

## Spontaneous Adverse Drug Reactions

### Subgroup report

César Hernandez García, ES (subgroup lead)

Luis Pinheiro, EMA

Miguel Ángel Maciá, ES

Roxana Stroe, RO (until January 2018)

Ada Georgescu, RO (until January 2018)

Roxana Dondera, RO (until January 2018)

Zsuzsanna Szabóné Cserjés, HU (until June 2018)

## Table of content

<b>Table of content</b> .....	<b>2</b>
<b>1. Summary</b> .....	<b>3</b>
<b>2. Background</b> .....	<b>3</b>
<b>3. Objectives</b> .....	<b>4</b>
<b>4. Methods</b> .....	<b>4</b>
<b>5. Data Characterisation</b> .....	<b>4</b>
5.1. Volume .....	5
5.2. Veracity .....	5
5.3. Variability.....	6
5.4. Velocity.....	6
5.5. Value .....	7
<b>6. Key issues related to pharmacovigilance databases</b> .....	<b>7</b>
6.1. Improving data collection .....	7
6.1.1. Sourcing data .....	8
6.1.2. Improving electronic reporting tools .....	9
6.1.3. Identifying and understanding biases.....	9
6.2. Integrating pharmacovigilance data with other data sources .....	10
6.2.1. Strengthen data collection and integration .....	10
6.2.2. Pharmacoepidemiological Research on Outcomes of Therapeutics (PROTECT) .....	11
6.2.3. The Observational Medical Outcomes Partnership and further developments.....	11
6.2.4. Exploring and Understanding Adverse Drug Reactions (EU-ADR) .....	12
6.2.5. Food and Drug Administration’s (FDA’s) Sentinel Initiative .....	12
6.2.6. Interplay with other data sources.....	12
6.3. Data analytics.....	13
6.3.1. Novel analytical tools to interrogate data .....	13
6.3.2. New processes to address efficiency and scalability .....	14
<b>7. Conclusions</b> .....	<b>15</b>
7.1. Table of recommendations.....	15
<b>8. References</b> .....	<b>17</b>

# 1. Summary

Pharmacovigilance reporting systems provide invaluable data from which the majority of signals of Adverse Drug Reactions (ADRs) originate. These systems are uniquely positioned in the field of pharmacoepidemiology and drug safety, due to the governance of the data collection systems, the diverse nature of the primary source of data and the clinical disorders being monitored.

The data collection system has a legal and regulatory framework that determines common technical specifications for the transmission of individual case safety reports (ICSRs) and a harmonised language at a global level used to code adverse reactions.

Different sources of information, i.e. healthcare professionals, patients, legal representatives, literature articles, clinical trials, etc., and disparate safety concerns, such as ADRs emerging from medication errors, quality defects, cases of abuse and misuse and occupational exposure, produce a multi-dimensional and large dataset.

While under-reporting, missing information and reporting of duplicates are well known limitations of pharmacovigilance reporting systems, other limitations come into play, namely misclassification, information bias, increase in databases size and variability of safety concerns.

The regulatory drive to increase the amount of data and improve the quality of databases of pharmacovigilance (PhV) reporting systems are likely to maintain these databases at the forefront of signal detection. Moreover, by increasing the dimensions of the data collected (i.e. collecting more features or variables) it may be possible to move beyond solely using the data for risk identification and attempt a first approach to risk characterisation and stratification where evidence from formal pharmacoepidemiological studies is lacking.

On the other hand, increased availability and variety of data will bring with it new challenges on interrogating increasingly large datasets and gaining useful insights to guide and inform decision-making and on the scalability of manual or semi-manual signal detection processes.

The insights gained with PROTECT provide useful tools to address some of these concerns, but going forward, these challenges are likely to pressure regulatory authorities and pharmaceutical companies into disruptive innovation. Increasing data-linkage and leveraging automation and artificial intelligence to address scalability concerns and to enhance data interrogation seems to be a natural step and one that particularly suits real-world data.

# 2. Background

Pharmacovigilance databases of individual cases of suspected Adverse Drug Reactions (ADRs) have remained a cornerstone of PhV signal detection methods despite increasing usage of other data sources and methodologies. They still account for the majority of signals triggered (Pacurariu et al, 2014) even with a more proactive approach and increased access to other data sources like electronic health records (EHR), registries, social media, among others

The European Union (EU) PhV legislation has stressed the role of spontaneous reporting by healthcare professionals (HCP) or patients either directly or through the marketing authorization holder and, despite under-reporting, these systems are competent at detecting new risks of medicines. Besides encouraging and facilitating as much as possible spontaneous reporting through the increasing use of electronic reporting or mobile devices, gateways between EHR or social media reports and PhV databases could allow combining different data sources in order to achieve the best performance of the system for signal detection.

It is noteworthy that, unlike other health databases, pivotal PhV databases are almost exclusively under the governance of regulatory or public health authorities. EudraVigilance, national databases at Member State level, the Canada Vigilance Program database, the FDA Adverse Event Reporting System (FAERS), the Japanese Adverse Drug Event Report database (JADER) and the Global Individual Case Safety Reports Database System (VigiBase) of the World Health Organisation (WHO) programme for international drug monitoring are examples of structured “big data”.

Leveraging the wealth of data in these databases has been an ongoing challenge that has led to the development of a number of statistical and qualitative methodologies for signal detection, which have been adapted and improved over the years as the characteristics of the data change.

### **3. Objectives**

The purpose of this work is to map and discuss 1) methods to strengthen PhV data collection and integration with other sources of data, 2) analytical tools that may serve to enhance the insights produced and 3) processes to address efficiency and scalability concerns as the data increases.

### **4. Methods**

In order to identify relevant initiatives with interest for the current mapping exercise, PhV databases were identified from the main worldwide medicines regulatory regions. Additional queries included the identification of previous and current ongoing initiatives identified in web-based search engines such as EU funded research projects and other non-EU regulatory initiatives., Literature searches were also conducted on relevant and selected data sources focusing on:

- Methods that facilitate the reporting of ADRs by HCPs (e.g., data gateways from EHR to ADRs databases) or by patients (e.g., apps or other systems that facilitate patient’s spontaneous reporting);
- Methods and systems that query information from other data sources, to support further assessment of the safety signals;
- Methods to conduct signal detection in PhV databases.

Initiatives were considered for mapping purposes according to their potential added value in terms of scalability of processes and enhancing the ability to extract insights and produce high-quality data-driven regulatory decision-making.

Data characterization of data sources other than PhV databases were not included in the scope of this analysis and will be mentioned in their respective subgroup reports of the Big Data Task Force. Also, out of the scope are data derived from clinical trials. However, these data sources will be mentioned to the extent that they may impact the analytical processes in PhV databases.

### **5. Data Characterisation**

An ever-evolving legal and regulatory framework in the EU determines data collection, management and submission of reports of suspected adverse reactions to medicinal products in PhV systems (EMA, 2017). Possibly uniquely to data standards in all other aspects of regulatory science, both the common technical specification for the transmission of ICSRs and the medical terminology used to code adverse reactions – the Medical dictionary for Regulatory Activities (MedDRA) - are harmonised at a global level.

Furthermore, in some regulatory jurisdictions, such as at European level, legal provisions make it mandatory to report serious suspected adverse reactions to products authorised in the EU occurring within and outside the jurisdiction, thus making the databases global in nature.

Another unique characteristic is that the pivotal PhV databases are owned by regulatory government agencies or public health organizations. The main PhV databases available are EudraVigilance in the EU<sup>1</sup>, the national databases at the Member state level, the Canada Vigilance Program database<sup>2</sup>, the FDA Adverse Event Reporting System (FAERS)<sup>3</sup>, the Japanese Adverse Drug Event Report database (JADER)<sup>4</sup> or the Global Individual Case Safety Reports Database System (VigiBase) of the WHO programme for international drug monitoring<sup>5</sup> are examples of structured “big data”.

## **5.1. Volume**

In the context of data held by regulatory authorities and of data used in drug regulation, global PhV databases can be considered as big data: by 2018, Eudravigilance held over 14.5 million ICSRs<sup>6</sup> and other international ADRs Databases like VigiBase hold several million reports of suspected ADRs (Wisniewski et al, 2012).

The legal provisions in the different jurisdictions imply that some case reports in these databases will overlap to some degree. As an example, case reports in the databases of the Member States of the EU are also included in the EudraVigilance database as well as some non-EU cases (for serious cases of medicinal products marketed in the EU).

Thus, merging these databases under an adequate agreement between the different data holders may not necessarily yield a significant increase in relevant cases.

While technically one of the biggest sources of data owned by regulatory agencies, probably the two most well recognized limitations of these databases are still the under-reporting of adverse reactions and missing data. These two limitations have been the ones that regulatory systems have most often tried to impact on, by increasing the ease of reporting, increasing training, running social campaigns, changing reporting requirements, etc.

## **5.2. Veracity**

The framework for data communication of PhV data is set to a high standard. The technical requirements and the process of transmission of ICSRs are laid down in the International Organization for Standardization (ISO) Individual Case Safety Report (ICSR) standard ISO EN 27953-2 which the ICH implemented as reporting requirements.

Furthermore, a harmonised terminology – MedDRA – is used to communicate the safety concerns. MedDRA is a rich and highly specific standardized medical terminology developed by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) to facilitate sharing of regulatory information internationally for human medicinal products.

MedDRA<sup>7</sup> is governed by the MedDRA Management Committee (MC) and maintained, developed and distributed by the Maintenance and Support Services Organization (MSSO), contracted by ICH with

---

<sup>1</sup> <http://www.adrreports.eu/>

<sup>2</sup> <https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-database.html>

<sup>3</sup> <https://open.fda.gov/data/faers/>

<sup>4</sup> <http://www.pmda.go.jp/english/safety/outline/0001.html>

<sup>5</sup> <https://www.who-umc.org/vigibase/vigibase/>

<sup>6</sup> [https://www.ema.europa.eu/en/documents/report/2018-annual-report-eudravigilance-european-parliament-council-commission-reporting-period-1-january\\_en.pdf](https://www.ema.europa.eu/en/documents/report/2018-annual-report-eudravigilance-european-parliament-council-commission-reporting-period-1-january_en.pdf)

<sup>7</sup> <https://www.meddra.org/>

technical and financial oversight of the MedDRA MC. The dictionary is vital to ensure consistency in PhV databases.

However, outside the regulatory environment other medical terminologies are more widely used, such as the International Statistical Classification of Diseases and Related Health Problems (ICD)<sup>8</sup> or the Systematized Nomenclature of Medicine (SNOMED)<sup>9</sup>. This raises the need to develop mapping models across medical terminologies for the purpose of data interoperability. The IMI WEB-RADR 2 project will deliver a mapping between MedDRA most frequently used ADR terms and SNOMED. For the mapping between ICD and MedDRA a concept paper has been prepared by the MedDRA MC followed by an initial feasibility analysis in collaboration with WHO.

Despite the structured environment for data collection and communication, the cases themselves may be of varied quality – assuming that quality is the degree of detail and consistency in the cases. Different primary sources of data and different concerns may affect significantly the data quality.

As an example, a case report that stems from the literature has most likely been peer-reviewed and improved upon, whereas a case identified on social media may be less detailed. Another example of missing information in case reports is the batch number: in EudraVigilance, the batch numbers were available for 21.1 % of the suspected biopharmaceutical products, compared with only 3.6 % of the small molecule drugs (Vermeer et al, 2013).

Cross-validation of data is not currently possible as patients do not have individual identification codes that could be used to link their case reports to other data sources.

Finally, other limitations such as misclassification, information bias, duplicate reporting; among others also affect spontaneous reporting systems.

### **5.3. Variability**

Variability in the data included in spontaneous reporting databases is related to the nature of the different stakeholders and procedures involved.

First, wide differences in under-reporting of ADRs are recognized among countries and regions depending on the existence and effectiveness of promotion campaigns.

Second, the level of detail and accuracy of the reported data are highly influenced by the willingness of the original reporter and the follow-up information obtained by the PhV staff in regulatory authorities and MAHs. Variability in this respect may reflect different practices among organizations.

Third, the evolving history of standards and regulation in this field implies differences between cases reported in the past and those reported in recent years.

### **5.4. Velocity**

Depending on the geographical coverage of the database and the reporting requirements, PhV databases may process, on average, several thousand case reports per day.

For databases that effectively have global coverage, the quickly accumulating data means that new information on possible risks can become available in short time intervals. This has led to the need of continuous monitoring of new data. For instance, monitoring of EudraVigilance for signal detection is being performed at frequencies that range from every two weeks to every six months.

---

<sup>8</sup> <http://www.who.int/classifications/icd/en/>

<sup>9</sup> <https://www.snomed.org/>

## **5.5. Value**

Pharmacovigilance databases are used for hypothesis-free data mining of ICSRs of suspected ADRs and thereof, for the expert review of case reports with a view to conduct formal causality assessment and signal detection.

The advantage of collating real-world adverse reaction data and of bottlenecking cases from different primary data sources, e.g. healthcare professional, literature reports, clinical trial data, etc. into these databases seems evident from the proportion of signals identified by the European Medicines Agency (EMA) that originate from EudraVigilance (81.8% in 2017). As scientific literature is also monitored in a separate screening exercise, the high proportion attests to the value of PhV databases.

While there are various methods to interrogate data developed over time (van Puijenbroek et al, 2002; Bate and Evans, 2009; Hauben and Bate, 2009; Arnaud et al, 2017), the vast majority of methods relies on two variables alone – the reaction and the medicinal product. Models including time series, geographical distribution of case reports or including more variables have proven to extract additional insights on the data. So, a study (Seabroke et al., 2016) investigated the impact of stratification and subgrouping in signal detection algorithms in spontaneous report databases of different sizes and characteristics using a range of key covariates (age, gender, calendar time period, country of origin, vaccines/non-vaccines, event seriousness, reporter type and report source). Also, an algorithm correctly identified higher than expected frequencies of reports of several historical concerns related to quality defects (Pinheiro et al, 2017), but prospective evaluations are lacking.

These models work by assisting in the prioritization of safety concerns, but the signal detection process relies heavily on causality assessment and case narrative reviews. As data quality improves with new business rules and technological development, fully leveraging the data harvested using established and new statistical models is likely to become part of the norm.

In addition, the analysis of data from PhV databases may benefit from combining them with other data sources, such as chemical information databases (Low et al, 2016), medical literature databases, and other regulatory databases.

Linkage at the individual patient level with observational data like EHR or patient registries is not possible since PhV databases are anonymized and do not contain any unique identifier of the patient. Thus, interplay with these other data sources is not possible at this level.

Nevertheless, healthcare professionals reporting suspected ADRs usually have access to the complete electronic clinical records of their patients and may facilitate the inclusion of the relevant medical information pertaining to an ICSR provided that the format of the ICSR is fully integrated in the prescribing and clinical record tool (i.e. EHR tool) available at the point of care.

## **6. Key issues related to pharmacovigilance databases**

Considering the challenges and opportunities that PhV databases will bring, three fundamental aspects were identified: 1) Improving data collection, 2) Data integration and linkage with other data sources and 3) Novel methods to interrogate data and ensure scalability of processes.

### **6.1. Improving data collection**

The recognised limitations of spontaneous reporting systems, social changes both in access to information by patients and consumers and use of social media, as well as the development of novel methods of data collection, mean that there are several opportunities to improve data collection in terms of quantity and quality.

### 6.1.1. Sourcing data

National competent authorities in the EU have implemented systems to receive ICSRs from patients and healthcare professionals thus empowering them to report suspected ADRs. However, reporting from patients in some other jurisdictions may vary.

So far, much attention has been devoted to facilitating patient reporting and to examine the usefulness of social media as a source of data on ADRs reported by patients (see below).

#### 6.1.1.1. Use of social media

**The WEB-RADR** (Recognising Adverse Drug Reactions) Project (Ghosh et al, 2015) was an IMI Project developing a mobile app for patients and healthcare professionals to report suspected ADRs to national EU regulators and investigating the potential for publicly available social media data for identifying drug safety issues. The project delivered an EU-wide mobile phone app that enables users to report ADRs directly to their national competent authority.

They also developed methods to scrape publicly available data on social media sites and run automated text mining filters to collect additional information on adverse reactions, thereby complementing existing methods of signal detection. The project was aligned with the European Commission (EC) Joint Action SCOPE (Strengthening Collaboration for Operating Pharmacovigilance in Europe).

Work Package 3a – Mobile Reporting Platform, involved the design of a mobile application to engage both the public and healthcare practitioners around issues of real-time PhV. The app has two main functions: alerting, and reporting.

Work Package 3b – User Based Evaluation, provided insight into barriers and facilitators for patients and healthcare professionals to use a mobile application for reporting ADRs and accessing safety information. The work package was led by the University of Groningen together with the University College London, EURORDIS, Amgen and Novartis Pharma. A report of the motivations for reporting through an app, has been already published (De Vries et al, 2017). Identified factors that may influence the use of the app were the type of feedback given on reported ADRs, how ADRs reports are stored and the type of drug news. Also mentioned were other functions of the app, ease of use, type of language, the source of safety information provided through the app, security of the app, layout, the operating systems on which the app can be used and the costs.

**MedWatcher** is the web gateway of the FDA to report suspected adverse reactions to drugs, medical devices, and vaccines. Medwatcher has an accompanying app that allows reporting from a mobile phone along with receiving alerts and information pertinent to the patients' status (Bahk et al, 2015).

MedWatcher is a project run out by Boston Children's Hospital and Harvard Medical School, created in collaboration with the FDA Center for Devices and Radiologic Health and the MedWatcher system is run by Epidemico, which also participated in the WEB-RADR IMI Project.

Although not considered big data, there are some **other initiatives** to promote, especially via apps, data gathering from patients with rare diseases who are been treated with orphan medicines. One example of this is the app WACEAN from the Dravet Foundation. This may not fit into the concept of big data but into the concept of "all data" which may be especially relevant for orphan medicines.

#### 6.1.1.2. Embedding reporting schemes in patient management systems

Besides the apps described above that are intended not only for patients reporting but also healthcare professionals reporting, the most recent literature focuses on facilitating the process of ADRs reporting.



It has been suggested that there is a need to develop systems to assist healthcare professionals with completing ADRs reporting within EHR because this approach seems to be an efficient method to increase the ADRs reporting rate (Ribeiro-Vaz et al, 2016).

Although there has been a recent report on the value of the help provided to HCP by adverse drug event managers (Vinther et al, 2017), it is generally believed that an increase in HCP reporting should pass through gateways that integrate EHR and PhV databases (see below).

### **6.1.2. Improving electronic reporting tools**

Equally important to increasing the amount of data is improving quality of the data in PhV databases. The ability to make assumptions from the data provided in PhV databases is related to the quality of the data. Going forward, an increase in the number of observations is likely to demand an increasing reliance in statistical analysis to summarise data, rather than manual review, thus it becomes increasingly important that at least the structured fields are properly coded.

This can be achieved with different approaches. Embedding reporting schemes in electronic medical records is one approach as mentioned in the previous section. Another approach is that national competent authorities organize web-based reporting tools that include structured fields streamlining the data entry towards current coding dictionaries for drugs and medical terms.

The Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) Joint Action has been created to support operations of PhV in the EU following the requirements introduced by the 2010 European PhV legislation. SCOPE was divided into eight separate work packages, with five work packages focusing on PhV topics to deliver specific and measurable objectives, ranging from improvements in ADRs reporting to assessment of quality management systems. Work Package 4 – ADR Collection was focused on national schemes for the spontaneous reporting of ADRs and was aimed to provide national competent authorities with a full understanding of good practices within national systems for collecting ADRs.

Work package 4 created a web-based form for reporting of ADRs by European healthcare professionals, patients, and their carers. The form was designed using the internationally agreed standard for ICSRs to enable the transmission of cases direct into national and EU databases. The system can also act as a national competent authority database if required. The web-form offers a simple solution for any national competent authority wishing to implement a new reporting web-form and can be tailored to the national competent authority's needs (SCOPE Joint Action).

### **6.1.3. Identifying and understanding biases**

Most limitations in data collection in PhV are well known and a certain degree of investment has been done to reduce them. However, as the data accumulates and the databases become more global in nature, they become affected by new concerns that must also be understood.

Recently, attention given to the spatio-temporal distribution of case reports may provide new insights on how to best use PhV data. For example, an analysis of the geographic distribution of case reports of interstitial lung disease hinted that there are localised phenomena that may not replicate across the world (Pinheiro et al, 2016).

Furthermore, concerns such as increased frequency of reporting over time need to be further explored in view of understanding whether they result from a true safety concern or are the result of increased media attention.

In this regard, attention to a real or perceived safety issue in the medical community or in public media may increase the reporting rate for that drug-event pair to such an extent that the overall

reporting of that event is affected and potentially masks alerts from other drugs. If the masking effect of drugs on adverse reactions or adverse reactions on drugs is substantial, applying an unmasking algorithm could be considered. In this context, several approaches have been proposed (Wisniewski et al, 2016).

### **6.1.3.1. Duplicate reporting**

Duplicate reporting can occur due to several reasons. However, typically duplicates stem from the reporting requirements for ADRs reported in the literature, which imply that for substances with multiple marketing authorisation holders, several reports of the same case could be submitted.

Algorithms that identify suspected duplicates are run on most PhV databases, such as the databases from FDA, EMA and WHO. In addition, the EMA has set up a literature monitoring system that provides a service to marketing authorisation holders, of screening for ADRs reports in the literature, in view of creating standardised high quality ICSRs and reducing duplicate reporting to EudraVigilance.

## **6.2. Integrating pharmacovigilance data with other data sources**

Due to the complementary usefulness of PhV databases and other observational data sources such as EHR, administrative claims data, registries and/or social media, there is a growing interest in finding ways to complement PhV databases with these alternative data sources (Ly et al, 2015).

There seems to be no evidence on overall superiority of any of them regarding the others in terms of the ability to provide safety information. Rather, their performance seems to depend on the specific characteristic of each safety concern. Costs may not be the same for all of them (Coloma et al, 2011; Pacurariu et al, 2015; EU-ADR webpage).

### **6.2.1. Strengthen data collection and integration**

Data in PhV databases could be complemented with data sourced from other databases. This could include data scrapped from social media, data from pharmacological or pharmacodynamic characteristics of the medicinal product and data from the disease.

#### **6.2.1.1. Use of social media data**

Social media is addressed in detail in a separate document. However, it is important to note that social media data shares many characteristics with spontaneously reported ICSRs. In fact, pharmaceutical industry has some responsibility over screening the internet<sup>10</sup> and will probably need further guidance on how to scrutinize social media to fulfil their PhV obligations (ABPI, 2013).

A recent project, WEB RADR, has addressed the use of social media data. Two work packages, in particular, deserve individual mention.

Work Package 2a – Social Media, led by Epidemico, had the purpose to provide access to classified social media data via a visualisation platform for signal identification and confirmation.

Work Package 2b – Analytics, led by World Health Organisation's Uppsala Monitoring Centre, aimed to develop and link new and existing analytical tools for the analysis of social media content for PhV purposes. Work package 2b was focusing on suspected ADRs identification, record linkage of duplicate reports, and signal detection.

---

<sup>10</sup> [https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vi-collection-management-submission-reports\\_en.pdf](https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vi-collection-management-submission-reports_en.pdf)

### **6.2.1.2. Biological mechanism data**

Data linkage between product dictionaries used in PhV and databases of molecular targets and other pharmacological and pharmacodynamic characteristics of the products could assist in reducing time to detection of ADRs, in particular where well known mechanisms crosstalk such as interactions and class effects.

### **6.2.2. Pharmacoepidemiological Research on Outcomes of Therapeutics (PROTECT)**

The Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (PROTECT) was a collaborative European IMI project that comprises a programme to address limitations of current methods in the field of pharmacoepidemiology and PhV. It included a multi-national consortium of 34 partners including academics, regulators, small and medium-sized enterprises and EFPIA companies. The PROTECT projects ran from 2009 to 2015 and rendered several outcomes.

A report summarizing the results and their impact on regulatory practice was published on September 2016 (PROTECT webpage<sup>11</sup>). Briefly, the goals of PROTECT included the enhancement of data collection using modern tools of communication and the improvement of regulatory operations through validation of methodologies and techniques on a variety of data sources such as clinical trials, observational data and spontaneous reports. PROTECT has generated a significant amount of scientific research across the EU.

Among PROTECT outputs relevant for this review, it should be cited a review of good detection practices for signal detection that was used to update methods for signal detection from EudraVigilance (Wisniewski et al, 2016) and the exploration of new methods to collect data directly from patients, including via the internet (Dreyer et al, 2015). A final list of 23 outputs was identified, 8 related to methods for signal detection and 3 related to data collection directly from patients and consumers.

Based on the work of a panel established within the EMA, sub-grouping and stratification in statistical signal detection was considered of high impact and high feasibility and was implemented; The development of accessible material to patients was considered high impact but moderate feasibility; The comparison of covariate adjustment methods and grouping of existing ADR terminologies were considered moderate impact and high feasibility; The statistical signal detection from clinical trials and from electronic health records were rated moderate impact and low feasibility.

A concrete implementation of outcomes is the use of the SmPC-ADR database. The PROTECT ADR database is a downloadable Excel file listing of all MedDRA Preferred Terms or Lowest Level Terms listed in section 4.8 'Undesirable effects' of the Summary of Product Characteristics (SPC) of centrally authorised medicinal products authorised in the EU.

### **6.2.3. The Observational Medical Outcomes Partnership and further developments**

The Observational Medical Outcomes Partnership (OMOP, <http://omop.org>) was a public-private partnership established to inform the appropriate use of observational healthcare databases for studying the effects of medical products. This project ended in 2013 and involved researchers from industry, government, and academia. One of the deliverables was the evaluation of various analytical methods on their ability to identify true associations and avoid false findings. This project also

---

<sup>11</sup> <http://www.imi-protect.eu/>

evaluated tools and capabilities for transforming, characterizing, and analysing disparate data sources across the health care delivery spectrum.

LAERTES (Large-scale adverse effects related to treatment evidence standardization) (Knowledge Base workgroup of the Observational Health Data Sciences and Informatics (OHDSI), 2017) provides a standardized, open, and scalable architecture for linking evidence sources relevant to the association of drugs with health outcomes of interest (HOIs) that can be useful, among others, for regulatory operations.

The OHDSI also has a method (Achilles Heel) to conduct data quality queries that has been already applied to 24 large healthcare datasets across seven different organizations (Huser et al, 2016).

#### **6.2.4. Exploring and Understanding Adverse Drug Reactions (EU-ADR)**

Exploring and Understanding Adverse Drug Reactions (EU-ADR, <http://euadr-project.org>) (Coloma et al, 2013) is a project aimed to exploit information from various EHR databases in Europe to produce a computerized integrated system for the early detection of drug safety signals and overcome some of the limitations of spontaneous reporting database. This reference standard was developed for the primary purpose of evaluating performance of methods for signal detection using EHR.

The system generates signals (drug-event pairs that may warrant further investigation) using epidemiological and computational, data and text mining techniques on the basis of a federated structure of data sources. Once generated, the signals are substantiated by applying causality criteria (based on biological plausibility). The purpose of this substantiation process is to place the signals in the context of the current biomedical knowledge that might explain the signal. The resulting EU-ADR platform allows exploring datasets, running specific substantiation modules and combining the evidence obtained from each of the methods, constituting an effective tool to help research work in PhV.

.

#### **6.2.5. Food and Drug Administration's (FDA's) Sentinel Initiative**

Sentinel is the FDA's national electronic system which has transformed the way researchers monitor the safety of FDA-regulated medical products.

The Sentinel System uses a distributed data infrastructure approach which allows the FDA to rapidly and securely access electronic healthcare data (such as EHR, insurance claims data and registries) from 193 million patients from multiple data partners while securing and safeguarding the privacy of patients. The active surveillance capability of the Sentinel System does not replace the FDA's existing surveillance tools but complements other FDA safety surveillance capabilities by allowing the FDA to proactively assess the safety of regulated medical products.

#### **6.2.6. Interplay with other data sources**

Besides EHR or registries, PhV databases may benefit from integrating other databases like chemical structure databases (Low et al, 2016), medical literature databases, genomic data, and regulatory databases.

SIDER (Kuhn et al, 2015) is another database that contains information on marketed medicines in the USA and their recorded ADRs. The information is extracted from public documents and package inserts. The available information includes adverse reactions frequencies, drugs and adverse reactions classifications as well as links to further information, for example drug-target relations.

There has been some scoping work done on the combined use of SIDER and FAERS to predict drug combinations where one drug could reduce the adverse reactions of another (Ly et al, 2017).

SPLICER ADR is another available database that summarizes structured product labels from FDA authorized products (Duke et al, 2013).

### **6.3. Data analytics**

Data analytics helps regulatory authorities to fully harness their PhV data to uncover new insights and inform decision-making.

While in PhV the role of the expert reviewer is unlikely to be challenged, it is likely that in the future sophisticated statistical models will help to identify patterns in large scale or high-dimensional data.

Furthermore, scalability concerns and efficiency drives will lead to increase the use of automation processes, such as natural language processing for data extraction and summary. Voos et al., for instance, used an automated data extraction and classification tool of different databases for aggregating disparate sources of information and to develop a predictive model to classify drug-adverse event relationships (Voos et al, 2017).

#### **6.3.1. Novel analytical tools to interrogate data**

##### **6.3.1.1. Enhancements in disproportionality metrics**

Years of use of disproportionality metrics have revealed, in detail, the limitations of these methods. PROTECT has addressed some of these concerns, with a view to enhancing the performance of these metrics.

Tatonetti et al (2012), have done work on statistical correction of uncharacterized bias (SCRUB) with a view to adjust the disproportionality metrics for co-reported drugs. This type of analyses may help reduce the number of false positive disproportionality signals and hence increase efficiency of the system. As of 2018, EMA is testing and validating results from a pilot implementation of the SCRUB method.

This field of research seems to be opened to further investment, particularly by harnessing additional variables and/or meta-data of the case reports.

##### **6.3.1.2. Improving decision support algorithms**

Decision support algorithms in the field of PhV help to triage the most relevant ADRs for each product. These decision support algorithms are typically assessed individually, for instance disproportionality, increase in fatal cases, focus on disorders with a high fraction of drug relatedness, can be used sequentially. However, it is not known if there are one or several combinations of these criteria, that could improve the performance of the decision support algorithm.

Novel methods using machine learning may help understand the best combination of criteria to identify a concern either by concern or by product.

##### **6.3.1.3. Exploring new dimensions of data**

Classical methods of signal detection rely on the use of disproportionality algorithms to prioritise a list of drug-event combinations, which is then reviewed manually.; The increase in the number of case reports allows extending the PhV toolkit beyond this triage and reviewing approach. Exploring other

dimensions of the data, including spatial-temporal distribution of cases and meta-data may provide useful insights into hitherto unexplored issues.

Recently there has been an increasing interest in the use of time-series and stochastic models including interrupted time-series and change point analysis (Xu et al, 2015), to monitor count data of adverse reactions as a proxy for interactions, quality defects, medication errors and other safety concerns (Pinheiro et al, 2017).

In addition, recent research suggests that for some concerns there may be a geographical distribution that needs to be considered in assessing the risks for each jurisdiction (Pinheiro et al, 2016).

#### **6.3.1.4. Machine learning methods**

As PhV data increases in volume, the potential to leverage machine learning to conduct predictive analytics to understand the likelihood of future outcomes based on individual risk factors increases.

The degree to which machine learning will pave the way to a more predictive PhV is unclear. What seems clear is that the implementation of machine learning methods will require a regulatory paradigm shift, the advantages and limitations of which are best summarised by the Data Analytics subgroup.

#### **6.3.1.5. Reproducible research and transparency**

Unlike most regulatory processes that rely on assessing data analysed by pharmaceutical companies, PhV databases are actively and routinely analysed by regulatory authorities.

Traditionally, in the European regulatory system, results of analyses are shared to the network.

Providing the evidence-based analytical pipeline, namely the data analysis plan, the annotated methodology, the data and related code, is fundamental for learning across the network as well as for reproducibility and transparency.

This will be particularly relevant once black box methods – i.e. models with opaque implementation such as neuronal networks, start being run on PhV data.

### **6.3.2. New processes to address efficiency and scalability**

#### **6.3.2.1. Natural Language Processing**

The advances achieved in Natural Language Processing (NLP) make it possible to automatically mine information from electronically created documents. Different annotated corpora have been created (Oronoz et al, 2015) allowing implementing of NLP algorithms which can then be analysed using machine learning techniques to detect ADRs automatically.

In a project initiated in April 2014, the FDA set a goal to use natural language processing and machine learning to analyse texts contained in FAERS and VAERS reports to improve efficiency and rigor of PhV activities<sup>12</sup>.

This methodology could equally be applied to social media (twitter, facebook or those specifically dealing with health issues in online communities). However, unlike corpora applied to NLP in health records, social media data sources require to take into account the use of colloquial language, jargon, misspellings, ambiguous assertions or sarcastic expressions.

Sequential filtering is also important because much of social media data are irrelevant for the purposes of ADRs detection (Yang et al, 2015). For this purpose, it is important to create specific corpus of

---

<sup>12</sup> <https://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm507301.htm>

annotated data for social media in order to apply NLP techniques and to test their performances in comparison with others (Sarker et al, 2015a; Sarker et al, 2015b).

## 7. Conclusions

Pharmacovigilance databases have proven to be important tools for the identification of ADRs and are likely to continue at the forefront of routine safety monitoring processes.

The outlook for the technological, scientific and legal framework of PhV indicates that more data, of different sources (case reports, biological targets, drug metabolism, social media, etc.) and in some respect, of higher quality, is likely to become available for data integration.

Regulatory authorities have an opportunity to facilitate data integration and harness its potential. The analytical methods of PhV data will likely have two main drivers, efficiency, as manual or semi-manual approaches start compromising scalability, and capacity, the ability to extract more insights, not just counts and disproportionality metrics.

For that purpose, regulatory authorities could consider:

- Investing in methods to integrate PhV and other real-world data with non-clinical data and methods to validate data integration;
- Exploring the use of new analytical tools, such as forecasting and machine learning, that leverage increased dimensions of data (spatial-temporal, other variables in case reports, meta-data);
- Fostering reproducible research as a way to ensure the network is made aware and can learn and execute new analytical approaches;
- Exploring how to implement automation and natural language processing to improve efficiency, data management quality and free expert reviewer time.

These recommendations should be predicated upon developing methods to ensure awareness of new research and development and designing a default collaborative approach to engage with key researchers and stakeholders.

### 7.1. Table of recommendations

Topic	Core Recommendation	Reinforcing Actions	Strategic Goal
Data analytics	Evaluate new analytical tools, such as forecasting and machine learning, that leverage increased dimensions of data (spatial-temporal, other variables in case reports, meta-data).	<ol style="list-style-type: none"> <li>1. Promote the development of a system of oversight and tracking of innovative methods in signal detection (and any other use of pharmacovigilance data).</li> <li>2. Strengthen the current processes, that determine research priorities, track them and harvest EU-wide regulatory science skillset to explore new analytical tools (e.g. PRAC's SMART Methods).</li> <li>3. Boost engagement with key researchers in academia and other stakeholders. For that purpose the following could be considered:</li> </ol>	An increased capacity and efficiency to analyse ADRs utilising novel analytical techniques.

		<ul style="list-style-type: none"> <li>Periodically publishing results from tracking of innovative methods and research priorities for the EU-regulatory system;</li> <li>Host symposia dedicated to showcasing novel methods and research initiatives from stakeholders;</li> <li>Host a competition with EudraVigilance data to improve signal detection methods. This would involve publishing a set of data from EV (anonymised) and setting research objectives.</li> </ul>	
Data quality	Explore how to implement automation and natural language processing to improve efficiency, data management quality and free expert reviewer time.	1. Investigate how to harvest the potential of automation in the EU-regulatory system particularly to improve the collection of data and it's quality, by facilitating structuring unstructured data (e.g. extracting relevant data from narrative fields such as social media, case narratives, medical notes) and assess the benefits and risks of increased automation.	To harvest automation where beneficial and increase efficiency and capability.
Data linkage	Investing in methods to integrate PhV and other real-world data with non-clinical data and methods to validate data integration.	<ol style="list-style-type: none"> <li>Promote linkage of data of most important parameters with a view to introduce new predictors to model/stratify on. E.g. information on target proteins and off-site targets may help gain new insights.</li> <li>Study how this data linkage can be facilitated.</li> </ol>	Linkage of data to the most important parameters could reveal new safety signals.
Skills and knowledge within the network	Fostering reproducible research as a way to ensure the network is made aware and can learn and execute new analytical approaches.	<ol style="list-style-type: none"> <li>Develop a set of core principles in reproducible research that are not language specific and can be shared across the network.</li> <li>Foster the use of open source analytical software, where possible, as a commitment to open science and to facilitate accessibility of research and analysis to all stakeholders, lay, academic or professional.</li> </ol>	To facilitate dissemination of methods and research across the network and to increase transparency through open science practices.



## 8. References

- ABPI. Guidance notes on the management of adverse events and product complaints from digital media; 2013. <http://www.abpi.org.uk/our-work/library/guidelines/Pages/safety-data-websites.aspx>.
- Bahk CY, Goshgarian M, Donahue K, et al. Increasing Patient Engagement in Pharmacovigilance Through Online Community Outreach and Mobile Reporting Applications: An Analysis of Adverse Event Reporting for the Essure Device in the US. *Pharmaceutical Medicine*. 2015;29(6):331-340. doi:10.1007/s40290-015-0106-6.
- Bate A, Evans SJ. Quantitative signal detection using spontaneous ADR reporting. *Pharmacoepidemiol Drug Saf*. 2009 Jun;18(6):427-36. doi: 10.1002/pds.1742. Review.
- Coloma PM, Schuemie MJ, Trifiro` G, Gini R, Herings R, Hippisley- Cox J, et al. Combining electronic healthcare databases in Europe to allow for large-scale drug safety monitoring: the EUADR Project. *Pharmacoepidemiol Drug Saf*. 2011;20:1-11.
- Coloma PM, Avillach P, Salvo F, Schuemie MJ, Ferrajolo C, Pariente A, Fourier-Réglat A, Molokhia M, Patadia V, van der Lei J, Sturkenboom M, Trifirò G. A reference standard for evaluation of methods for drug safety signal detection using electronic healthcare record databases. *Drug Saf*. 2013 Jan;36(1):13-23.
- De Vries ST, Wong L, Sutcliffe A, et al. Factors Influencing the Use of a Mobile App for Reporting Adverse Drug Reactions and Receiving Safety Information: A Qualitative Study. *Drug Safety*. 2017;40(5):443-455. doi:10.1007/s40264-016-0494-x.
- Dreyer NA, Blackburn SC, Mt-Isa S, et al. Direct-to-Patient Research: Piloting a New Approach to Understanding Drug Safety During Pregnancy. *JMIR Public Health Surveill* 2015;1(2):e22
- Duke J, Friedlin J, Li X. Consistency in the safety labeling of bioequivalent medications. *Pharmacoepidemiol Drug Saf*. 2013 Mar;22(3):294-301. doi:10.1002/pds.3351. Epub 2012 Oct 8. PubMed PMID: 23042584
- EU-ADR webpage. Available from: <https://bioinformatics.ua.pt/euadr/>.
- EMA, European Medicines Agency. Guideline on good pharmacovigilance practices (GVP) – Module VI (Rev 2) EMA/873138/2011 Rev 2, 2017.
- Food and Drug Administration. Data Mining at FDA -- White Paper <https://www.fda.gov/scienceresearch/dataminingatfda/ucm446239.htm>
- Ghosh R, Lewis D. Aims and approaches of Web-RADR: a consortium ensuring reliable ADR reporting via mobile devices and new insights from social media. *Expert Opin Drug Saf*. 2015;14(12):1845-53. doi: 10.1517/14740338.2015.1096342
- Hauben M, Bate A. Decision support methods for the detection of adverse events in post-marketing data. *Drug Discov Today*. 2009 Apr;14(7-8):343-57. doi:10.1016/j.drudis.2008.12.012. Epub 2009 Jan 31. Review.
- Huser V, et al. Multisite Evaluation of a Data Quality Tool for Patient-Level Clinical Data Sets. *EGEMS (Wash DC)*. 2016 Nov 30;4(1):1239. doi: 10.13063/2327-9214.1239. eCollection 2016.
- Knowledge Base workgroup of the Observational Health Data Sciences and Informatics (OHDSI) collaborative. Large-scale adverse effects related to treatment evidence standardization (LAERTES): an open scalable system for linking pharmacovigilance evidence sources with clinical data. *J Biomed Semantics*. 2017 Mar 7;8(1):11. doi: 10.1186/s13326-017-0115-3.

Kuhn M, Letunic I, Jensen LJ, Bork P. The SIDER database of drugs and side effects. *Nucleic Acids Res.* 2015 Oct 19. doi: 10.1093/nar/gkv1075

Li Y, Ryan PB, Wei Y, Friedman C. A Method to Combine Signals from Spontaneous Reporting Systems and Observational Healthcare Data to Detect Adverse Drug Reactions. *Drug Safety.* 2015;38(10):895-908. doi:10.1007/s40264-015-0314-8.

Li Y, Zhang P, Sun Z, Hu J. Data-Driven Prediction of Beneficial Drug Combinations in Spontaneous Reporting Systems. *AMIA Annu Symp Proc.* 2017 Feb 10;2016:808-817

Low Y.S, et al. *J Am Med Inform Assoc* 2016;23:968–978. doi:10.1093/jamia/ocv127

Ornoz m, Gojenola K, Pérez A, Díaz de Ilarraza A, Casillas A. On the creation of a clinical gold standard corpus in Spanish: Mining adverse drug reactions. *Journal of Biomedical Informatics* 56 (2015) 318–332

Pacurariu AC1, Coloma PM, van Haren A, Genov G, Sturkenboom MC, Straus SM. A description of signals during the first 18 months of the EMA pharmacovigilance risk assessment committee. *Drug Saf.* 2014 Dec;37(12):1059-66. doi: 10.1007/s40264-014-0240-1.

Pacurariu AC, Straus SM, Trifirò G, et al. Useful Interplay Between Spontaneous ADR Reports and Electronic Healthcare Records in Signal Detection. *Drug Saf.* 2015 Dec;38(12):1201-10. doi: 10.1007/s40264-015-0341-5.

Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium [PROTECT]. Available from: <http://www.imi-protect.eu/>.

Pinheiro L, Blake K, Januskiene J, Yue QY, Arlett P. Geographical variation in reporting Interstitial Lung Disease as an adverse drug reaction: findings from an European Medicines Agency analysis of reports in EudraVigilance. *Pharmacoepidemiol Drug Saf.* 2016 Jun;25(6):705-12. doi: 10.1002/pds.3998. Epub 2016 Mar 22. PubMed PMID: 27004571

Pinheiro LC, Candore G, Zaccaria C, Slattery J, Arlett P. An algorithm to detect unexpected increases in frequency of reports of adverse events in EudraVigilance. *Pharmacoepidemiol Drug Saf.* 2018 Jan;27(1):38-45. doi: 10.1002/pds.4344. Epub 2017 Nov 16.

van Puijenbroek EP, Bate A, Leufkens HG, Lindquist M, Orre R, Egberts AC. A comparison of measures of disproportionality for signal detection in spontaneous reporting systems for adverse drug reactions. *Pharmacoepidemiol Drug Saf.* 2002 Jan-Feb;11(1):3-10.

Ribeiro-Vaz I, Silva AM, Costa Santos C, Cruz-Correia R. How to promote adverse drug reaction reports using information systems – a systematic review and meta-analysis, *BMC Med Inform Decis Mak.* 2016 Mar 1;16:27. doi: 10.1186/s12911-016-0265-8.

Sarker A, Gonzalez G. Portable automatic text classification for adverse drug reaction detection via multi-corpus training. *J Biomed Inform.* 2015 Feb;53:196-207.

Sarker A, Ginn R, Nikfarjam A, O'Connor K, Smith K, Jayaraman S, Upadhaya T, Gonzalez G. Utilizing social media data for pharmacovigilance: A review. *J Biomed Inform.* 2015 Apr;54:202-12.

Seabroke S, Candore G, Juhlin K, Quarcoo N, Wisniewski A, Arani R, Painter J, Tregunno P, Norén GN, Slattery J. Performance of stratified and subgrouped disproportionality analyses in spontaneous databases. *Drug Saf.* 2016.

Stang PE, Ryan PB, Racoosin JA, Overhage JM, Hartzema AG, Reich C, et al. Advancing the science for active surveillance: rationale and design for the Observational Medical Outcomes Partnership. *Ann Intern Med.* 2010;153:600–6.

SCOPE Joint Action (<http://www.scopejointaction.eu/>)

Tatonetti N, Ye P, Daneshjou R, Altman R. Data-Driven Prediction of Drug Effects and Interactions. *Sci Transl Med*. 2012 Mar 14; 4(125): 125ra31.

Vermeer N, Straus S, K Mantel-Teeuwisse A, Domergue F, Egberts T, G M Leufkens H, L De Bruin, M. Traceability of Biopharmaceuticals in Spontaneous Reporting Systems: A Cross-Sectional Study in the FDA Adverse Event Reporting System (FAERS) and EudraVigilance Databases. *Drug safety : an international journal of medical toxicology and drug experience*. 2013, 36. 10.1007/s40264-013-0073-3.

Vinther S, Klarskov P, Borgeskov H, Darsø P, Christophersen AK, Borck B, et al. An adverse drug event manager facilitates spontaneous reporting of adverse drug reactions *Dan Med J*. 2017 Jan;64(1). pii: A5315.

Voss EA, Boyce RD, Ryan PB, van der Lei J, Rijnbeek PR, Schuemie MJ. Accuracy of an automated knowledge base for identifying drug adverse reactions. *J Biomed Inform*. 2017 Feb;66:72-81.

Wisniewski et al, [Characterisation of databases \(DBs\) used for signal detection \(SD\): results of a survey of IMI PROTECT work package \(WP\) 3 participants](#); 28th International Conference on Pharmacoepidemiology & Therapeutic Risk Management, 23-26 Aug 2012, Barcelona (<http://www.imi-protect.eu/documents/WisniewskietalCharacterisationofdatabasesusedorsignaldetectionposterfinalICPE2012.pdf>)

Wisniewski, A.F.Z., Bate, A., Bousquet, C. et al. Good Signal Detection Practices: Evidence from IMI PROTECT. *Drug Saf* (2016) 39: 469. doi:10.1007/s40264-016-0405-1.

Xu Z, Kass-Hout T, Anderson-Smits C, Gray G. Signal detection using change point analysis in postmarket surveillance. *Pharmacoepidemiol Drug Saf*. 2015 Jun;24(6):663-8. doi: 10.1002/pds.3783.

Yang M, Kiang M, Shang W. Filtering big data from social media--Building an early warning system for adverse drug reactions. *J Biomed Inform*. 2015 Apr;54:230-40.