New Trends in Drug Safety and the Growing Role of Real-World Evidence

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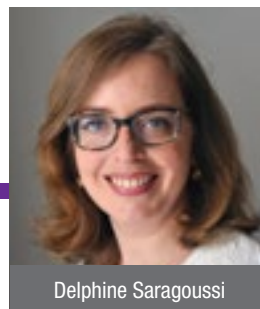
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Introduction

A renewed focus on drug safety has emerged with the increased number of approved drugs, greater availability of information, and more direct involvement of patients in their treatments. Major drug safety issues in the past several decades (e.g., thalidomide in the '60s, diethylstilbestrol in the '70s, cerivastatin, rofecoxib, and benfluorex in the 2000s) have contributed to an evolution of the regulatory framework for drug safety, particularly in the post-approval period, supported by scientific developments and technological innovations that have enhanced traditional passive pharmacovigilance activities with active surveillance and pharmacoepidemiological studies to bolster the precision and granularity of drug safety information.

The current period is marked by a focus on accelerated approvals of cancer drugs, immunotherapies, and orphan indications, and an increase in the use of biomarkers and surrogate endpoints in an environment where the amount of and accessibility to data seems to be exploding. Between 2001 and 2010, nearly one-third of drugs approved by the U.S. Food and Drug Administration (FDA) had major safety issues uncovered over four years, on average, after approval.[1] With this backdrop, we explore the recent developments of drug safety from the perspective of multiple stakeholders to bring a clearer global picture of:
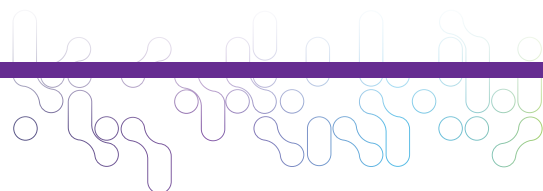
● where we stand and where we go in terms of regulations, data sources, and methods

● what is needed to ensure state-of-the-art real-world evidence (RWE) generation in drug safety.

Delphine Saragoussi
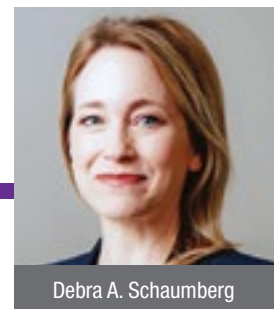
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Shifts in Regulatory Thinking

The Evolving Focus

The focus around drug safety has moved through the different steps represented in Figure 1.

- **Passive surveillance** and signal detection based on continuous monitoring of spontaneous reports of adverse drug reactions sent by physicians and compiled by biopharma companies and regulatory authorities.[2] Although signal detection approaches have been refined with adoption of metrics such as disproportionality measures,[3,4] this approach remains reactive and hypothesis-generating.

- **Risk management planning and evaluation** was originally applied beginning in the late '80s to specific drugs and evolved towards current Risk Evaluation and Mitigation Strategies (REMS) in the U.S. and the Good Pharmacovigilance Practice (GVP) in Europe and was formalized by the ICH-E2E guideline.[5] Risk management planning led to post-authorization safety studies, required by regulatory authorities or voluntary, to detect and/or monitor risks associated with newly-approved drugs and evaluate the effectiveness of risk minimization measures.

- **Active surveillance** became possible with the wider availability of real-world data sources and methodological innovation. It can be complemented with subsequent investigation to further define the magnitude of any new or known risk, and characteristics of patients that might alter the benefit-risk equation. A major example is the Sentinel System launched by the FDA to develop a systematic approach to leverage electronic healthcare databases to enable active post-marketing safety surveillance.[6] Another example is the EU-ADR project, a large European initiative based on a public-private partnership to enable analyses across different European electronic medical records data sources to improve signal detection.[7]
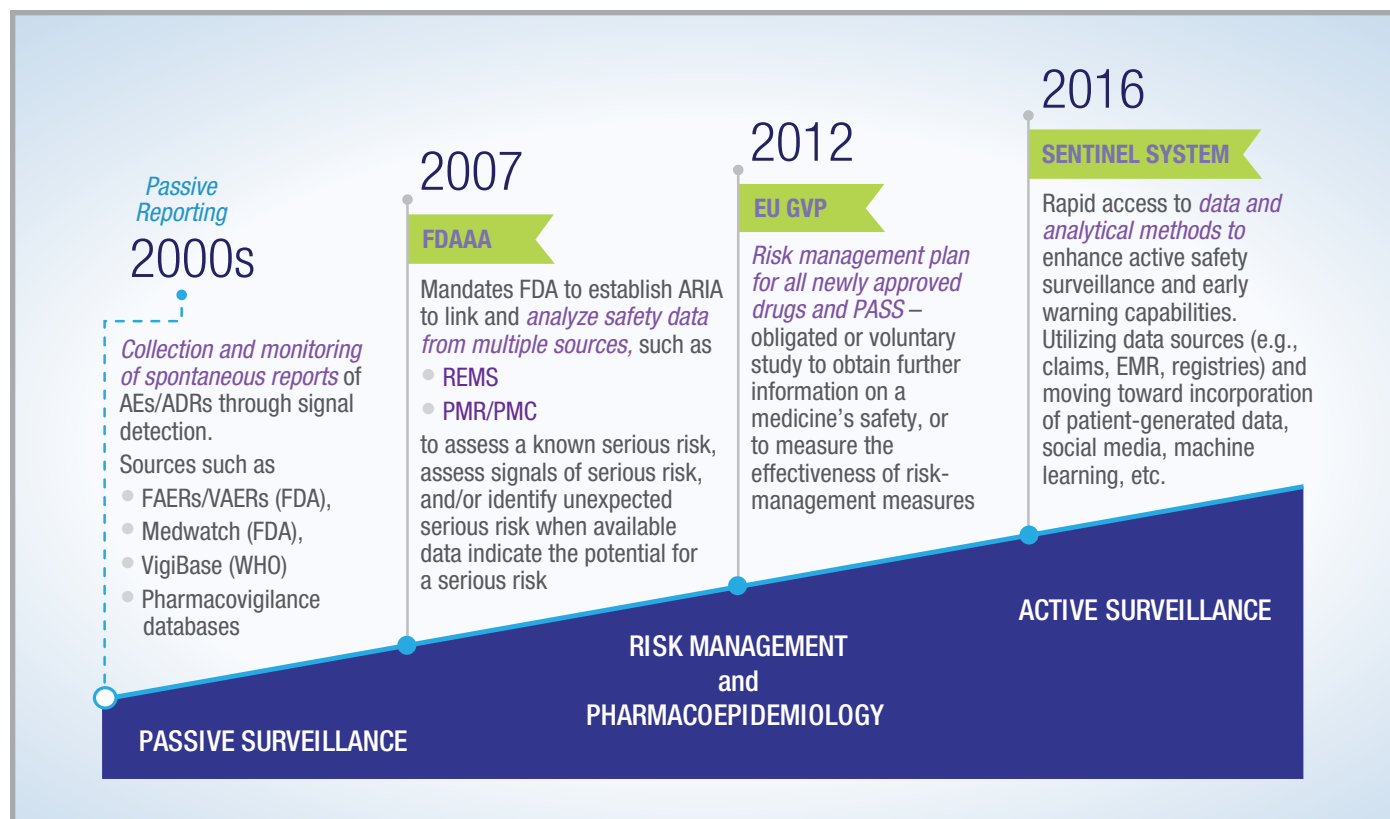
An Expanding Scope

Increased Role of Real-World Evidence in Drug Safety

Post-authorization safety studies (PASS) in Europe, and post-marketing requirements (PMR) or commitments (PMC) in the U.S., have become more frequent. Figure 2 shows the number of PASS currently registered in the EU Post-Authorization Studies (PAS) Register by category.
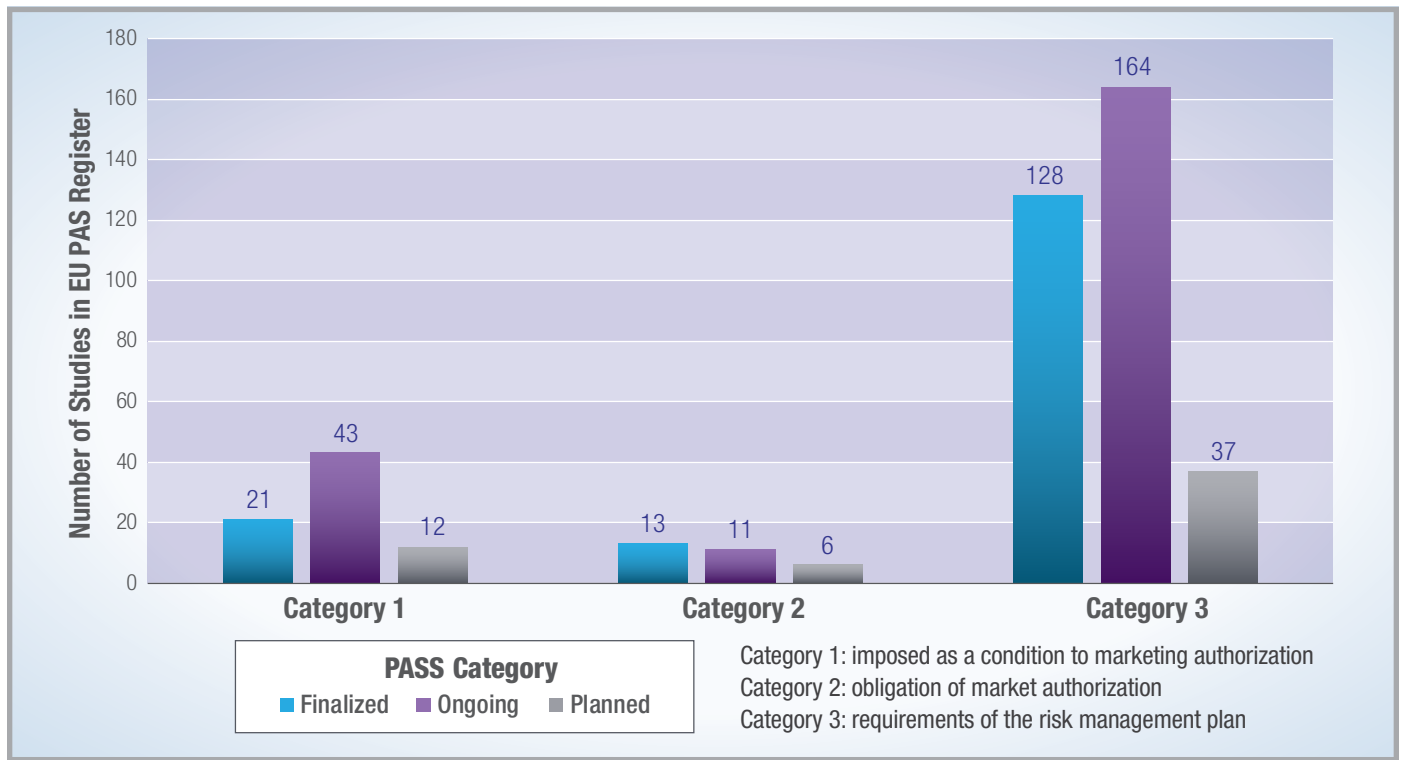
The European GVP acknowledges RWE approaches for PASS (for both primary or secondary data).[8,9] Most PASS

Figure 1. An Overview of the Regulatory Focus around Safety Surveillance and Evaluation over Time

Passive Reporting
2000s

Collection and monitoring of spontaneous reports of AEs/ADRs through signal detection.

Sources such as
- FAERs/VAERs (FDA),
- Medwatch (FDA),
- VigiBase (WHO)
- Pharmacovigilance databases

PASSIVE SURVEILLANCE

2007

FDAAA

Mandates FDA to establish ARIA to link and *analyze safety data from multiple sources,* such as
- REMS
- PMR/PMC

to assess a known serious risk, assess signals of serious risk, and/or identify unexpected serious risk when available data indicate the potential for a serious risk

2012

EU GVP

Risk management plan for all newly approved drugs and PASS – obligated or voluntary study to obtain further information on a medicine's safety, or to measure the effectiveness of risk-management measures

RISK MANAGEMENT and PHARMACOEPIDEMIOLOGY

2016

SENTINEL SYSTEM

Rapid access to *data and analytical methods to* enhance active safety surveillance and early warning capabilities. Utilizing data sources (e.g., claims, EMR, registries) and moving toward incorporation of patient-generated data, social media, machine learning, etc.

ACTIVE SURVEILLANCE

ADR = Adverse Drug Reaction; **AE** = Adverse Events; **ARIA** = Active Post-Market Risk Identification and Analysis; **EMR** = Electronic Medical Records; **EU** = European Union; **FAER** = FDA Adverse Event Reporting System; **FDAAA** = Food and Drug Administration Amendments Act; **GVP** = European Union Good Pharmacovigilance Practices; **PASS** = Post-Approval Safety Studies; **PMC** = Post-Marketing Commitments; **PMR** = Post-Marketing Requirements; **REMS** = Risk Evaluation and Mitigation Strategies; **VAER** = Vaccine Adverse Event Reporting System

Figure 2. Status of PASS in the EU PAS Register by Study Category as of April 2018

Category 1: imposed as a condition to marketing authorization
Category 2: obligation of market authorization
Category 3: requirements of the risk management plan

are observational studies,[10] and increasingly introduce real-world utilization (in particular, to describe exposure in groups not exposed in clinical trials) and effectiveness outcomes on top of safety outcomes. A recent article by Carroll et al. focused on non-interventional, post-authorization studies (PAS) in the EU PAS Register showed that many of the studies (65%) covered safety objectives,

followed by drug utilization objectives in 42%, and effectiveness objectives in 30%.[10]

In the U.S., the use of RWE for regulatory decision-making has been acknowledged and defined in the 21st Century Act of December 2016.[11] Although specific guidance is under development, the Cures Act provides sponsors with an array of study design options for the post-approval setting.

Figure 3. Type of PAS Registered in the EU PAS Register by Study Status (Finalized, Ongoing, or Planned) as of October 2016 (extracted from Carroll et al, 2017[10])
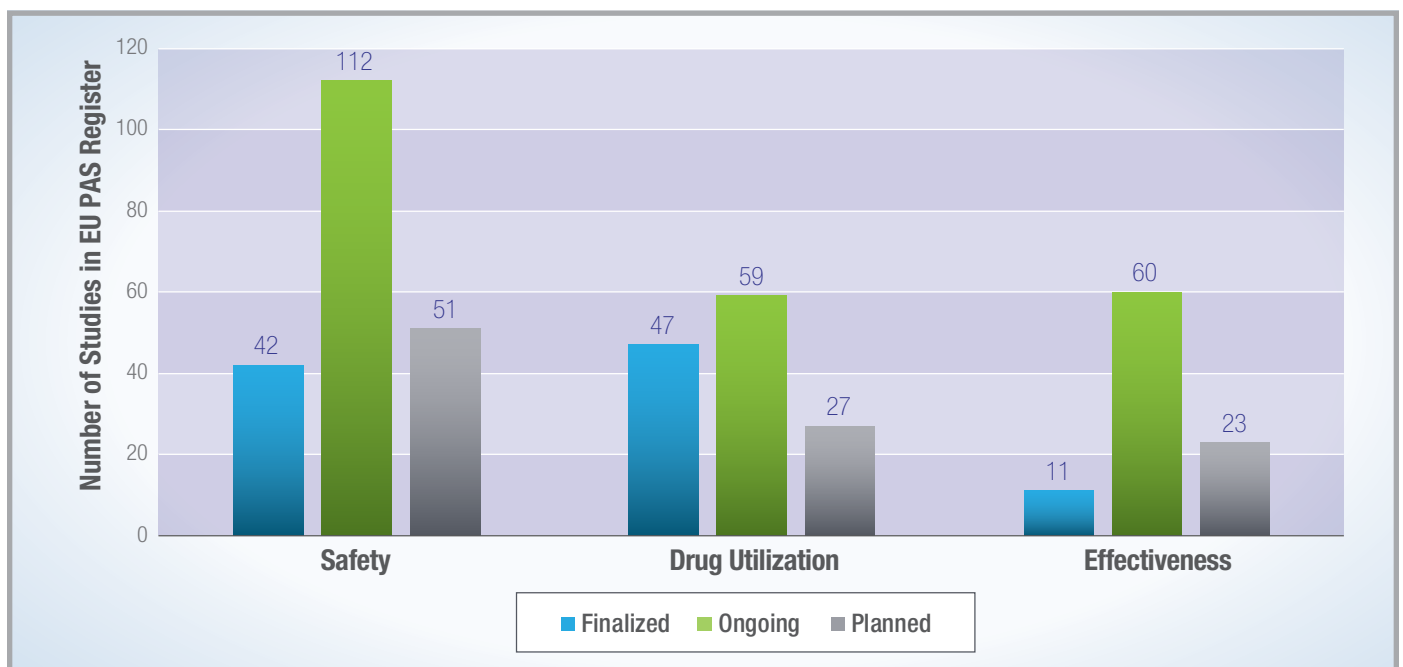
> "Real-world evidence for drug safety has been around for more than 20 years, but it has now become a hot topic, with much more recognition, emphasis, and requests by the regulatory authorities."
>
> —*Beth Nordstrom*, *PhD, MPH, Senior Research Leader, Real-World Evidence, Evidera*

The FDA has integrated RWE as an important part of the activity in the Center of Drug Evaluation and Research (CDER) Drug Safety Priorities 2017 report and stated an expectation that RWE will begin to play a greater role in regulatory decisions.[12] This is already the case with the use of Sentinel data via the Active post-market Risk Identification and Analysis (ARIA) system that is now used in FDA regulatory decisions.

An increasing number of public-private initiatives has contributed to greater consideration of RWE. The Sentinel System has provided opportunities for partnerships between the FDA and data providers as well as healthcare centers. For example, the Innovation in Medical Evidence Development and Surveillance (IMEDS) collaboration allows public and private partners to access Sentinel data while ensuring data security and integrity.[12] In Europe, the Innovative Medicines Initiative (IMI) is the biggest public-private partnership on drug development. Recently, IMI issued a call for proposals on several topics, including medicine safety in pregnancy and during breastfeeding, and predicting drug safety early in development. These projects will be funded jointly by the EU's Horizon 2020 program and the European Federation of Pharmaceutical Industries and Associations (EFPIA). Currently, public-private partnerships govern most of the innovative projects aimed at pooling data sources and/or delivering standardized methods.

Beyond Europe and the U.S., which have been followed closely by Canada and Australia, Asian countries such as South Korea, India, Japan, and mainland China now request post-marketing real-world evidence to observe drug effects in routine practice conditions and in larger and more diverse populations.[13] Although the availability of electronic health-care databases is increasing, the trend in these countries is to request primary data collection of large cohorts of exposed patients with a prospective follow-up.[14] In Latin America, Mexico also typically requires post-marketing studies as part of their market authorization process.[13]

Expanding to New Populations

Understanding the safety of drugs in populations usually excluded from clinical trials is an important concern of regulators and biopharma companies. Regarding pregnancy and breastfeeding, the FDA issued guidance for industry in 2002 to establish pregnancy exposure registries[15] and

Real-World Data Definition According to the 21st Century Cures Act

Data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than randomized clinical trials (RCTs) and covering:

- Large simple trials or pragmatic clinical trials
- Prospective observational or registry studies
- Retrospective database studies
- Case reports
- Administrative and healthcare claims
- Electronic health records
- Data obtained as part of a public health investigation or routine public health surveillance
- Data gathered through personal devices and health

the European Medicines Agency (EMA) introduced the need for post-authorization data in 2005.[16] More recently, the Pregnancy and Lactation Labeling Rule (PLLR) issued by the FDA in 2015 brought more emphasis on evidence supporting the label and benefit-risk evaluation in pregnancy, including the existence of a pregnancy registry, and the impact of the underlying disease.[17] A recent study shows that the PLLR so far has had an impact on methodological requirements for pregnancy registries.[18]

There is an increased acknowledgment of the specific challenges of assessing drug safety in children (e.g., long-term outcomes such as impact on growth and development), especially in chronic and rare diseases. The 21st Century Cures Act acknowledges these challenges by promoting pediatric research, supporting, amongst others, the implementation of the 2013 National Pediatric Research Network Act.[11]

Increased development of therapies for rare diseases, often under special regulatory requirements, has also contributed to a need for active surveillance. The FDA has announced an Orphan Drug Designation Modernization Plan and established an Orphan Products Council. The European Union and other countries have followed.[19] The 21st Century Cures Act has also brought focus on regenerative advanced therapies and pathways for early approval.[11] As the need for continuous safety data generation is high for these drugs, and their use is limited to small patient populations, rare disease/orphan drug registries provide a good solution for long-term safety studies.

The Era of Patient Centricity

Patients were allowed to report adverse drug reactions in the early 2000s in the U.S. and as late as 2010 in the EU,[20] and were then invited to participate in the decision-making process through the Patient Representative Program[sm] at the FDA and later in scientific advisory groups at the EMA. Patient surveys also became a key source of data to assess the effectiveness of risk minimization measures in Europe and for REMS in the U.S. More recently, the 21st Century Cures Act has expanded the focus on patient centricity by introducing "Patient-Focused Drug Development" and developing a plan to issue guidance on how to include the patient experience in drug development and regulatory decision-making.[11]

The inclusion of patient centricity in drug development can involve a multitude of activities. One aspect is the use of patient-reported outcomes (PROs) to collect patient experiences, however, this remains infrequent with a recent study showing only 6 out of 30 registries collected data on measures of quality of life.[21] Drug safety studies could benefit from more patient-reported feedback, such as quality of life studies which can help understand the impact of the disease, treatment, and safety events on patients' lives. One illustration is the Fabry Outcome Study, a long-term registry of patients with Fabry Disease with or without specific treatments, which includes a number of pediatric and adult PROs.[22]

How to collect data with minimal burden to patients is another important aspect of patient centricity. As an example, rare disease registries pose specific operational challenges related to the need to include and retain small numbers of patients, often children, scattered geographically, sometimes far away from research sites, with a low number of patients per site. One solution is to build a patient-centric registry, with one single reference site, where this site, the patients, their caregivers, and primary care providers can access an electronic data collection platform and record study-specific data.[23] (See Figure 4.)

New Conditions of Market Approval and Access

Accelerated regulatory processes (e.g., adaptive pathways, conditional market approval) and early access programs now allow patients with no other therapeutic options or who are ineligible for clinical trials to access new drugs more rapidly. In these programs, regulatory decision making is based on more limited clinical evidence than usually required. In some cases (e.g., regenerative medicine advanced therapy [RMAT] designation in the U.S.), preliminary clinical data could potentially arise from real-world evidence, for example in the case of one-arm clinical trials with observational historical or synthetic control arms. In return, the market authorization holder (MAH) is expected to continue generating evidence on the marketed drug or from patients in the early access program. Safety data are particularly sought after to clarify the benefit-risk ratio over time, due to the limited number of patients exposed during clinical trials.[24, 25]

As an example, pazopanib was initially conditionally approved by the EMA for renal cell carcinoma. During the conditional approval period, a post-marketing study was required to better understand the hepatotoxicity profile of the drug.[26] In addition, during the regulatory process,

Figure 4. The Traditional Site-Centric Model Versus the Patient-Centric Model
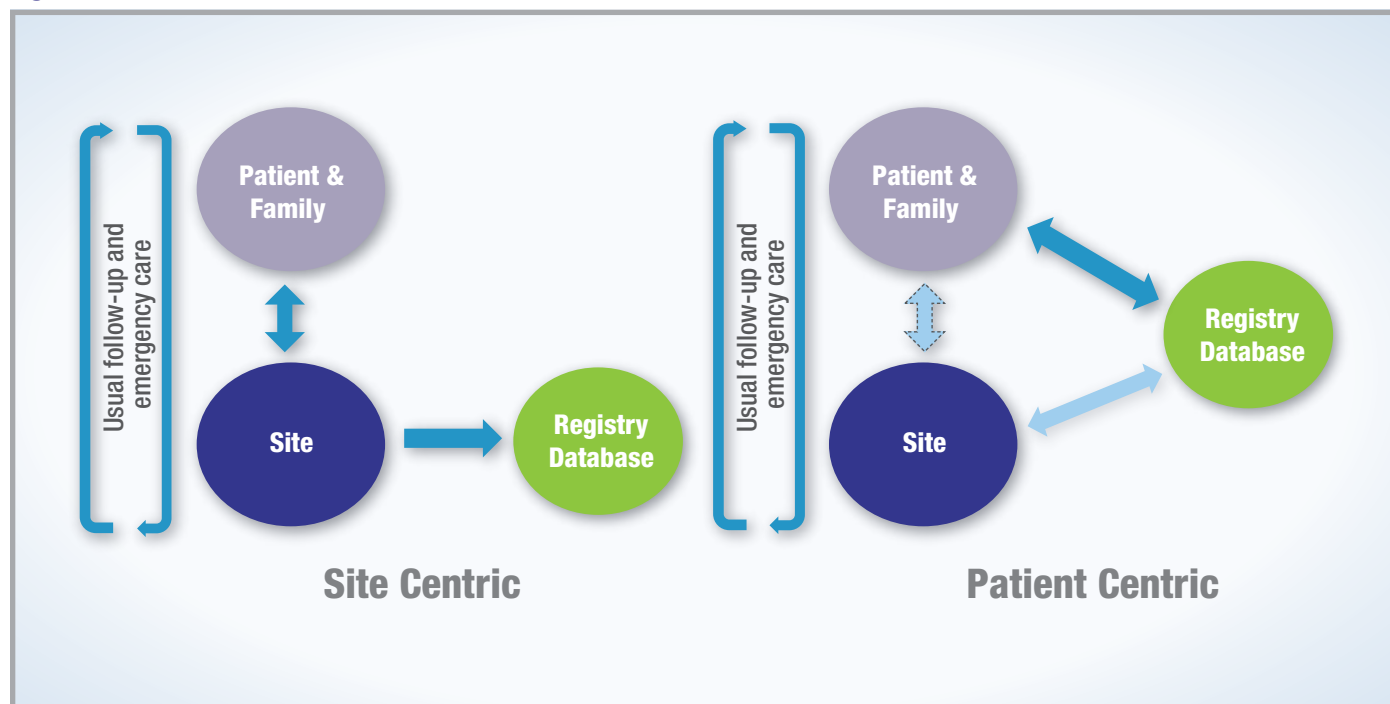
a named patient program in soft tissue sarcoma was launched. A chart review study of the effectiveness and safety of pazopanib was conducted in patients included in the named patient program and confirmed the effectiveness and safety results from clinical trials.[27] Pazopanib now has full European market approval in both indications.

> "There is an increasing trend towards integration of real-world evidence within the standard clinical development programs. This is most obvious in the case of conditional approval and adaptive pathways, where real-world evidence plays a major role towards helping to obtain full approval, for example by providing pre-marketing comparison data and post-marketing confirmatory effectiveness and safety data."
>
> —*Patrice Verpillat*, *MD, MPH, PhD, Head of Global Epidemiology, Merck KGaA, EFPIA Observer at ENCePP Steering Committee, Darmstadt, Germany*

Rapidly Evolving Technologies and Methods

Data Sources

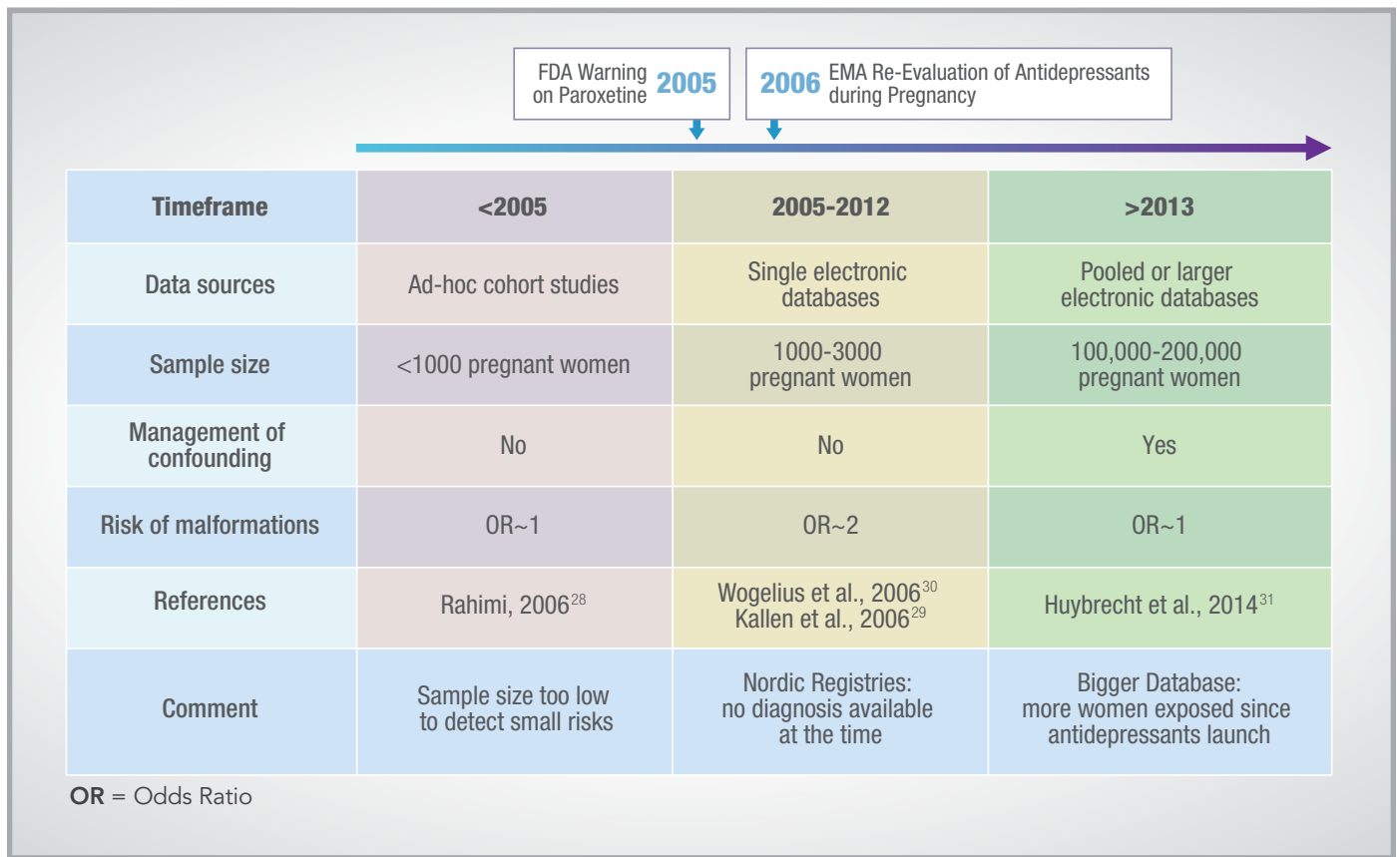#### Electronic Databases: Expansion in Number and Size

Epidemiology and pharmacoepidemiology investigations for drug safety are evolving with the greater availability and expanded content of existing data sources such as electronic medical records (EMR) databases and claims databases. One example of this evolution is the exposure to antidepressants during pregnancy and the risk of birth defects. Before the generalized use of large electronic data sources, the ad hoc studies performed were too small to be able to detect risks of malformation below 1 percent.[28] As large databases started being used, methods improved, and risks were shown to increase, but with major caveats such as the absence of adjustment on the underlying disease,[29,30] often due to a lack of information (e.g., Danish and Swedish national registers in the early 2000s, although these were the first examples of linkage of different data sources via the patient anonymized number). The use of a big U.S. database and the application of propensity scores changed the conclusions regarding the risk of birth defects associated with antidepressants.[31] This illustrates that access to novel data sources must be accompanied by a strong study design and reliable methods.

Figure 5. Data Sources by Drug Safety Objective

	Signal Detection	Active Surveillance	Drug Utilization	Risk Assessment Descriptive/Comparative + Effectiveness	Risk Minimization REMS/Effectiveness of aRMM
Registries		✖	✖	✖	
Other Primary Data Collection (including PROs)			✖ In some circumstances	✖	
Electronic Healthcare Databases	✖ Linked/pooled databases	✖	✖	✖	✖ In some circumstances
Patient Surveys					✖
Physician Surveys					✖
Spontaneous Reports	✖				
Social Media	✖		?	?	

aRMM = Additional Risk Minimization Measures

Figure 6. Antidepressants and Risk of Birth Defects – Evolution of Data Sources, Methods, and Conclusions

	FDA Warning on Paroxetine **2005**	**2006** EMA Re-Evaluation of Antidepressants during Pregnancy	
Timeframe	**<2005**	**2005-2012**	**>2013**
Data sources	Ad-hoc cohort studies	Single electronic databases	Pooled or larger electronic databases
Sample size	<1000 pregnant women	1000-3000 pregnant women	100,000-200,000 pregnant women
Management of confounding	No	No	Yes
Risk of malformations	OR~1	OR~2	OR~1
References	Rahimi, 2006[28]	Wogelius et al., 2006[30] Kallen et al., 2006[29]	Huybrecht et al., 2014[31]
Comment	Sample size too low to detect small risks	Nordic Registries: no diagnosis available at the time	Bigger Database: more women exposed since antidepressants launch

OR = Odds Ratio

The number of available data sources is still increasing, for example with the opening of the French national claims database (Système National des Données de Santé or SNDS) to private researchers in 2017.[32] The content of databases is also increasing, with new linkages developed between different data sources via anonymized patient identifiers (e.g., linkage between primary care medical records, hospital data, and death registries in the Clinical Practice Research Database, or between outpatient claims and inpatient data in the SNDS). The latest trend is now to pool several databases from several systems or countries together to increase the size of the populations.[33]

> "Drug safety in pregnancy is often an area where only collaboration between databases allows the identification of a sufficient number of exposed pregnancies to assess the safety of a new drug with acceptable uncertainty, assuming no systematic errors."
>
> —**Sonia Hernandez-Diaz**, *MD, MPH, DrPH, FISPE, Professor of Epidemiology, Director, Pharmacoepidemiology Program, Harvard School of Public Health*

> "There is a trend towards using multiple databases (in parallel and via linkage) to expand the patient population and/or deepen the data available on the patients of interest."
>
> —**Matthew Reynolds**, *PhD, Vice President, Epidemiology, Evidera*

Patient Networks, Social Media, and Wearables: New Sources of Data

Social media can comprise several entities, including patient networks, forums, blogs, and social networks such as Facebook and Twitter. Data derived from such sources are by nature unstructured and unsolicited. With some similarity in this respect to passive surveillance using spontaneous adverse events reporting, an early application of social media data for safety focused on signal detection. An example is the exploration by the FDA of the potential of Facebook and Twitter for safety signal detection by checking signals based on these social networks' data against known signals.[34]

PatientsLikeMe, a web-based network on which patients can connect with others with the same condition and share

their experiences, is an example of a patient network. In 2008, PatientsLikeMe launched a drug safety initiative facilitating direct patient reports of adverse events to the FDA, adding to the FDAERs spontaneously reported events. Since 2015, the network has been in a structured collaboration with the FDA covering several research topics, with the aim of clarifying if data from such patient networks can help with earlier identification of adverse events or support the implementation of REMS.

Remote access to patients for healthcare research has been facilitated by the development of wearable devices, such as smartphones equipped with specific applications, but also watches, clothes, glasses, etc. As long as the wearer agrees to share personal data via the device, a great amount of data can be collected, whether actively by the patient (e.g., answering questionnaires) or passively (e.g., heart rate, sleep rhythms, typing speed).

> "Although there will inevitably be some push back at first, data collected from wearables will be used more and more to assess exposures and safety risks, and for signal detection. This is open to creativity."
>
> —*Javier Cid*, *MD, DrPH, MBA, Senior Research Scientist, Real-World Evidence, Evidera*

New Approaches to Existing Data Sources
Registries

Some research questions still require bespoke studies and data collection. Registries are often used to generate safety data for rare diseases, orphan drugs, or pregnancy. They can be exhaustive (including all the patients treated with a given drug; registry is a condition for prescription) or not (e.g., pregnancy registry with or without a non-exposed arm; inclusion on a voluntary basis). It is estimated that between 2005 and 2013, a registry was required in almost 10 percent of newly approved drugs to provide additional data on safety. Most of these drugs were approved under exceptional circumstances or orphan designation.[21]

Registries often have long follow-up and require strong operational organization to ensure adequate recruitment and retention. These can now be supported by new technologies. For example, the recruitment in pregnancy registries has been augmented by leveraging social networks and other communication platforms, enabling more rapid recruitment and improved patient diversity.[35]

> "Different technological approaches to recruitment must be used to achieve recruitment goals more quickly."
>
> —*Doug Eckley*, *Executive Director, Peri- and Post-Approval Research Operations, Evidera*

The Case of EMRs

To date, EMRs have been most easily used when compiled into databases. Such databases can be found in Europe (e.g., UK, Netherlands) but are less frequent in the U.S. EMR databases contain mostly structured data for clinical information, such as vital signs, lab test, or drug prescriptions that can be used for safety research. Current EMR databases are more often focused on outpatient care. Unstructured data contained in clinical narratives have generally required a chart review protocol involving the support of trained research staff, but new methods of text mining have opened new possibilities to analyze free text.

In parallel, the possibility of automated digital data extraction from the EMRs with direct exportation into a study database is developing. Challenges to such automation include variations in record structure and format. Feasibility of this approach includes assessment of extent of EMR coverage, access to individual EMR platforms, understanding the format of the data and technical requirements, checking on the authorization needed, and the respect of data privacy.[36] This approach can be particularly interesting when hospital prescription data are needed.

New Methodological and Analytical Approaches to Match New Data Sources
Common Data Models and Software Platforms

Common data models (CDMs) have been developed with four main objectives: standardize, analyze, visualize, and optimize the use of multiple databases for pooled analyses. CDMs will bring the expected benefits only if built and designed based on the anticipated objectives of the analyses, and if the quality of all the processes (including data protection, transparency, and reproducibility) is ensured.[37]

For example, the FDA Sentinel System developed its own CDM, which is in turn used by the CNODES (Canadian Network for Observational Drug Effects Studies) project which aims at pooling the provincial claims databases throughout Canada,[38] and by the AsPEN (Asian PharmacoEpidemiology Network).[39]

Another CDM is the OMOP (Observational Medical Outcomes Partnership).[37] The OMOP model is used, for example, by the EMIF (European Medical Information

What about Data Privacy?

- The expansion of new data sources leads to a reinforcement of the legislation around data privacy, in particular in Europe with the General Data Protection Regulation (GDPR) enforced on the 28th of May 2018.

- The GDPR aims to protect EU citizens' personal data in general and also addresses healthcare research.[27] The GDPR applies to any data treatment involving European subjects, whether or not the sponsor is based in the EU.

- Safety studies, especially when requested by regulatory authorities, can most often demonstrate a clear public health interest and thus justify the collection and treatment of personal data, provided a rigorous framework is applied to protect them.

- Primary data collections involve informed consent and usually already comply with the GDPR.

- However, the use of new types of data will be more closely scrutinized and some new modes of data protection and consent will emerge, especially for data initially collected for other purposes and only recently used for healthcare research (e.g., data from social media).

> "There is pressure for data to be analyzed and results delivered even more quickly. Common data models allow streamlined programming and analytics for pooled database analyses, which are necessary for fast accrual of patients on newly approved drugs."
>
> —*Beth Nordstrom*, *PhD, MPH, Senior Research Leader, Real-World Evidence, Evidera*

Framework) project, part of the IMI, which aims to develop a common information framework of patient-level data that will link up and facilitate access to diverse medical and research data sources.[40] The challenge of putting together several European databases is even greater due to the diversity of data collected (e.g., Danish hospital data, Spanish primary care electronic medical records, Italian administrative data). The OMOP model is also used by the Observational Health Data Sciences and Informatics (OHDSI). This collaborative program develops and provides open-source solutions to standardize, analyze, and visualize data from different databases.[41]

Some pharma companies have now started putting together their own data platforms with the perspective to analyze both external sources of data as well as internal sources from their own clinical trial and observational studies.

Natural Language Processing (NLP)

In pharmacoepidemiologic research, natural language processing (NLP) is used to identify events/outcomes/risk factors in unstructured data such as clinical text from labels, electronic medical records (EMRs), or social media data. NLP technology has improved in recent years and can be more widely applied. The main applications of NLP in drug safety are:

- **Identification of adverse events for signal detection**: within the WEB-RADR initiative (part of IMI projects and issued from a private-public European partnership), NLP was applied to social media such as Twitter to extract data on drug usage and health events, create drug-event pairs, and analyse their occurrence via disproportionality analyze, thus potentially contributing to signal detection.[42]

- **Definition of outcomes in pharmacoepidemiologic studies**: for example, Lin and colleagues demonstrated the new possibility to directly identify arthralgias in EMRs, and to compare the risk of arthralgias related between two drugs in patients with inflammatory bowel diseases.[43] Validation of such methods is needed, but work to date tends to highlight the accuracy of NLP definitions.[44]

- Other applications include identification of drug-drug interactions.[45]

Machine Learning

In machine learning, the computer can learn from existing data and apply that knowledge to new data to develop insights. In the field of drug safety, machine learning is at the pilot testing stage for performance, however, the main foreseen applications include:

- **Predictive models of adverse events occurrence for new drugs, or unknown adverse events, based on the current knowledge and using large datasets.** This could lead to a new era of predictive safety in which, for example, post-approval safety requirements are predicted on sophisticated analysis of likely risks prioritized for interrogation. For example, Bean et al. could validate their predictive model of new adverse events of marketed products against electronic medical records and show new unknown associations.[46]

- **Management of confounding in pharmacoepidemiologic studies via the propensity scores.** A most recent version of the propensity score is the high-dimensional propensity score (HDPS). The HDPS is typically a method that can be automated (in particular the covariates identification and prioritization), and there are attempts at machine learning extensions of the HDPS.[47]

NLP and Machine Learning in Practice?

Innovative methods are building the future but some of these methods and technologies are for the moment limited to pilot-testing before they are deemed reliable enough to be used by the regulatory authorities. In the meantime, the priority is for biopharma to implement current post-marketing commitments and comply to regulatory obligations. We are at a technological turning point, and choices need to be made between implementing post-marketing commitments in the traditional way or daring to try new approaches. The trend currently is that innovative methods are tested and implemented by regulatory authorities, non-profit organizations, and public-private partnerships in a research perspective. Some pharma companies are also investing in research in these areas but are still in the pilot testing phase. When it comes to implementing post-marketing commitments, pharma companies and regulatory authorities are usually in agreement to use standard recognized data sources and methods until newer approaches are validated.

Current and Emerging Needs

Validated Systems and Methods

Safety studies require the use of efficient technologies and methods to optimize the internal and external validity by minimizing biases and ensuring transparency and reproducibility. For a primary data collection study, the use of validated 21 CFR part 11-compliant electronic code of federal regulations (eCFR) systems with electronic audit trails is a minimum to ensure the traceability and quality of data collection. In new patient-centric study models, eCFR platforms must be able to collect and combine data from physicians, patients, and caregivers. They need to integrate with central databases containing other data such as from EMRs or wearables.

In electronic databases, using validated algorithms to define inclusion criteria or outcomes/events of interest is highly recommended. If validated algorithms are not available, a validation step must be planned.[48,49] A major example is the definition of pregnancy and pregnancy outcomes in electronic databases, which can be quite complex according to the database type. So far, algorithms have been developed separately for different databases; this can be justified by the different types of data and structure across them. However, there are now attempts at creating standardized algorithms across databases to allow for comparability or pooling.[50]

Using these systems and methods will deliver their full value only if reported in a transparent manner, with enough information to ensure reproducibility. This is fully part of the validity and credibility of a study. In the case of a database analysis, where so many design decisions are made that can all influence the results, it is key to follow the guidelines issued by ISPOR in 2017.[49]

Sufficient Real-World Exposure Time Needed to Assess Safety Outcomes

Real-world safety data can only be collected if the drug of interest is prescribed in routine practice. Keeping up to date with the market access status is key to assess the feasibility, sample size, and timelines of the study. This may be frustrating to the regulator and to the market authorization holder but needs to be considered in plans for safety evidence generation.

In pregnancy studies, this constraint now tends to be addressed by planning both an observational pregnancy registry and database study.[51] The registry allows for real-time assessment of exposure and signal detection after drug launch (although on a limited population), while the database analysis allows it to generate a helicopter view of the drug's safety profile in larger populations and with a defined denominator.

> "Regarding pregnancy studies, we are at a transition between the registry and the database era. At the moment, the optimal approach is a combination of both."
>
> —***Deborah Covington***, *DrPH, FISPE, Senior Research Leader, Real-World Evidence, Evidera*

Organizational Optimization: Shared REMS, Registries, or RWE Platforms

A current trend initiated by the regulatory authorities is sharing projects between different MAHs of the same product. For example, the FDA very recently issued a guidance on shared REMS that reinforces the injunction for MAHs to pool resources.[52] Expectations are to share the costs between the MAHs and maximize the collection, reporting, and use of data. Another expectation is to decrease the strain on the healthcare system and optimize the participation of healthcare providers and patients. This requires an externalized, rigorous, and centralized organization with a clear definition of all the practical aspects of the collaboration between MAHs.

Another example is registries. Due to their higher cost and similar designs, registries are good candidates for pooling resources, whether across several MAHs of the same product that will be requested to merge their registries into one shared registry; or, within the same company, that

Figure 7. Shared REMS Components
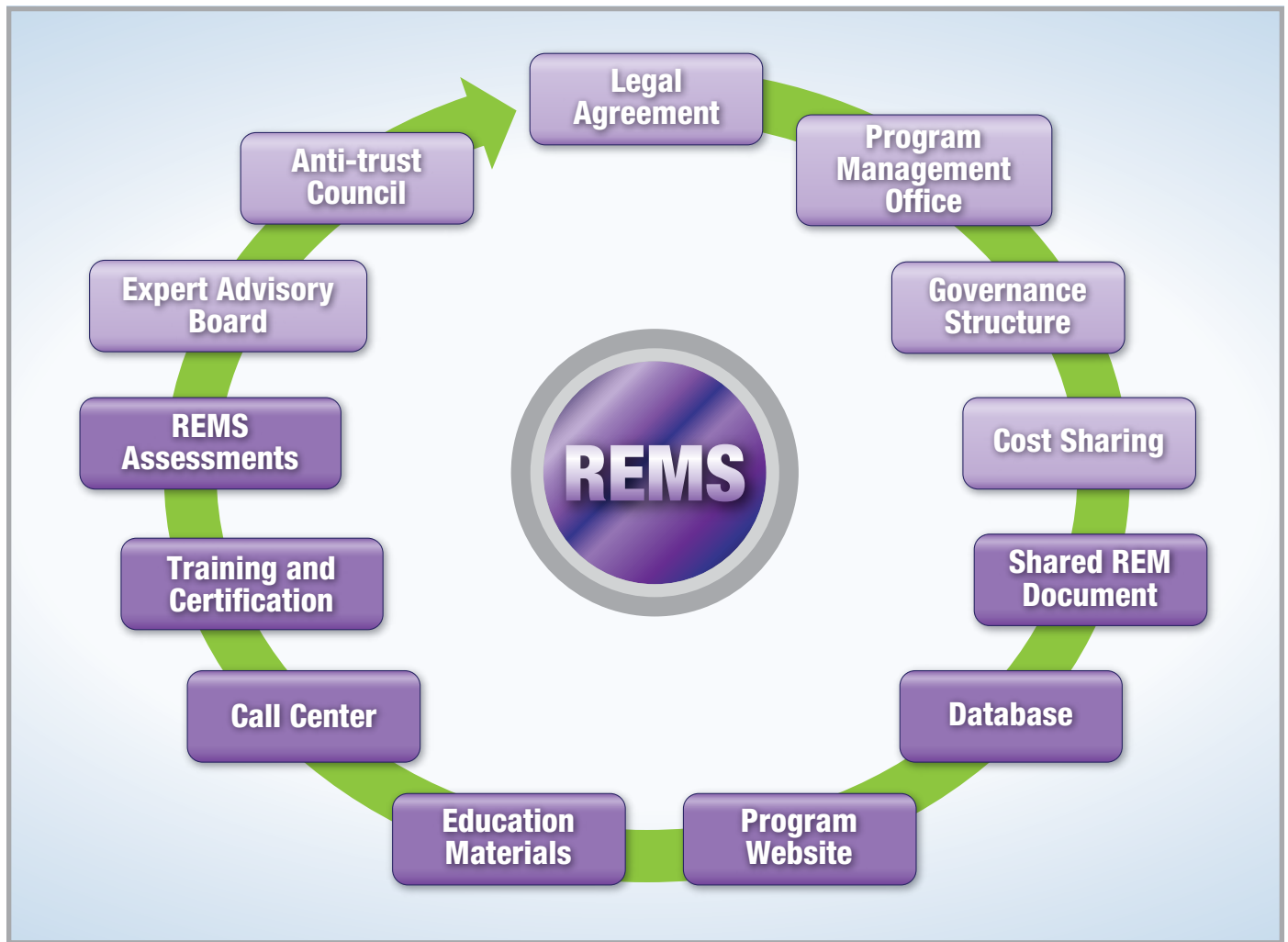
could, in case of several registries in different therapeutic areas, invest in a platform allowing the optimization of human and technical resources. Beyond savings, such platforms can increase the collaborations between therapeutic areas or regions within the same company by facilitating experience sharing and learning.

> "One success factor for shared REMS is the coordination by a dedicated project management office that will manage all the organizational aspects, including the decision-making process, but also the relationships between the different market authorization holders."
>
> —*Robin Kinard, Senior Director, Risk Management Programs, Peri- and Post-Approval Research Operations, Evidera; and, Kristin Veley, PharmD, MPH, Research Scientist and Director, REMS and Pregnancy Registries, Real-World Evidence, Evidera*

Faster Turnaround Time

The need for rapid analyses to increase the reactivity of the public health response by the regulatory authorities has been clearly highlighted by the EMA.[53] The FDA also used this argument when presenting and justifying their new initiatives towards active surveillance systems and common data models.[54] The objective is to reduce the time to detect issues and launch corrective actions. However, quickness should not reduce quality. Accuracy, transparency, and reproducibility are needed for credible drug safety studies.

The need for faster turnaround contributed to the success of electronic healthcare databases, and timelines could be further reduced by the use of CDM and more technology-driven approaches.

For primary data collection studies (e.g., registries), optimization is possible via careful planning and organization, by clearly identifying the key points for enhanced quality procedures, and by not falling into the trap of increasing all the study procedures (e.g., on-site monitoring) beyond the acceptable for a non-interventional study.

Figure 8. Key Enhanced Quality Points for Non-Interventional Safety Studies

SAP = Statistical Analysis Plan   CRF = Case Report Form
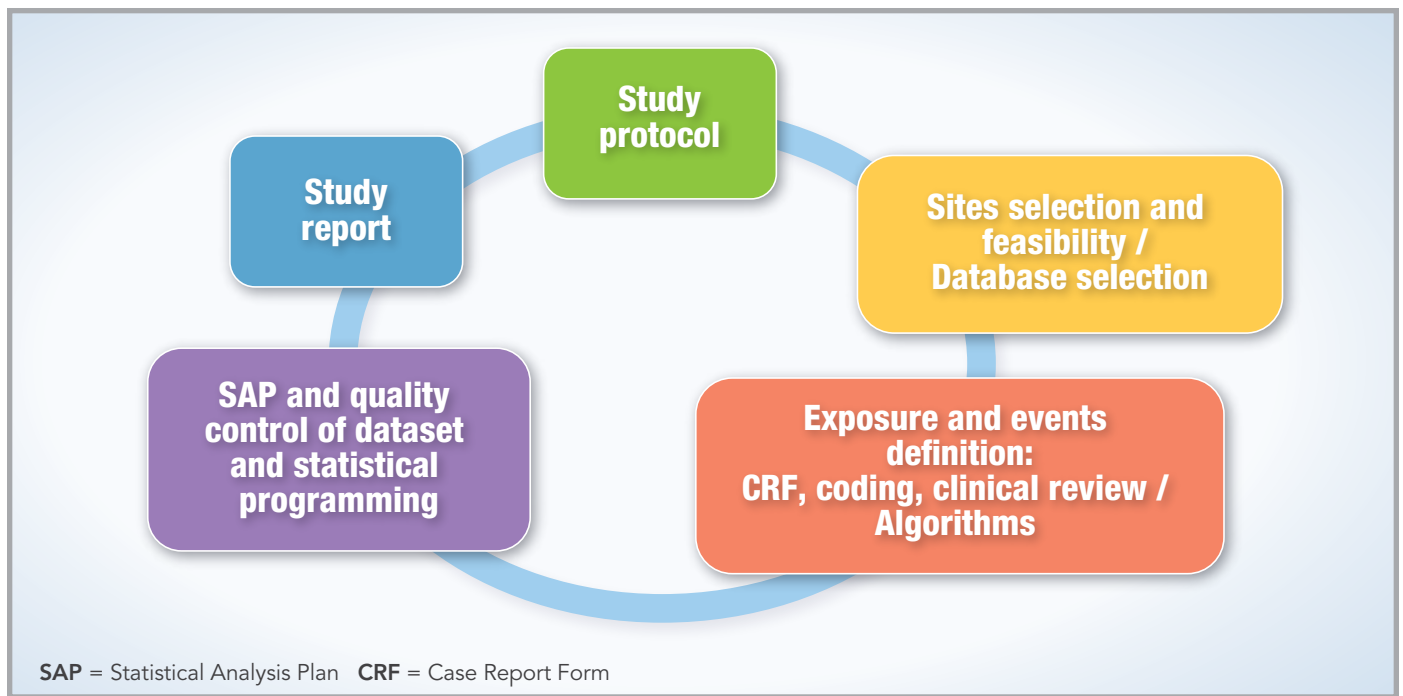
"Close collaboration between the science, strategy, and operations is the only way to achieve the right balance between quality and speed in primary data collection within non-interventional safety studies."
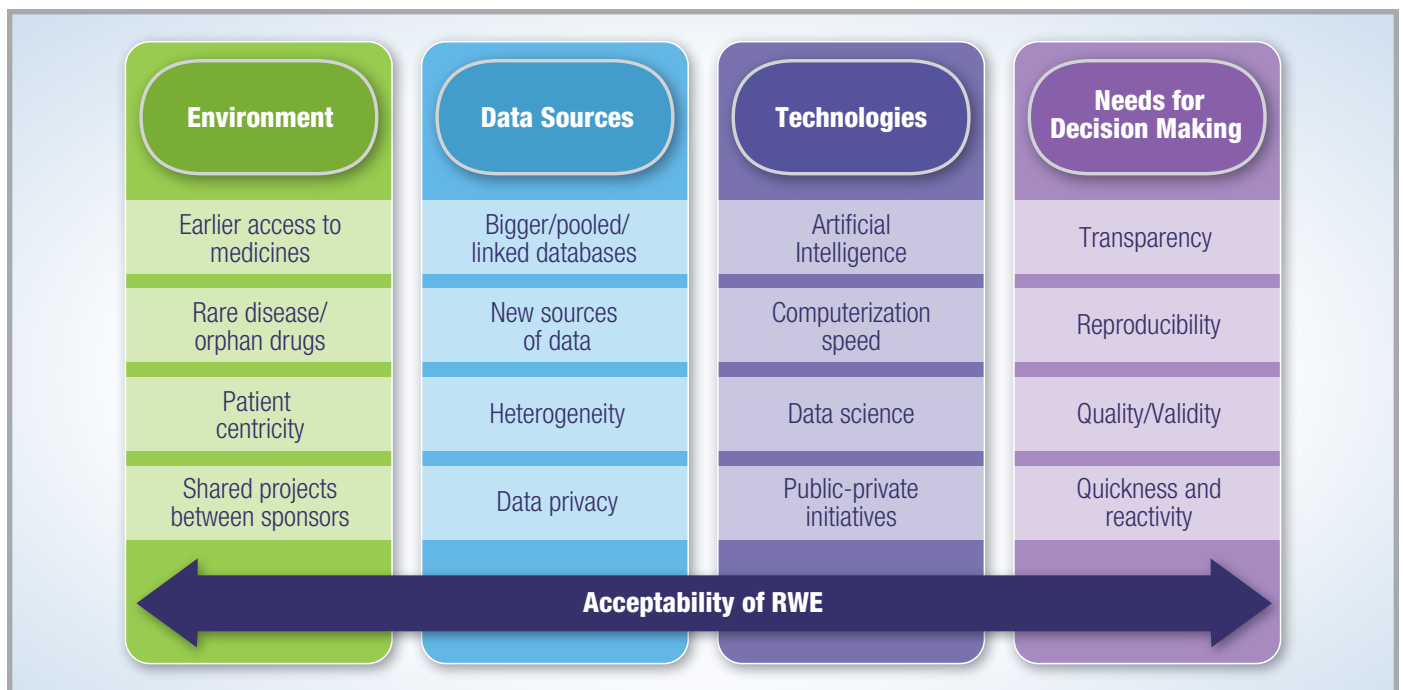
—*Javier Cid*, *MD, DrPH, MBA, Senior Research Scientist, Real-World Evidence, Evidera*

Conclusion

In the last twenty years, generation of safety data outside of clinical trials has developed from a single-source, passive system to a holistic and proactive approach based on the combination of data generation systems and a multitude of data sources and designs. Within an evolving regulatory environment, RWE safety data has moved from supportive data to a key element in regulatory decisions.

Real-world data sources are increasing in number, size, and diversity. They are very well suited for new analytical

Figure 9. Summary of Trends in Drug Safety

Environment	Data Sources	Technologies	Needs for Decision Making
Earlier access to medicines	Bigger/pooled/ linked databases	Artificial Intelligence	Transparency
Rare disease/ orphan drugs	New sources of data	Computerization speed	Reproducibility
Patient centricity	Heterogeneity	Data science	Quality/Validity
Shared projects between sponsors	Data privacy	Public-private initiatives	Quickness and reactivity

Acceptability of RWE

technologies such as standardization, automatization, and artificial intelligence, thus increasing the granularity of the available information.

As the field expands, a thorough understanding of the safety landscape, possible study options, and available methods is crucial to implement a fit for purpose study design to ensure the continuous assessment of benefit/risk for patients. ■

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