Digital Pharmacovigilance: Role of Software in Adverse Drug Reaction (ADR) Monitoring and Reporting"

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Abstract;

Pharmacovigilance is defined by the World Health Organization as the science and practice related to the detection, assessment, understanding and prevention of adverse drug reactions (ADRs). In a well-functioning pharmacovigilance system, information on possible ADRs is collected from patients, health professionals and marketing authorisation holders. Of all data sources for drug safety monitoring, spontaneous reporting systems provide the highest volume of information at the lowest maintenance cost and have proven their value in the early detection of product-related safety issues. At the beginning of 2018, the Brazilian Health Regulatory Agency (*Agência Nacional de Vigilância Sanitária*—Anvisa) decided to replace the national electronic reporting system in Brazil (Notivisa) with the system provided by Uppsala Monitoring Centre (VigiFlow) for ADR reporting. This paper describes that process and reports on the progress made by Anvisa in terms of making Brazil compliant with international pharmacovigilance standards as well as significantly increasing the number of individual case safety reports collected.

Keywords:

Pharmacovigilance; Adverse Drug Reactions; Spontaneous Reporting Systems; VigiFlow; Uppsala Monitoring Centre; Brazil; Anvisa; Drug Safety Monitoring; Individual Case Safety Reports; Digital Reporting System'

Introduction

Before medicines are approved for sale they must be tested for quality, safety and efficacy. Clinical trials in particular provide regulatory agencies with the evidence they need on safety and efficacy for market approval. However, such studies have limitations, and the information collected during the pre-marketing phase is incomplete when it comes to possible adverse drug reactions (ADRs). This is because the patients in clinical trials are selected and few in number, and studies are limited in duration. The conditions of use also differ from clinical practice and information about rare adverse reactions, chronic toxicity, use in special groups (children, elderly, pregnant women) or drug interactions are usually incomplete or unavailable [1].

Consequently, it has been necessary to establish drug monitoring mechanisms related to the detection, assessment, understanding and prevention of adverse events or any other problems related to medicines [2]. Pharmacovigilance, or medicine safety, implies a constant state of watchfulness to recognise when things are going wrong, to take action to solve immediate problems, and to share information about the causes of harm to influence future policy and practice [3]. Among the different methods of reporting suspected ADRs, spontaneous reporting systems provide the highest volume of information at the lowest maintenance cost and have proven their value in the early detection of drug-related problems [4].

The need for rapid information sharing, which became evident in the late 1950s and early 1960s with the thalidomide tragedy, led the World Health Organization (WHO) to organise a systematic data collection for ADRs [5]. At the end of the 1960s, a pilot project was launched with the 10 founder member countries of the WHO Programme for International Drug Monitoring (WHO PIDM) [6].

Today there are 136 countries in the WHO PIDM that share their data with VigiBase, the WHO global database of individual case study reports (ICSRs), which is maintained by Uppsala Monitoring Centre (UMC) in its role as the WHO Collaborating Centre for International Drug Monitoring. As of January 2020, VigiBase contained more than 20 million ICSRs that are used for detecting possible safety signals [7, 8].

In Brazil, the Ministry of Health directive No. 696 of 7 May 2001 appointed the Pharmacovigilance Office of the Brazilian Health Regulatory Agency (*Agência Nacional de Vigilância Sanitária*—Anvisa) as its national pharmacovigilance centre [9], and in 2007 a national spontaneous electronic reporting system – the Health Surveillance Reporting System Notivisa—was set up with its own database. As a member of the WHO PIDM since 2001, Brazil is required to send reports of suspected ADRs to VigiBase in a format compatible with the international standard for electronic transmission of ICSRs, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E2B [10]. This format is a standardised structure for sending information electronically between databases and contains all the relevant data elements to assess ICSRs [11]. However, as Notivisa is not compatible with the ICH E2B format, it meant manually entering data from Notivisa to a limited, free version of VigiFlow.

In addition to not being compliant with ICH E2B, Notivisa was also limited by system instability, an inability to import data series or export the database for analysis, lack of analytical and statistical tools, and only working with the internet browser Internet Explorer.

The need for a replacement was reinforced in 2016 when Brazil joined the ICH, which made the incorporation of ICH guidelines mandatory [12].

Adverse Drug Reactions;

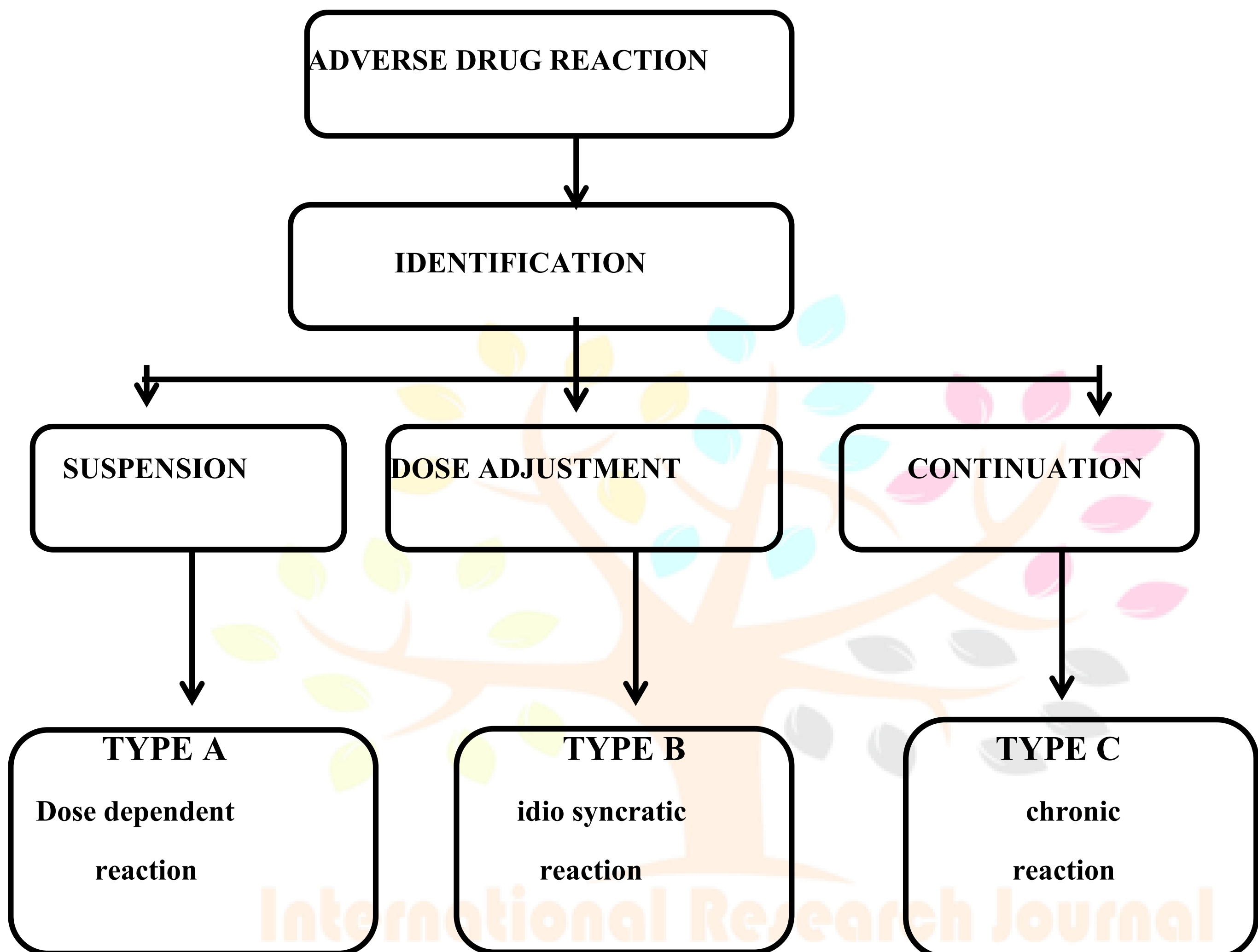
An adverse drug reaction (ADR) can be defined as 'an appreciably harmful or unpleasant reaction resulting from an intervention related to the use of a medicinal product; adverse effects usually predict hazard from future administration and warrant prevention, or specific treatment, or alteration of the dosage regimen, or withdrawal of the product'(13). Since 2012, the definition has included reactions occurring as a result of error, misuse or abuse, and to suspected reactions to medicines that are unlicensed or being used off-label in addition to the authorised use of a medicinal product in normal doses (14). While this change potentially alters the reporting and surveillance carried out by manufactures and medicines regulators, in clinical practice it should not affect our approach to managing ADRs.

Seminal research undertaken in the late 20th and early 21st century in the USA and the UK demonstrated that ADRs are a common manifestation in clinical practice, including as a cause of unscheduled hospital admissions, occurring during hospital admission and manifesting after discharge (14-16) The incidence of ADRs has remained relatively unchanged over time, with research suggesting that between 5% and 10% of patients may suffer from an ADR at admission, during admission or at discharge, despite various preventative efforts. Inevitably, the event frequency is associated with the method used to identify such events and the majority of ADRs do not cause serious systemic manifestations. Nevertheless, this frequency of potential harm needs to be considered carefully because it has associated morbidity and mortality, can be financially costly and has a potentially negative effect on the prescriber-patient relationship.

Medicines that have been particularly implicated in ADR-related hospital admissions include antiplatelets, anticoagulants, cytotoxics, immunosuppressants, diuretics, antidiabetics and antibiotics. Fatal ADRs, when they occur, are often attributable to haemorrhage, the most common suspected cause being an antithrombotic/anticoagulant co-administered with a non-steroidal anti-inflammatory drug (NSAID) (17).

Classification of adverse drug reactions

Traditionally, ADRs have been classified into two types:



1. Type A reactions – sometimes referred to as augmented reactions – which are 'dose-dependent' and predictable on the basis of the pharmacology of the drug

2. Type B reactions – bizarre reactions – which are idiosyncratic and not predictable on the basis of the pharmacology (18).

Although still widely quoted, this basic classification does not work for all ADRs, such as with chronic adverse effects associated with cumulative drug exposure (eg osteoporosis with long-term corticosteroid treatment) or withdrawal reactions (eg rebound hypertension with centrally-acting antihypertensive cessation). An alternative and perhaps more comprehensive classification scheme is 'DoTS', which classifies reactions dependent on the Dose of the drug, the Time course of the reaction and relevant Susceptibility factors (such as genetic, pathological and other biological differences)(19). As well as classifying reactions, DoTS has the advantage of being helpful to consider the diagnosis and prevention of ADRs in practice.

Spontaneous Reporting Systems;

Spontaneous reporting has been defined as:

'An unsolicited communication by a healthcare professional or consumer to a company, regulatory authority or other organization (e.g. WHO, Regional Centre, Poison Control Centre) that describes one or more adverse drug reactions in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection scheme'(ICH 2003).

Spontaneous reporting is by nature a passive approach to pharmacovigilance (PV), relying entirely on the motivation of individuals to report suspected adverse drug reactions (ADRs) to a local or national pharmacovigilance centre. Spontaneous reporting systems (SRS) can be paper based (e.g. the UK 'Yellow Card' system) or electronic (online reporting or mobile applications). Single reports from individual patients submitted to pharmacovigilance centres via these systems are known as Individual Case Study Reports (ICSRs). Information from multiple ICSRs is then used to identify potential 'signals' – suggestions of casual associations between a medicinal product and a previously unknown reaction. Detection and confirmation of these signals, though various methods, can identify previously unknown adverse or beneficial effects of a medication. An important feature of SRS is that they cover all medicine use within a whole population for an unlimited time period (WHO 2006), encompassing the entire product life cycle of each medicine.

Spontaneous reporting is so much considered the mainstay of ADR reporting that the existence of a national spontaneous reporting system is one of the World Health Organization's (WHO) five minimum requirements for a functional national PV system (WHO 2010). It is the basis of the WHO Programme for International Drug Monitoring's (PIDM) reporting system VigiBase (managed by the Uppsala Monitoring Centre, UMC, Sweden), to which member states of the programme submit ICSRs for accurate international analysis (UMC 2019). The UMC, alongside the various Marketing Authorisation Holders (MAHs) and national Regulatory Authorities (RAs), are one of the 3 main players in PV at a global level. Each of these has its own goals and perspectives when conducting PV activities (Schurer 2019).

1. The UMC: To successfully integrate PV data from all WHO member countries and to perform statistical analysis and continuous monitoring of the global PV landscape.

2. MAHs: To achieve and maintain regulatory compliance, mitigation of financial and market risks, as well as being able to make informed marketing decisions.

3. RAs: To protect and promote patient safety within their public health programs and thus alleviate pressure on their health system.

It is important to note that the strength of the global PV system lies in the integration of national and industry PV systems. While the UMC offers substantial support to the WHO member countries, many developing member countries lack the capacity and capability to take full advantage of the services offered (Schurer 2019). Nevertheless, PV systems in Low-Middle Income Countries (LMIC) are based primarily on spontaneous reporting (Isah, Pal et al. 2012). In 2011, 74% of Sub-Saharan African countries had such a system in place (SPS 2011). Given an increase in African membership to the WHO PIDM ever since, this percentage is certain to have grown.

Spontaneous reporting has some intrinsic advantages over more active reporting methods. The wide coverage means rare, serious ADRs not detected during earlier trials or through other pharmacovigilance methodologies may be revealed (WHO 2006). Indeed, spontaneous reporting during the post-marketing phase generates most drug safety data, even more so than clinical trials during drug development (Lester et al., 2013). The relative ease of operation and low cost, coverage of whole patient populations and lifecycle follow up of medicines, non-

interference with prescribing habits and potential to allow for follow-up studies make them a practical and inviting approach for LMICs (Isah, Pal et al. 2012).

However, SRS are not without their drawbacks. A primary issue is the reliance on individual motivation for reporting, as in practice this results in only a very small percentage (around 5%) of adverse effects being reported (UMC 2019). Implementation of SRS in LMICs can be hampered by other pressing health priorities and specific challenges, such as remote location, poor telecommunications services and low numbers and level of education of health professionals (Sevene 2008). Health workers may also fail to recognise ADRs, be ignorant of reporting requirements, lack reporting forms, feel guilty about adverse effects or fear litigation (Isah, Pal et al. 2012). In addition, not all existing SRS address the full scope of PV; in Sub-Saharan Africa it is reported that only 50 percent of reports are used for quality defects, 43 percent for treatment ineffectiveness and only 37 percent for medication errors (SPS 2011).

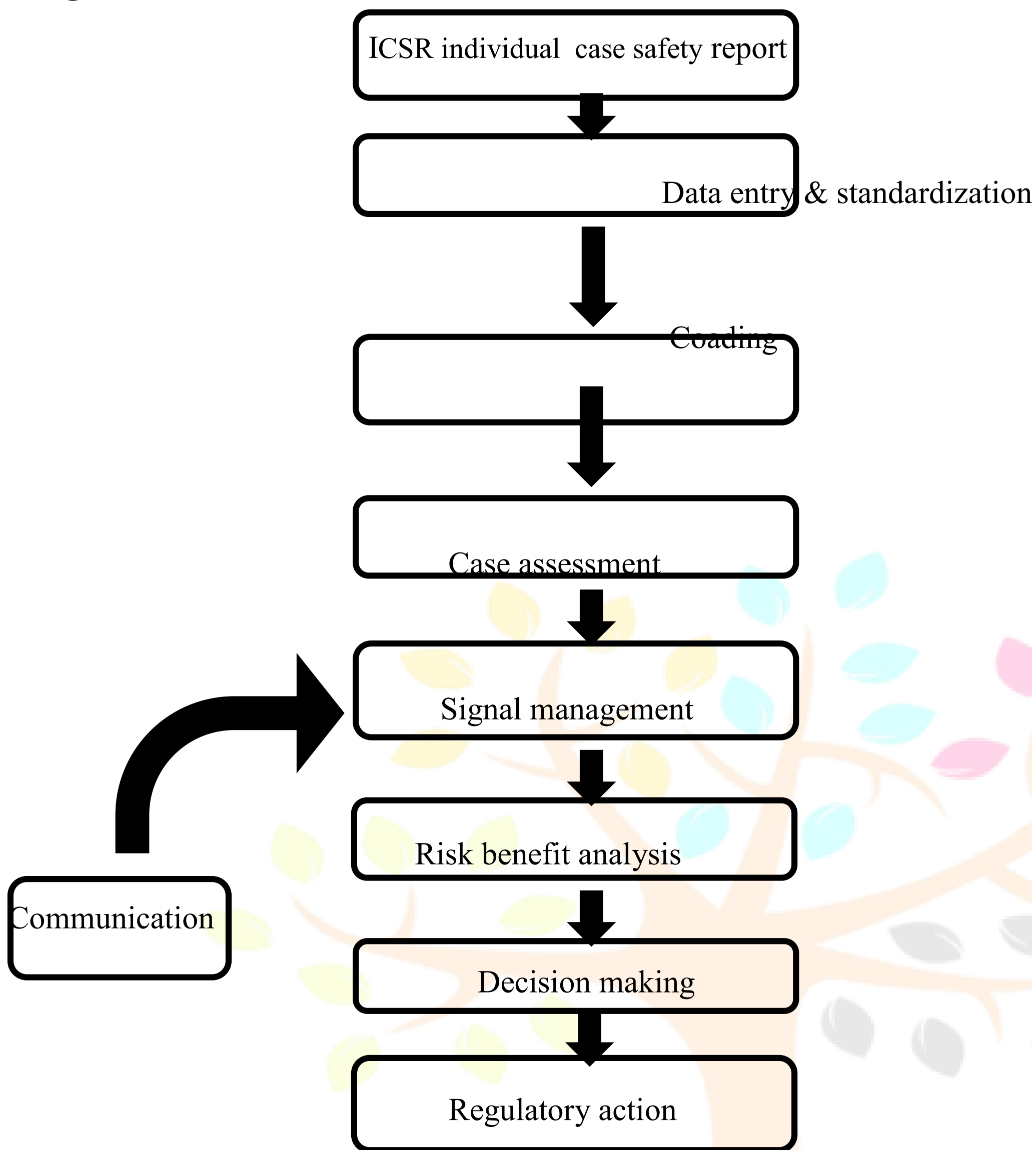
PV systems are complex. The large number of different PV systems, the equally large number of stakeholders within such systems, and the significant dimensions along which effectiveness and efficiency could be measured, adds to this complexity. The primary obstacle to standardising and achieving interoperability between such systems globally is the fundamental difference in purpose of each system (Schurer 2019).

To overcome these challenges, robust active reporting systems should also be used to complement spontaneous reporting. In addition, reporting should be encouraged from all sectors of the healthcare system, including patients, doctors, nurses, pharmacists, traditional practitioners and providers of herbal medicine in order to increase reporting and provide more representative data (WHO 2006). Ehealth tools, particularly via smartphones, are increasingly recognised as valuable for reporting in LMICs where broad mobile phone service can be managed more cheaply than Internet communication, and in more rural areas alternative methods of report communication have been trialled (Sevene 2008, Berrewaerts, Delbecque et al. 2016).

The electronic transmission of ICSRs is outlined in the newly developed ICH E2B(R3) standard, developed to expedite exchange of safety information between systems subjected to various national and international regulations. Interoperability is of vital importance when it comes to avoiding difficulties in reconciling ICSRs on a global level. Adoption and implementation of these standards will be key (Schurer 2019).

Ensuring SRS are utilised and operate to their full potential is challenging, above all in LMICs. Further collaborative research is needed in order to highlight barriers to their implementation to reflect upon and identify potential methodological improvements(20).

Vigiflow;



VigiFlow is an ICSRs management system for countries that require an electronic pharmacovigilance database for the collection, processing and sharing of ICSRs for effective data analysis. It was initially developed for Switzerland's regulatory agency Swissmedic. Today it is offered to national centres in low- and middle-income countries as a low-cost way of managing their pharmacovigilance data. Previously, a free version of VigiFlow with limited functionality was also available to support countries reporting ICSRs to VigiBase.

VigiFlow is compatible with the international ICH E2B standard—and uses the international Medical Dictionary for Regulatory Activities (MedDRA) terminology—for efficient data exchange between pharmaceutical companies and regulatory agencies using xml files. It supports the setup of a decentralised system for data collection, allows integration with an electronic form for the general public and healthcare professionals to report adverse events with medicines or vaccines (eReporting), and offers direct sending of ICSRs to VigiBase.

Currently, VigiFlow is used by more than 90 countries worldwide. The system is continuously updated, and the latest version of VigiFlow launched in January 2018 is compliant with the updated standard ICH E2B(R3), which includes improvements in manual data entry and data structure of ADR and AEFI (adverse events following immunisation) reports, as well as better workflow support for pharmacovigilance centres. The new version of VigiFlow is the same for all countries, with a free, limited version no longer available.

To find out how VigiFlow works in detail and present its needs and requirements, Anvisa held several phone conferences with UMC, and in November 2018 five team members travelled to Uppsala, Sweden on a technical visit. The characteristics and functionalities of VigiFlow were compared with those of Notivisa and the

requirements of the National Pharmacovigilance System of Brazil. Table 1 shows the results of the comparative analysis that justified the replacement of Notivisa by VigiFlow.

Table 1.

Advantages, challenges and limitations of VigiFlow in comparison to Anvisa's needs and Notivisa

Anvisa's needs	Situation in Notivisa	VigiFlow advantages	VigiFlow challenges/limitations
Quick implementation to meet deadlines for adoption of ICH guidelines	Not compatible with ICH guidelines and use of WHO-ART terminology, which stopped being updated in 2015	Quick and easy implementation—the process basically just requires account setup	VigiFlow does not allow integration with local systems from national regulatory authorities, which prevents the use of Anvisa's database of authorised products and the database of current Notivisa users
		The international medical terminology MedDRA is already embedded in VigiFlow, which allows Brazil to fulfil its commitment to ICH, whose deadline for implementation is 2021	As VigiFlow uses the official translations of MedDRA, which at the time included only the Iberic Portuguese, the need to create MedDRA in Brazilian Portuguese was raised due to language differences
		Data import and export (xml files in ICH E2B format) that meets the requirements of ICH, whose deadline for implementation is 2021	N/A
Low cost	High maintenance	Offered by a non-profit organisation, it is cheaper than other technical solutions on the market	VigiFlow is not customisable
		VigiFlow does not have the maintenance costs of self-managed systems since all system corrections and improvements are UMC's responsibility	N/A
System stability	Regular system instability	High scalability allows simultaneous use by several users	N/A

Anvisa's needs	Situation in Notivisa	VigiFlow advantages	VigiFlow challenges/limitations
User-friendly system	Worked only on Internet Explorer	Compatible with main web browsers: Google Chrome, Internet Explorer and Mozilla Firefox	N/A
	Required all reporters to fill in a registration form and have a username and password, which did not encourage the general public to report	Patients and health professionals do not need to register to send in their report, which could help prevent under-reporting	N/A
	Allowed causality assessment only by the WHO-UMC method	The causality assessment process can be carried out using different methods, such as WHO-UMC, Naranjo and WHO AEFI	N/A
Have all data accessible in one place	National data are fragmented between Notivisa and other systems, such as Periweb used by the Health Surveillance Centre of the state of São Paulo	Agreed to be used by all levels of Brazil's UHS across the country	Notivisa data must be migrated to VigiFlow to maintain Brazil's reporting history
		Possibility to create hierarchical access profiles according to the work process at the time, including national and regional pharmacovigilance centres	Considering that the UHS in Brazil is decentralised both politically and administratively (National, States and Municipalities), VigiFlow had to mirror that structure in hierarchical profiles below the national centre
	Notivisa is used for safety monitoring of different types of products and medical services	N/A	VigiFlow is meant to be used for reports on adverse events caused by medicines or vaccines. The system is not developed to manage adverse event reports related to other types of products or medical events
Analytical tools for signal detection	Notivisa did not contain analytical tools to evaluate trends and disproportionality	Access to VigiLyze, which presents consolidated data from over 20 million ICSRs sent in by more than 130 countries to VigiBase	To make the most of VigiLyze, all ICSRs must be copied to the WHO global database of ICSRs

Anvisa's needs	Situation in Notivisa	VigiFlow advantages	VigiFlow challenges/limitations
Fulfil responsibilities as a member of the WHO Programme for International Drug Monitoring	Unfeasible to send all Notivisa data to the WHO global database as the ICSRs had to be manually entered into the previous version of VigiFlow for them to be sent to VigiBase	Automatic sending of ICSRs to VigiBase	N/A

Uppsala Monitoring Centre (UMC) , Brazil, Anvisa;

Is the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring, responsible for managing VigiBase, the world's largest global database of adverse drug reactions (ADRs). UMC develops global pharmacovigilance tools such as VigiFlow, VigiLyze, and VigiAccess, enabling countries to collect, analyze, and share safety data for improving drug safety worldwide.

Its mission sparkles with quiet heroism: tracking medicine safety signals across the globe like a satellite that never sleeps. (22)

The major obstacle with this step was to find a solution for decentralised access to the system. As the administrative structure for healthcare is decentralised in Brazil, there was a need to create hierarchical access profiles based on the public Unified Health System (UHS). Accordingly, three hierarchical levels were created within VigiFlow, as follows:

- Anvisa: highest hierarchical level, corresponding to the complexity of pharmacovigilance activities, with access to all system functionality and all ICSRs created by other levels. As Brazil's national pharmacovigilance centre, Anvisa is responsible for sending ICSRs to VigiBase once they have been assessed.
- State Health Surveillance units (SHSUs): hierarchical level immediately below Anvisa, considered as regional centres with access to their own ICSRs and local healthcare services, including hospitals from the Sentinel Network that actively monitor the products regulated by Anvisa [23).
- Healthcare services, including hospitals from the Sentinel Network: lowest hierarchical level, comprising healthcare units legally obligated to have a Patient Safety Unit in their organisational structure. These are also classed as regional centres but are subordinate to State Health Surveillance units according to their geographical location. Each healthcare service has access only to its own ICSRs.

To make the transition process easier for regional centres, Anvisa established a communication and training plan. First, PVO created an e-mail address for requesting user accounts and general questions. Additionally, an FAQ was compiled during the pilot phase with the six sentinel hospitals. Later, training was provided via webinars and printed materials.

Drug Safety Monitoring;

Drug safety monitoring is the beating heart of pharmacovigilance, a continuous process that evaluates the safety profile of medicines once they move from controlled clinical trials into the unpredictable real world. In the digital era, pharmacovigilance has evolved from paper-based reporting and slow manual assessments to a fast, interconnected system powered by software, automation and real-world data.

Digital pharmacovigilance uses modern technologies to strengthen drug safety monitoring by:

• collecting adverse drug reaction (ADR) reports electronically through portals and mobile apps
• detecting safety signals using advanced algorithms, including machine learning and natural language processing
• analyzing data from electronic health records, prescription databases, and even social media to identify early warning trends
• integrating global ADR data through platforms like VigiFlow and VigiBase hosted by the Uppsala Monitoring Centre
• enabling real-time dashboards that support faster regulatory decisions

Think of drug safety monitoring in digital pharmacovigilance like a high-tech radar scanning the horizon for safety threats. Every report, whether from a doctor or a patient, becomes a tiny beacon of information that software aggregate, analyze and transform into actionable insights. This improves the speed of safety signal detection and reduces the risk of adverse drug events going unnoticed.

With digital transformation, pharmacovigilance is shifting from reactive case processing to proactive, predictive safety surveillance. The result benefits everyone: regulators gain clarity, healthcare providers receive faster alerts, and patients receive safer medicines.(24)

3. Major Classes Of PV Software And Platforms

3.1 Centralized safety databases & e-reporting platforms

Global and national PV centers use structured databases and case-management software to collect ICSRs, perform coding (MedDRA/WHODrug), deduplicate, and prepare regulatory submissions. Notable examples and functionalities include VigiBase (WHO/UMC), VigiFlow/VigiLyze tools, and national portals that accept electronic ICSRs and feed central repositories. These platforms standardize data capture and enable aggregated analytics for signal detection.

3.2 Commercial and enterprise PV safety systems

Large pharmaceutical companies and CROs commonly use validated safety databases (Oracle Argus, ArisGlobal LifeSphere, Veeva Vault Safety, Ennov, etc.) providing end-to-end case intake, expedited reporting, workflow automation, aggregate reporting and regulatory submissions. These systems integrate with pharmacovigilance operations to ensure compliance with regional regulations.

3.3 Analytics and signal detection software (data mining)

Disproportionality analysis (reporting odds ratio, proportional reporting ratio) and advanced data-mining approaches run in commercial suites and specialized tools (VigiLyze). Modern systems increasingly incorporate ML models for pattern discovery, duplicate detection, temporal trend analysis and prioritization of signals.

3.4 NLP, AI and automation for case processing

NLP extracts structured fields from unstructured narrative reports (free text from patients, HCPs, literature and social media); AI automates triage, seriousness assessment, coding suggestions, and duplicate detection—reducing manual workload and processing time. Recent reviews highlight clear gains in throughput and information capture, though human oversight remains essential.

3.5 Mobile/web reporting apps and QR/QR-linked forms

Patient-facing mobile apps and simplified web forms (and innovations like QR codes) lower the barrier to reporting and increase consumer participation. Evidence shows mobile apps can improve completeness and quality of reports although sustained increases in reporting rates require promotion and integration into PV workflows.

3.6 Social media and RWD mining tools

Tools that mine social media, forums, and EHRs provide near-real-time signals and supplementary context, but face challenges around noise, data veracity, representativeness, and privacy. Methodological advances using NLP and ML improve adverse event extraction from free text.

4. Benefits Of Software-Driven Pharmacovigilance

- **Speed and scale.** Software enables processing of far larger datasets than manual systems, accelerating signal detection and trend analysis across populations.
- **Automation of repetitive tasks.** NLP/AI reduce manual coding and duplicate checks, lowering time-to-action for safety teams.
- **Inclusion of new data sources.** Mobile apps, social media, and EHR integration broaden the evidence base, capturing patient experiences and real-world events outside clinical trials.
- **Improved user experience & accessibility.** Simplified reporting (apps, QR codes) increases engagement, particularly from consumers.

5. Key Challenges And Limitations

5.1 Data quality, heterogeneity and signal-to-noise ratio

Spontaneous reports may be incomplete; social media contains high noise and ambiguous language. Automated extraction can misclassify or miss context without robust validation and human review.

5.2 Interoperability and standards

Multiple systems and terminologies (MedDRA, WHODrug) require mapping and harmonization. Lack of standardized APIs or data models can hamper integration between EHRs, national portals and industry safety systems.

5.3 Regulatory, privacy and access constraints

Regulatory requirements demand validated systems, auditable trails and clear governance. Data protection laws complicate use of social media and cross-border data sharing; WHO/UMC and regulators periodically update access and sharing policies.

5.4 Algorithmic transparency and bias

ML models trained on skewed datasets risk bias in signal prioritization and may produce false positives/negatives. Explainability and human oversight are essential.

5.5 Resource & implementation challenges

Adopting and validating enterprise PV software is resource-intensive; LMICs and smaller centres may face barriers to implementation and sustainment.

6. Evidence On Effectiveness (Selected Findings)

- Electronic reporting systems and VigiFlow have improved national case handling and data standardization in implemented settings.
- Mobile apps show promise to improve the quality of ADR reports and patient engagement, though evidence on large sustained increases in reporting is still maturing. Systematic and recent reviews conclude mobile tools can improve data completeness but require promotion and integration.

- AI/NLP demonstrably reduce manual processing time and assist in information capture; however, prospective real-world validation and governance frameworks are still being established.

7. Good Practice Recommendations For PV Software Adoption

1. **Standards first:** enforce MedDRA/WHODrug coding and ICH-compliant data structures to ensure interoperability.

2. **Human-in-the-loop AI:** use automation to augment—not replace—expert review, especially for seriousness, causality and regulatory submissions.

3. **Privacy by design:** ensure lawful basis for data use, de-identification where possible, and region-appropriate consent practices.

4. **Validation and audit trails:** validate algorithms and software per regulatory guidance and maintain auditable logs.

5. **User-centric reporting tools:** design patient/HCP apps for simplicity (free text + structured fields) and actively promote them to improve uptake.

8. Future Directions

- **Improved RWD integration:** more robust EHR-to-PV pipelines and federated learning approaches that preserve privacy while enabling model training.

- **Explainable AI:** development of transparent ML models for signal detection acceptable to regulators.

- **Standardized APIs & global data governance:** smoother data flows between national systems, industry safety databases, and global repositories (with clear access rules).

- **Evaluation frameworks:** prospective, real-world evaluations of digital tools to quantify impact on patient safety outcomes.(25)

Individual Case Safety Reports; Digital Reporting System;

Individual Case Safety Reports (ICSRs) are structured reports submitted to pharmacovigilance authorities that document a suspected adverse drug reaction (ADR) experienced by a patient. An ICSR typically includes information about the patient, the suspected drug, the adverse event, clinical outcomes, and reporter details.

ICSRs are the backbone of spontaneous reporting systems and form the primary data source for signal detection in pharmacovigilance.

A digital reporting system is a software platform used for electronic submission, storage, and processing of ICSRs. These systems automate ADR reporting and integrate real-world data sources such as web portals, mobile apps, EHRs, and databases to support faster signal detection and regulatory decision-making.

Examples include:
- VigiFlow (used by WHO member countries for ADR reporting)
- EudraVigilance (European Medicines Agency)
- MedWatch (U.S. FDA)

9. Conclusions

Software and digital methods are reshaping pharmacovigilance by increasing scale, speeding case processing, enabling modern signal detection, and broadening data sources. Benefits are real but depend on robust standards,

validation, governance, and human oversight. Ongoing collaboration among regulators, PV centres, industry and researchers is essential to translate digital innovations into improved patient safety.

Reference;

1.Uppsala Monitoring Centre, World Health Organization. Safety monitoring of medicinal products: guidelines for setting up and running a pharmacovigilance centre. Uppsala: Uppsala Monitoring Centre; 2000.

2.World Health Organization. Pharmacovigilance. 2020. https://www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en/. Accessed 4 Mar 2020.

3.Uppsala Monitoring Centre. 50 years of pharmacovigilance. 2020. https://www.who-umc.org/global-pharmacovigilance/global-pharmacovigilance/50-years-of-pharmacovigilance/. Accessed 4 Mar 2020.

4.Pal SN, Duncombe C, Falzon D, Olsson S. WHO strategy for collecting safety data in public health programmes: complementing spontaneous reporting systems. Drug Saf. 2013;36:75–81. doi: 10.1007/s40264-012-0014-6. [DOI] [PMC free article] [PubMed] [Google Scholar]

5.Uppsala Monitoring Centre . Making medicines safer: Uppsala Monitoring Centre—40 years of pioneering pharmacovigilance. Uppsala: Uppsala Monitoring Centre; 2018. [Google Scholar]

6.Venulet J, Helling-Borda M. WHO's International Drug Monitoring—the formative years, 1968–1975: preparatory, pilot and early operational phases. Drug Saf. 2010;33:e1–e23. doi: 10.2165/11532410-000000000-00000. [DOI] [PubMed] [Google Scholar]

7.Uppsala Monitoring Centre. VigiBase. In: VigiBase. 2020. https://www.who-umc.org/vigibase/vigibase/. Accessed 6 Jan 2020.

8.Uppsala Monitoring Centre. WHO Programme for International Drug Monitoring. 2020. https://www.who-umc.org/global-pharmacovigilance/who-programme-for-international-drug-monitoring/. Accessed 16 Jan 2020.

9.Ministério da Saúde. Portaria no 696, de 7 de maio de 2001—Institui o Centro Nacional de Monitorização de Medicamentos (CNMM) sediado na Unidade de Farmacovigilância da Anvisa. 2001. https://bvsms.saude.gov.br/bvs/saudelegis/gm/2001/prt0696_07_05_2001.html. Accessed Mar 2020.

10.Uppsala Monitoring Centre. Being a member of the WHO Programme for International Drug Monitoring. 2020. https://www.who-umc.org/global-pharmacovigilance/who-programme-for-international-drug-monitoring/being-a-member/. Accessed 12 Feb 2020.

11.International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use - ICH. E2B(R3) Individual Case Safety Report (ICSR) specification and related files. 2018. https://ich.org/page/e2br3-individual-case-safety-report-icsr-specification-and-related-files. Accessed 25 Feb 2020.

12.International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. ICH Association . Annual Report. Geneva: ICH; 2016. p. 2017. [Google Scholar]

13.Aronson JK. Ferner RE. Clarification of terminology in drug safety. Drug Saf. 2005;28:851–70. doi: 10.2165/00002018-200528100-00003. [DOI] [PubMed] [Google Scholar]

14.European Directive 2010/84/EU of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use

15.Bates DW. Leape LL. Petrycki S. Incidence and preventability of adverse drug events in hospitalized adults. J Gen Intern Med. 1993;8:289–94. doi: 10.1007/BF02600138. [DOI] [PubMed] [Google Scholar]

16.Lazarou J. Pomeranz BH. Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA. 1998;279:1200–5. doi: 10.1001/jama.279.15.1200. [DOI] [PubMed] [Google Scholar]

17.Pirmohamed M. James S. Meakin S, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ. 2004;329:15–9. doi: 10.1136/bmj.329.7456.15. [DOI] [PMC free article] [PubMed] [Google Scholar]

18.Davies EC. Green CF. Taylor S, et al. Adverse drug reactions in hospital in-patients: a prospective analysis of 3695 patient-episodes. PLoS One. 2009;4:e4439. doi: 10.1371/journal.pone.0004439. [DOI] [PMC free article] [PubMed] [Google Scholar]

19.Wester K. Jönsson AK. Spigset O. Druid H. Hägg S. Incidence of fatal adverse drug reactions: a population based study. Br J Clin Pharmacol. 2008;65:573–9. doi: 10.1111/j.1365-2125.2007.03064.x. [DOI] [PMC free article] [PubMed] [Google Scholar]

20.Rawlins MD. Thompson JW. Pathogenesis of adverse drug reactions. In: Davies DM, editor. Textbook of adverse drug reactions. Oxford:: Oxford University Press; 1977. p. 10. [Google Scholar]

21.Aronson JK. Ferner RE. Joining the DoTS: new approach to classifying adverse drug reactions. BMJ. 2003;327:1222–5. doi: 10.1136/bmj.327.7425.1222. [DOI] [PMC free article] [PubMed] [Google Scholar].

22. **https://www.who-umc.org**

23. Agência Nacional de Vigilância Sanitária. Rede Sentinela. 2020. http://portal.anvisa.gov.br/rede-sentinela-apresentacao. Accessed 4 Mar 2020.

24. https://www.who-umc.org

25. Dong F, et al. *Pharmacovigilance in the digital age: gaining insight from social media data.* 2025. PMC.