistical disproportionality tools should be applied to the geriatric population in order to increase the ability to detect signals. The same approach recommended for the paediatric population of using within-group disproportionality statistics that are significantly higher than those in the non-geriatric group is advocated with the only difference to not reduce the threshold on the number of individual cases due to the larger size of the geriatric subgroup.

Implemented recommendation in EudraVigilance

In the EV signal detection system (eRMR), for the geriatric population within-group disproportionality is used as follow:

Relative Geriatr ROR = $ROR_{Geriatr}$ / ROR_{Rest}

An SDR is defined when the following criteria are applied:

- The lower bound of the 95% confidence interval of the $ROR_{Geriatr}$ is greater than one;
- The lower bound of the 95% confidence interval of the Relative Geriatr ROR is greater than one;
- The number of individual cases in the geriatric population greater than or equal to

  3 for active substances contained in medicinal products included in the additional monitoring list in accordance with REG Art 23 (see GVP Module X), unless the sole reason for inclusion on the list is the request of a post-authorisation safety study (PASS);

  5 for the other active substances;
- The event belongs to the IME list.

6.2.2. Clinical based methods

No advantage was found in EV in supplementing the DME list with a TME list for the older age group and hence the DME form of signal detection in the total dataset also covers this subgroup.

6.2.3. Conclusions

Implemented recommendation in EudraVigilance
In the EV signal detection system (eRMR) ICSRs from the geriatric population are clearly identified.
A DEC is highlighted for review if the condition of the statistical (SDR) method is satisfied.

7. Other areas of interest

In addition to the methods described, other information can play an important role in the decision whether a DEC merits further investigation. In this section the three most important areas are described; however, depending on the specific DEC being investigated, other information can also play an important role and this is the reason why in the eRMR much more signal detection data is visualised (e.g. seriousness, health care professional reports, route of administration, indication of use,…for more details refer to the User manual of the electronic Reaction Monitoring Report).

7.1. Abuse, misuse, overdose, medication error or occupational exposure

Besides the description of the clinical manifestation of the suspected adverse reaction, ICSRs may include information on the potential causal mechanisms for the reaction. Such information may relate to the circumstances of medicine exposure which could have contributed to the occurrence of the adverse reaction, e.g. abuse, misuse, overdose, medication error and/or occupational exposure. Although the coding of these circumstances is enabled as Preferred Terms in MedDRA (see GVP Annex IV), they are qualitatively different from the clinical circumstances which are the focus of disproportionality-based signal detection. Firstly, they are manifestly related to at least one medicinal product identified in the ICSR. With suspected adverse reactions in normal circumstances of use this relationship is a matter of clinical judgement. Secondly, the circumstances described by each of these terms differ depending on the product concerned. Hence between-medicine comparisons of reporting frequency of ICSRs with MedDRA-codes describing these circumstances are both unnecessary and potentially misleading.

However, knowledge of these circumstances can appreciably alter the assessment of causality when reviewing a potential signal. Thus, it is recommended that the numbers of ICSRs with reported MedDRA codes related to abuse, misuse, overdose, medication error and/or occupational exposure should be displayed and highlighted for each DEC in signal detection listings and that these cases are readily retrievable.

7.2. Positive re-challenge

An adverse event that has been reported to have reoccurred after renewed exposure, referred to as positive re-challenge, can be consistent with a causal relationship and should be clearly identified. The caution advised in section 5 should be noted as this circumstance may also have influenced the decision to send the ICSR.

7.3. Literature cases

Cases derived from literature should also be highlighted when new reports arise. This is important as it indicates that more detailed information on the case and additional review of the scientific case for a causal relationship may be available through retrieval of the article that prompted the report. The signal detection reviewer may wish to take advantage of this if any uncertainty remains following the initial assessment.

7.4. Conclusions

Implemented recommendation in EudraVigilance

In the EV signal detection system (eRMR) the following information are separately visualised and highlighted for each DEC when new reports are submitted:

- Abuse, misuse, overdose, medication error or occupational exposure*;
- Positive re-challenge;
- Literature cases.

* This feature is an option requested by the European Regulatory Network, in the eRMR version for industry only medication error has been considered

8. Application to other reporting systems

The signal detection methods described in this document are those that have been found useful in the EV database. Many of these, mainly the ones related to the disproportionalities methods in the overall population, were investigated in the IMI PROTECT project. The finding of PROTECT can be directly applied only to the databases in which they were produced. However, the changes in signal detection performance associated with changes in methods or thresholds were similar within the PROTECT databases and thus this may generalise to other databases.

Hence, if the performance has been measured for one SDA within a database, it is possible to use the PROTECT results to estimate how this performance might be modified when changing to another SDA within the group of SDAs studied. Probably this process should not be used in databases very different from those used in PROTECT which ranged in size from about 500,000 to 5,000,000 reports but the databases were both publicly owned and company.

If no measure of performance has been made then it is necessary to do so before attempting to establish thresholds to achieve any desired performance level. Tools for such an assessment can be downloaded from the PROTECT website (http://www.imi-protect.eu/).

9. Areas for further development

Spontaneous report databases remain a highly productive and effective source of early information on ADRs and the search for new or improved methods of signal detection in these databases generates a constant stream of ideas with potential to increase the effectiveness of pharmacovigilance. These ideas require extensive testing. Typically they are initially developed in proof-of-concept studies in a limited setting but then require further development to assess their added value in the context of a signal detection system that may incorporate several competing signal detection procedures. Moreover, it appears that different databases may have properties that influence the effectiveness of signal detection procedures and thus it is best to test new methods on the database in which it is hoped to use them.

We list here some methods that appear promising or areas of research that are currently not fully investigated. These are an un-prioritised and partial list but represent possible directions for development in EV:

- Methods based on parametric modelling for time to onset for products for which exposure times can be determined, in particular vaccines. Some research that provides a good starting point for further development is Van Holle 2012;
- Investigation of MedDRA PT 'synonyms': although it has proven difficult to find more effective levels of MedDRA than the Preferred Term for signal detection (Hill 2013) it appears likely that some PTs are similar enough that they are interchangeably used in ICSRs by an appreciable proportion of reporters. This reduces the power to detect signals and such effective synonyms should probably be combined at the point of signal detection analysis. Such combination should be guided by empirical proof that the signal detection is improved;
- Use of additional information in statistical signal detection: there is some evidence that VigiRank and, possibly, adjustment using logistic regression can improve signal detection and this requires further investigation;
- Treatment of combination products in signal detection: monitoring the safety of substances that are used within a number of different combination products presents a challenge. Should ICSRs from all such products be combined, kept separate, or some intermediate level of combination designed based on additional factors such as the nature of the other substances in the combination?
- Products used in combinations: certain products tend to be used simultaneously; should these also be combined in routine signal detection and if so how can they be identified?
- Detecting drug-drug interactions: statistical methods to detect interactions appear of limited utility. Further work into incorporating information on the potential mechanism of interaction is suggested (Strandell 2013);
- Statistical signal detection within therapeutic/clinical areas: a study (Grundmark 2014) has suggested that restricting signal detection to within therapeutic areas may improve signal detection. Two areas were reported and positive trends were noted. Further development is required.
- Occasionally pharmacovigilance initiatives may focus on a specific group of products and cause unrepresentative reporting. In these cases comparison to products reported under the standard rules is inappropriate and within-group comparisons should be used. Some work has been done on direct comparison of these products (Kurz 2011) and this should also be developed.
- Investigation of processes based on critical review: although direct review of spontaneous reports has been used for many years no data appear to exist either on the inter-reviewer reliability or the effectiveness for signal detection. This is important as such review is often the fall-back position in challenging areas of signal detection;
- Quality assurance of existing signal detection processes: ongoing assessment of the effectiveness of signal detection processes should be designed into every system. Thought should be given into how to define stages of the evolution of a signal and calculate useful measures of effectiveness of the decision making process that can be calculated over appropriate time intervals and used to monitor the processes;

- Different thresholds and/or frequency of monitoring for older and well established products: investigate whether there is any efficiency in increasing the thresholds and/or frequency of screening for medicinal products with a well-established safety profile;
- Subgrouping effect on time to detection of an ADR: splitting the database in smaller parts might delay reaching the thresholds on the number of case. This aspect was not studied in PROTECT and is important to gain a clear understanding of the subgrouping performance based on smaller groups. Moreover, the fact that some of the calculations based on random subgroups appeared to give better performance than the crude also requires further investigation;
- Use of literature cases: literature cases submitted to EV arise from a fairly heterogeneous set of articles ranging over simple case reports, observational studies, systematic reviews etc. They are also characterised by many reports from the same source (with some of these coming via other routes creating duplicates) and are concentrated on specific drugs. It is not obvious that such reports are analysable by any single method and it would be interesting to investigate how they can be used most productively;
- Whether the effectiveness of signal detection in a database changes over time: results from PROTECT suggest that SDA performance may reduce with time. This raises a question of whether such changes are predictable, for instance if they reflect size or increasing heterogeneity in the background, and whether they can be controlled;
- Comparison across spontaneous databases: it would be interesting to quantify the added value of smaller specialised spontaneous databases in signal detection;
- Methods for products with few spontaneous reports, in particular products that are new to the market or have very limited exposure. In the previous guideline (EMEA/106464/2006 rev. 1) it was suggested that: "When a medicinal product is new to the market and only a small number of ICSRs have been received, it is feasible and probably more appropriate to assess these ICSRs individually than to rely on statistical methods. This is partly due to the fact that the reliability of the statistical screening is limited by the small numbers of ICSRs." This, of course, is an unstructured review process and it raises the question of whether a systematic process can be developed with reasonable inter-reviewer agreement.

10. Conclusion

As the size and complexity of spontaneous reporting databases has grown, the importance of a well-defined process of initial signal detection has increased. The use of such a process allows the overall workload involved in signal detection to be predicted and the available resources to be focused in an efficient manner on to DECs of most concern.

This document details how these requirements have influenced the development of signal detection processes in EV and how those processes have been evaluated. The recommended methods have the potential to allow more signals to be detected compared to the previously implemented methodology without increasing workload. Implementation in business processes and through revised guidance was preceded by a prospective pilot phase in real-world signal detection and, to gather further evidence of the expected benefits, a protocol to study the changes in efficiency over time is being developed. This methodology will form the basis of future quality assurance.

Signal detection is a subject of ongoing research and areas of potential promise have been identified.

11. List of abbreviations

ADR: Adverse Drug Reaction

DEC: Drug Event Combination

DME: Designated Medical Events

EVDAS: EudraVigilance Data Analysis System

EBGM: Empirical Bayes Geometric Mean

eRMR: electronic Reaction Monitoring Report

EV: EudraVigilance

IC: Information Component

ICSR: Individual Case Safety Report

IME: Important Medical Events

IMI: Innovative Medicines Initiative

MAH: Marketing Authorisation Holder

MedDRA: Medical Dictionary for Regulatory Activities

NCA: National Competent Authority

PPV: Positive Predictive Value

PROTECT: Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

PRR: Proportional Reporting Ratio

PT: Preferred Term

ROR: Reporting Odds Ratio

SDR: Signal of Disproportionality Reporting

SDA: Signal Detection Algorithm

TME: Targeted Medical Events

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13. Appendix

13.1. ROR calculation

Calculation of the ROR is based on a classification of the individual cases in the database into four categories based on two dichotomous variables. This is shown below:

Medicinal products \ Events	Event R	Not event R
Medicinal product P	a	b
Not product P	c	d

The general metrics to calculate the ROR are as follows:

- The value 'a' indicates the number of individual cases that list the suspected medicinal product P and the adverse event R;
- The value 'b' indicates the number of individual cases that list the suspected medicinal product P but not the adverse event R;
- The value 'c' indicates the number of individual cases that list the adverse event R but not the medicinal product P of interest;
- The value 'd' indicates the number of individual cases that do not list the adverse event R or the medicinal product P of interest.

The ROR is computed as follows[18]:

$$ROR = \frac{a/b}{c/d}$$

The utility of this statistic for signal detection is based on the consideration that when a product causes the event the number of observed reports for the DEC will tend to exceed the number based on chance alone and the ROR will thus tend to exceed 1. A necessary assumption for this to function is that a fair diversity of products is assumed to exist in the dataset so that most of those included in the denominator will not cause the event.

Example 1:

- The odds of individual cases of nausea amongst all the reports involving a particular medicinal product P is equal to 0.05 (e.g. 5 reports of nausea amongst a total of 105 reports reported with this medicinal product P; A = 5, B = 100);
- The odds of reports of nausea amongst all the reports involving all the other medicinal products of the database (but not the medicinal product P) is also equal to 0.05 (e.g. 5,000 reports of nausea amongst 105,000 reports reported with all other medicinal products; C = 5,000, D = 100,000).

In this example, the ROR is equal to 1 (i.e. (5/100) / (5,000/100,000) = 0.05 / 0.05 = 1). This can be interpreted as the odds of reports of nausea within all reports involving the medicinal product P are the same as the odds of reports of nausea among all other reports in the database,

[18] When c is equals to 0, the ROR cannot be computed. In EudraVigilance, the value of the ROR is arbitrarily set at 99.9 to reflect the presence of a possible SDR.

Example 2:

- The odds of individual cases of nausea amongst all the reports involving a particular medicinal product P is equal to 0.15 (e.g. there are 15 reports of nausea amongst a total of 115 reports reported with this medicinal product P; A = 15, B = 100).
- The odds of individual cases of nausea amongst all the reports involving all the other medicinal products of the database (but not medicinal product P) is equal to 0.05 (e.g. 5,000 reports of nausea amongst 105,000 reports reported with all other medicinal products; C = 5,000, D = 100,000).

In this second example, the ROR is equal to 3 (i.e. (15/100) / (5,000/100,000) = 0.15 / 0.05 = 3). This can be interpreted as the odds of reports of nausea within all reports involving the medicinal product P are three times higher than the odds of reports of nausea among all other reports in the database,

The 95% confidence interval gives an indication of the precision of the estimate of the reporting odds ratio. The 95% confidence interval of the ROR is also computed in the eRMR and EVDAS output. In order to do this we first estimate the standard deviation of the natural logarithm of the ROR by the following formula:

$$s = \sqrt{(1/a + 1/b + 1/c + 1/d}$$

The 95% confidence interval for ln(ROR) is then estimated as ln(ROR) ± 1.96s and, taking the exponential of this, we get:

95% confidence interval for ROR = (ROR / exp(1.96s), ROR x exp(1.96s))

In case of the relative ROR, the standard deviation of the natural logarithm can be estimated by the following formula:

$$s = \sqrt{s^2_{ROR_{Paed/Geritatr}} + s^2_{ROR_{Rest}}}$$

The 95% confidence interval for ln(Relative ROR) is then estimated as ln(Relative ROR) ± 1.96s and, taking the exponential of this, we get:

95% confidence interval for Relative ROR = (Relative ROR / exp(1.96s), Relative ROR x exp(1.96s))

13.2. Methodological considerations for subgroup analysis and stratification

A complication in specifying which subgroups to consider for routine signal detection is that different thresholds for continuous covariates may generate large numbers of potential groupings and these are further multiplied by combinations of two or more covariates. In PROTECT prior definitions of subgroups were constructed on the basis of clinical and pragmatic considerations; this allowed control of the over-estimation of performance that can result from unrestricted multiple testing. This process of restriction of the subsets in combination with the large reference set of ADRs used to calculate the sensitivity and precision resulted in accurate estimates of these parameters and this was verified by running a Bayesian model to calculate the shrunken estimates. These were very close in value to the un-shrunk estimates suggesting that multiplicity of subgroups had little impact.

A more interesting concern than multiplicity was whether the difference between the performance estimates from the crude analysis and sub-grouped or stratified analysis reflected some adjustment for the variable on which the subgroups were based or if it resulted simply from the fact that the criteria

for an SDR are based on smaller groupings. In order to investigate this we performed control calculations for each sub-grouped or stratified analysis dividing the underlying data into subgroups of the same size but in a random fashion – not based on the values of any variable. Interestingly this produced different estimates both from the crude and the sub-grouped or stratified analysis. For example, random division of the dataset into groups of the same size as those associated with separating by reporting region gave higher PPV than the crude ROR analysis but did not increase the sensitivity as instead the analysis using the specific subgroups based on continent. Multiple repetitions of the selection of the random subgroups showed highly consistent results. This revealed that part of the changes observed in performance were not associated with the information contained in the subgrouping variable but that appreciable proportions of the change could be attributed to this source. Hence the systematic subgrouping on some variables appeared to be worthwhile. An odd feature of this calculation was that some of the calculations based on random subgroups appeared to give better performance than the crude and this requires further investigation.

In PROTECT a sensitivity analysis using a threshold for the number of reports summed across subgroups, in other words the total used in the crude analysis, – results not shown – revealed that almost all subgroup analyses gave appreciable losses in PPV but higher sensitivity. This would result in reduced efficiency and is not useful in a resource limited signal detection system and thus this strategy can be excluded.

13.3. Additional information for Figure 1 and 3 and summary table

Table 4. Signal detection methods in PROTECT Study (see Figure 1)

Statistical method	Signal detection algorithm	Current use	Conditions for SDR
EBGM	EB05 (1.8, 3, 2.5)	MHRA	EB05 ≥ 1.8 & n ≥ 3 & EBGM ≥ 2.5
	EB05 (1.8, trend)	AZ	EB05 ≥ 1.8 **or** positive trend flag (1)
	EB05 (2.0, trend)	GSK	EB05 > 2.0 **or** positive trend flag (2)
IC	IC	UMC	IC lower bound 95% confidence interval (c.i.) > 0
PRR	PRR025 (1.0, 3)	EMA	PRR lower bound 95% c.i. ≥ 1 & n ≥ 3
	PRR025 (1.0, 5)	EMA	PRR lower bound 95% c.i. ≥ 1 & n ≥ 5
	PRR (3.0, 3, 4.0)	No	PRR ≥ 3 & χ^2 ≥ 4 & n ≥ 3 (3)
	PRR (2.0, 3, 4.0)	Bayer	PRR ≥ 2 & χ^2 ≥ 4 & n ≥ 3 (4)
	PRR (2.0, 3, 3.84)	Roche	PRR ≥ 2 & p (χ^2) <= 0.05 & n ≥ 3
ROR	ROR025 (1.0, SHR)	UMC	ROR with shrinkage, lower bound 95% c.i. > 1 (5)
	ROR025 (2.0, 5)	MEB	ROR lower bound 95% c.i. > 2 & n ≥ 5
	ROR025 (1.0, 3)	No	ROR lower bound 95% c.i. ≥ 1 & n ≥ 3
	ROR025 (1.0, 5)	No	ROR lower bound 95% c.i. ≥ 1 & n ≥ 5
URN	URN1	No	Reporting Ratio > 1 & unexpectedeness > 1 / 0.05
	URN500	No	Reporting Ratio > 1 & unexpectedeness > 500 / 0.05

Table 5. Details on the variables used for subgroup analysis in PROTECT (see Figure 3)

Covariate	Strata	Legend in the graph
Age	0–23 months, 2–11, 12–17, 18–35, 36–64, 65–74, 75 years, unknown	Age
Gender	Male, female, unknown	Gender
Time period	5-yearly	Year
Event seriousness	Serious, non-serious	CIOMS Serious
Reporter qualification	Consumer only, healthcare professional only, mixed	Reporter
Report source	Spontaneous (excluding solicited/legal cases)	Reporter
Country of origin	Individual country of origin	Country
Region of origin	North America, Europe, Japan, rest of Asia, rest of the world	Continent

Table 6. Summary of the methods recommended

Population	Disproportionality methods	Clinical based methods	Other areas of interest
Total	Selection of the method: • ROR	• DME • IME Fatal events	• Abuse, misuse, overdose, medication error or occupational exposure** • Positive re-challenge • Literature cases
	Thresholds defining SDRs: • Lower bound of the 95% c.i. > 1 • Number of individual cases ≥ 3 for active substances contained in medicinal products included in the additional monitoring list* 5 for the other active substances • Event belongs to the IME list		
	Subgroup analysis: • Exclusion of litigation cases • Use of subgrouping by geographical region of reporting		
Paediatric	Selection of the method: • Relative Paed ROR = ROR_{Paed} / ROR_{Rest}	• TME**	
	Thresholds defining SDRs: • Lower bound of the 95% c.i. ROR_{Paed} > 1 • Lower bound of the 95% c.i. Relative Paed ROR > 1 • Number of individual cases in the geriatric population ≥ 2 for active substances contained in medicinal products included in the additional monitoring list* 3 for the other active substances • Event belongs to the IME list		
	Subgroup analysis: • Exclusion of litigation cases		
Geriatric	Selection of the method: • Relative Geriatr ROR = $ROR_{Geriatr}$ / ROR_{Rest}		
	Thresholds defining SDRs: • Lower bound of the 95% c.i. $ROR_{Geriatr}$ > 1 • Lower bound of the 95% c.i. Relative Geriatr ROR > 1 • Number of individual cases in the geriatric population ≥ 3 for active substances contained in medicinal products included in the additional monitoring list* 5 for the other active substances • Event belongs to the IME list		
	Subgroup analysis: • Exclusion of litigation cases		

* In accordance with REG Art 23 (see GVP Module X) unless the sole reason for inclusion on the list is the request of a post-authorisation safety study (PASS)

** This feature is an option requested by the European Regulatory Network; in the eRMR version for industry, TME has not been implemented and only medication error has been considered