**Pharmacovigilance and Drug Safety in the Digital Age**

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**Abstract:**

The digital revolution has redefined the landscape of pharmacovigilance and drug safety, introducing both transformative possibilities and new complexities. In this study, we explore the impact of digital technologies on pharmacovigilance, presenting an analysis of the potential opportunities, challenges, and implications for the future of drug safety.

The digital age, marked by the advent of advanced algorithms, artificial intelligence (AI), machine learning (ML), and the Internet of Things (IoT), has ushered in a new era of data collection and analysis in healthcare. These advancements allow for real-time monitoring, comprehensive data collection, and predictive modelling, fundamentally changing the way adverse drug reactions (ADRs) are identified, reported, and managed. Moreover, the widespread use of electronic health records (EHRs), wearables, and social media platforms contribute to 'big data', offering novel methods to enhance signal detection in pharmacovigilance.

However, the digital transformation also introduces significant challenges. These include data privacy concerns, regulatory hurdles, the need for technological competency, and the challenge of managing high-volume, diverse, and unstructured data. Furthermore, the ethical implications of AI applications in pharmacovigilance and the potential for algorithmic bias also warrant consideration.

In conclusion, while the digital age presents promising prospects for improving drug safety and pharmacovigilance, it also necessitates a comprehensive, thoughtful approach to navigate its complexities. To fully leverage the potential of digital technologies, we must invest in strategic planning, multidisciplinary collaboration, regulatory updates, and ongoing education. Only then can we unlock the full potential of the digital age for the future of pharmacovigilance.

**Introduction**

**a. Definition and Importance of Pharmacovigilance**

The Australian physician W. McBride, who first hypothesized a connection between thalidomide, a medication used during pregnancy, and severe fetal abnormalities (phocomelia), officially established pharmacovigilance (PV) in December 1961 with the publication of a letter in the Lancet. In pregnant women, thalidomide was administered as an antiemetic and sedative [17]. PV is described by WHO as "the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or other potential drug-related problems [16]."The science of PV aims to minimize the chance that consumers will suffer damage as a result of using drugs. PV is the process of identifying pharmacological adverse effects, treating them, documenting, reporting, and making regulatory decisions in light of these results. PV, in its broadest sense, is the science of gathering, monitoring, analysing, and evaluating data from healthcare providers and patients on the adverse effects of pharmaceuticals, including herbal and conventional treatments. The global campaign to increase patient safety is gaining traction, making drug safety an even more important topic in the modern world. The practice of pharmacovigilance is expanding in India as well, keeping up with the times [13].

**b. Overview of Drug Safety in the Digital Age**

Drug In order to track the occurrence of ADRs, post-marketing surveillance systems are necessary in every nation because domestically generated data may influence national regulatory policy. These initiatives might aid in a reduction in ADR-related morbidity, death, hospitalizations, medical expenses, and liability. The majority of ADRs frequently go unnoticed or unreported. A structured ADR monitoring program is one way to more actively discover ADRs, which will subsequently improve the standard of patient care. The numerous processes for assessing and monitoring the safety of medications in clinical use are crucial to preventing or minimizing harm to patients and enhancing public health. This suggests a well-functioning Pharmacovigilance system in clinical practice. Pharmacovigilance, which was initially defined as "The detection in the community of drug effects, usually adverse," focused exclusively on keeping an eye on negative medication reactions in the early 1990s. Pharmacovigilance can be organized or passive, with the former involving the gathering of spontaneous reports. As it helps to avoid, identify, and evaluate adverse responses to medications intended for human use, pharmacovigilance is crucial for the protection of public health. It includes full life-cycle management of pharmaceuticals for human use while keeping safety in mind. We must therefore emphasize the importance of pharmacovigilance as a continuation and completion of the analysis conducted on medicines beginning from the clinical trials when the treatment is delivered for the first time in humans, and not simply after they have been launched. The threat posed by the ever-growing list of medications, each of which carries an unavoidable risk of unanticipated potential for harm, is addressed in large part through pharmacovigilance. It is mandatory that adverse effects and toxicity be documented, examined, and their significance effectively communicated to those qualified to evaluate the information if they do occur, especially when they were previously unknown. By ensuring that therapeutic items of high quality, safety, and efficacy are utilized intelligently, the harm can be minimized. Additionally, when making therapeutic decisions, the patient's expectations and worries regarding results are taken into account. To achieve this goal and increase patient trust, make sure that medication usage risks are anticipated, effectively managed, and shared with regulatory bodies and other healthcare professionals [19].

The ways in which people interact with health-related information are being redefined by the Internet. In this digital age, using new media to communicate with patients and their support systems provides medical and public health professionals with an unmatched opportunity to find the information they require. Drug safety is one area where these skills may have broad, yet as-yet-unknown implications. Important questions have surfaced as the amount of health-related material on the Internet has increased. We chose new drug-safety notifications pertaining to prescription medications that were released by the U.S. Food and Drug Administration (FDA) throughout a 2-year span between January 1, 2011, and December 31, 2012, in order to investigate these topics. Additionally, we looked through Wikipedia articles for any mentions of safety precautions. We looked at data from a 120-day window surrounding the announcement date (from 60 days prior to the announcement to 60 days after it) in order to account for secular trends. We also created a baseline period for comparison that stretched from 60 days to 10 days prior to the time of interest. 22 prescription medications with indications for a variety of clinical diseases, such as primary hypertension, chronic myelogenous leukemia, and hepatitis, were found to include safety warnings. Over the course of the trial, these medications caused 13 million Google searches and 5 million Wikipedia page views. In comparison to baseline trends, FDA safety warnings were linked to an average 82% increase in Google searches for the drugs the week following the announcement and a 175% increase in views of the drugs' Wikipedia pages the day of the announcement (see line graph and Fig. S1 in the Supplementary Appendix). Did users discover reliable data about the safety of the drugs? We discovered that 41% of Wikipedia entries relating to medications with new safety warnings were updated with information from the FDA within two weeks of the warning's release. Wikipedia pages for medications intended to treat conditions with a high prevalence (more than 1 million Americans affected) were more likely to be updated quickly (58% within 2 weeks) than those for medications intended to treat conditions with a lower prevalence (20% within 2 weeks, etc.). On average, 42 days passed before a Wikipedia article was modified more than two weeks after the FDA issued its warning, and as of January 2014, 36% of pages were still unaltered after more than a year. Due to the FDA's decision to add a new black-box warning on this danger to the medicinal label, Google searches for the medication increased by 50% the following week and the number of views on its Wikipedia page increased by 141%. Additionally, they might know more about when to seek medical attention for signs of a possible medication reaction. When prescribing a medication, doctors can offer some crucial information, but the Pew survey reveals that many patients still independently consult other sources. The FDA's "Dear Health Care Provider" letters and printed drug labels have historically been the focus of public health officials, but new technologies give them the chance to communicate with patients and doctors more effectively and efficiently. We think the first move should be to make the drug information on the FDA website more easily accessible. Currently, electronic drug labels providing data on effectiveness, dosage, and contraindications are used instead of the MedWatch to house safety communications.

c. Evolution and Impact of Technologies on Pharmacovigilance

Digital adoption within Pharmacovigilance has historically been staggered due to various concerns such as Regulatory compliance, Data Privacy, Interoperability and perceived disruption to established PV operations. The journey thus far has been more about laying the foundation. The industry is now geared up to leverage the foundational work and accelerate digital adoption. However, the choices must be smart and the processes methodical to ensure success in such an undertaking. However, over the years, technology has made steady strides in Pharmacovigilance and made it easier and more efficient for companies to monitor and report adverse drug reactions. With secure and cost-effective hosted datacenters becoming available, pharma companies are gradually getting comfortable with hosting their PV data in external data centers. This was an important step that has book-marked the rapid evolution of our Technology journey.

**Traditional Pharmacovigilance Methods**

**a. Adverse Drug Reactions (ADR) Reporting Systems**

Worldwide, adverse drug reactions (ADRs) constitute a major cause of illness and mortality. ADRs account for 6.5% of hospital admissions in the UK, posing significant health, financial, and labor costs [14]. In order to centralize global data on adverse drug reactions (ADRs), the WHO developed the "Programme for International Drug Monitoring" in 1968. The "WHO Programme" has the specific objective of locating the first PV indications. A French group of pharmacologists and toxicologists coined the word PV in the middle of the 1970s to describe the actions supporting "The assessment of the risks of side effects of potential drug treatment[17]."

"Even a strong poison can become an excellent medicine if used properly," says Charaka. However, if used carelessly, even the most beneficial medicine might become poisonous. A harmful and unanticipated reaction to a health product that has been marketed that takes place at dosages typically employed or tested for the diagnosis, treatment, or prevention of a disease or the alteration of an organic function is known as an ADRs[13].

Throughout the whole life cycle of a product, post-marketing PV and clinical trial safety are both essential. The pharmaceutical business and regulatory organizations have increased the bar in response to a number of recent high-profile drug withdrawals. Major pharmaceutical companies are now adapting early signal detection from both clinical trials and post-marketing surveillance studies in order to identify the risks associated with the medicinal product and effectively manage the risks by implementing robust risk management plans throughout the life cycle of the product. PV has taken on a new dimension with the addition of signal detection and risk management, and as a discipline that is still developing, it still has to be improved in order to be more applicable and valuable to public health. The PV Program of India's mission is to gather, compile, and analyze data in order to draw conclusions and suggest regulatory measures in addition to informing healthcare professionals and the public about hazards.15

The largest global centers for the development of pharmaceuticals have strict regulations governing pharmacovigilance. The three main regulatory organizations that are in charge of regulating worldwide pharmacovigilance are the European Medicines Agency (EMA), Food and Drug Administration (FDA), and Pharmaceuticals and Medical Devices Agency (PMDA). To define the department's organizational structure, individual duties, and processes as well as to create the competencies required to carry out pharmacovigilance effectively, legislation, regulations, guidance, and guidelines are put in place. National laws and ordinances in Europe and the United States, as well as the Code of Federal Regulations, are both enforceable. Pharmacovigilance has developed into a regulatory activity thanks to cooperation between the World Health Organization, the Council for International Organizations of Medical Sciences (CIOMS), and the International Conference on Harmonization (ICH). There are three pharmacovigilance programs that are accepted globally: the European Union (EU) program, the WHO Uppsala Monitoring Center program, and the International Conference on Harmonization (ICH) program. They each have different pharmacovigilance traits, yet they could all lead to safe clinical medication usage. In recent years, the approval for novel pharmaceuticals has been accelerated, given top priority, and reviewed quickly. The advent of fast and conditional approval pathways necessitates new pharmacovigilance procedures as well as more frequent and innovative risk management techniques. The FDA has implemented additional procedures to address the new issues.11

**b. Adverse Event Reporting**

The cornerstone of pharmacovigilance is the reporting of adverse events, which is why regulatory bodies regularly monitor it. The following are the definitions provided by ICH E2A for adverse events (AEs), adverse drug reactions (ADRs), and serious adverse events (SAEs).

1. **Adverse event**

Any undesirable medical event in a patient or clinical research subject given a pharmaceutical substance, even though it doesn't necessarily have to be related to this treatment. An negative and undesired sign, symptom, or condition that is temporally linked to the use of a pharmaceutical product might therefore be termed an adverse event (AE), whether or not it is thought to be related to the medicinal product (including, for example, an aberrant laboratory finding).

1. **Adverse drug reaction**

All unpleasant and unanticipated reactions to a medicinal product connected to any dose should be regarded adverse drug reactions in the pre-approval clinical experience with a novel medicinal product or its new usages, especially as the therapeutic dose(s) may not be identified. The term "responses to a medicinal product" denotes that there is at least a remote potential that a medicinal product caused an unfavourable event; in other words, the relationship cannot be ruled out[1].

**Pharmacovigilance in clinical trials**

Clinical trials are used everywhere to discover a chemical or biological compound’s safety and efficacy concerning its actions on marks or a known disease process. Pharmacovigilance drives with clinical trials that provide data on the risks and advantages of the drug.

[Pharmacovigilance in clinical research](https://sollers.edu/life-science/drug-safety-and-pharmacovigilanc/) tries to discover whether the benefits exceed the risks; if they do, drug manufacturers take steps to obtain approval to market the new drug.

Trials are strictly monitored by an investigator and the pharmaceutical company involved in developing a medicinal product. However, the process also benefits from an independent review by drug safety firms. Pharmacovigilance matches this process; to provide an extra security level to assure those safe & effective products touch patients. As part of the global healthcare, drug developers, manufacturers, pharmaceutical systems, and investigators are responsible for implementing the best possible care for the patients and consumers worldwide.

Phase I, II, and III clinical trials are needed before a drug company can apply for a new medicine’s market authorization. They are responsible for the research’s conduct and then feed it back to the sponsor (the pharma company). During clinical trials, the analyst gathers and analyzes serious adverse events (SAEs), finding whether the drug in question caused the SAEs. If they conclude that the adverse side effects were causal, they are categorized as adverse drug reactions (ADRs).

The analyst gives this data to the pharmaceutical company responsible for the drug’s R&D (research and development). It is imposed by the pharmaceutical company’s in-house PV team, and the patient files undergo medical review. The PV team fixes if the drug is effective and safe to advance to the next stage of clinical research or to submit an application to the regulatory authority for approval to go to market.

If approved, the drug company may conduct Phase IV clinical trials to produce additional data on the efficiency and safety profile. These studies help provide data in a less controlled environment, representing how patients are using the drug.

### **What is the pharmacovigilance role in clinical research?**

PV in clinical trials is necessary for healthcare professionals and consumers to update the potential risks of medications. The drug company may facilitate postmarketing drug safety surveillance to observe the product’s safety and effectiveness in the real world as it is not possible to predict all possible adverse effects of a drug based on pre-approval studies. Numerous approaches can be adopted, such as; drug registries, spontaneous reporting systems, electronic health records.

### **Why is pharmacovigilance important?**

PV analysis conducted in Phase I, Phase II, and Phase III clinical trials gives drug companies data on the drug’s safety profile. This data can be used for extra R&D if required or can be proposed to regulatory authorities to admit new markets to be obtained.

PV practices in clinical research give valuable insights into pharmaceutical medications’ safety profile. When a distinct adverse reaction is recognized, the list of side effects on the label must be updated. At times, PV data can remove a drug from the market (drug recall) due to dangerous side effects.

 The risk-benefit ratio is improved, monitored, and updated accordingly. After completing Phase III clinical trials and marketing authorization, the pharmaceutical company may conduct phase IV trials to monitor the drug on a much larger scale and in a less controlled real-world environment.

It is a notable factor that effective, relevant training plays an essential role in overall career development. In very specialized industries such as clinical research, acquiring the right knowledge is immensely important.

Clinical trials have significantly increased in both industrialized and developing nations in recent years. Between 1990 and 1998, the number of clinical studies conducted in the United States alone than doubled. Clinical research on potential novel pharmacological therapies is projected to grow considerably more as a result of the sequencing of the human genome. A growing partnership exists between academia and the biotechnology and pharmaceutical businesses. This has caused grave and widespread worry regarding moral and scientific matters like

1. possibility of a conflict of interest
2. unethical patient recruitment techniques
3. inadequate informed consent
4. inability to guarantee ongoing clinical trial monitoring
5. adherence to ethical and sound clinical practice standards
6. in-adequate reporting and management of adverse events.

The growing patterns in clinical trial conduct over the past few years have given drug regulators particular and urgent problems, particularly in ensuring the protection of patients' rights and health as well as those of their communities. Before approving clinical trials, regulatory organizations take the safety and efficacy of novel products under investigation into account. They must be aware of the general standards of care and the security of study participants in addition to the required institutional review boards (IRBs). prescription medicines for diseases like tuberculosis, HIV/AIDS, malaria, and meningococcal Meningitis and those that may have a problematic or confusing effectiveness-safety profile necessitate special supervision when first being introduced on a broad scale to populations. The intricacy of clinical studies presents significant challenges for regulators. Safety monitoring during clinical trials is currently recognised as one of the major challenges for the development of innovative medications

Assuming complete information exchange between regulatory authorities and ethical committees (institutional review boards) and the investigators and sponsors, a standardized reporting system for safety issues raised during clinical trials could be a useful tool. The reporting process has been made a little easier in ICH countries thanks to expedited electronic submission of safety reports.

Signal Detection and Risk Assessment

##### The goal of the signal management procedure in pharmacovigilance is to identify any new risks connected with a given medicinal product or any recognized dangers linked with a certain medicine that have altered in frequency or severity. Signal identification, Signal Validation, and Signal Reduction comprise the systematic method to signal management. Prioritizing signals, evaluating signals, recommending actions, and exchanging information are the last steps. The most important aspect of signal management is signal detection. Traditional approaches use isolated algorithms without any additional qualitative data mining elements, which leads to subpar results. The development of the quantitative and qualitative detection algorithms requires significant work. To get around this restriction, we developed a hybrid technique where the algorithm is fueled to evaluate a signal and also manage it for efficient grading based on a qualitative approach. The current essay gives a thorough and in-depth explanation of our hybrid methodology. All medications that have been given the go-ahead to be administered in a controlled environment have been shown to have advantages while also having disadvantages. To guarantee patient safety, it's critical to identify these unidentified dangers. In order to identify case reports of adverse events (AE) that are worthy of further investigation, individual case safety reports (ICSR) must be continuously monitored as part of the signal identification and management process in pharmacovigilance. Signals are often detected quantitatively or qualitatively. Comparative detection uses statistical methods such disproportionality analysis, whereas qualitative detection requires a manual assessment of the ICSR in an individual or cumulative manner. In pharmacovigilance, the signal management process involves a number of actions that assess the hazards connected to a certain pharmaceutical medication. The most important aspect of signal management is signal detection. The hybrid approach was developed by TCS scientists, who use an algorithm to evaluate a signal and also manage it for efficient grading using a qualitative approach. We give a thorough and in-depth explanation of this hybrid technique in this work.

##### **Digital Technologies in Pharmacovigilance**

1. **Role of Big Data and Real-World Evidence:** As Contract research organizations (CROs) progressively embrace digital transformation, the usage of conventional paper-based case record forms (CRFs) is becoming obsolete. This allows for greater data quality and dependability, security in pharmacovigilance, cooperation, innovation, and speed of processing. As Contract research organizations (CROs) increasingly embrace digital transformation, the use of conventional paper-based case record forms (CRFs) is becoming obsolete. This allows for greater accuracy and reliability of data, security in pharmacovigilance, collaboration, innovation, and speed of operations. Life science organizations are increasingly feeling the effects of pharmacovigilance (PV). Large pharmaceutical businesses deal with an average of 700,000 adverse event (AE) incidents yearly, according to EY research1, and IDC2 has discovered that this figure is fast rising by 30 to 50% annually. The pandemic has made the problem worse, and some industry participants are now dealing with more over one million AE cases annually due to the quick tracking of COVID-19 vaccinations. Companies are under pressure to successfully handle this rising caseload while keeping their current cost structure. Data sources are multiplying, making it difficult for safety teams to go through the chaos of data points to provide insightful findings while simultaneously satisfying various regulatory requirements for safety reporting. As a result, costs for PV departments have skyrocketed. Since scientific information is acquired during ordinary clinical large-scale practice and not experimentally as occurs in the highly controlled traditional clinical trials, real world data (RWD) and realworld evidence (RWE) plays an increasingly essential role in clinical research. Electronic health records (EHRs) in particular are a useful source of information. However, there are also considerable obstacles to using and interpreting EHR data correctly, such as bias, population heterogeneity, and missing or unstandardized data formats. The advantages of ensuring efficacy, safety, and cost effectiveness in addition to the gold standards of the randomized controlled trial (RCT), namely by providing a complete picture regarding factors and variables that can guide sound clinical decisions, easily outweigh the difficulties that RWD and RWE have identified.
2. **Social media and Patient reported data:** Clinical trial enrolments and patient support programs. It presents new channels and methods that can enable companies to move away from traditional PV systems and safety reporting methods towards more patient-centric models for reporting, analysing and monitoring of safety data. Biopharmaceutical companies operating in the social media space have a responsibility to document and follow-up on any potential adverse event (AE) reports communicated through these forums in compliance with the applicable regulatory guidance. Most of the regulatory guidance and hence PV activities involving social media and internet are primarily focused around screening of social media sites and follow-up of reported safety data. A systematic literature search was conducted in studies were included if they contained: (i) reviews about patient reporting; (ii) evaluation of patient reports to national or supranational pharmacovigilance authorities; (iii) a comparison between patient and healthcare professional (HCP) reports submitted to pharmacovigilance authorities; and (iv) surveys of patient experiences, opinions and awareness about reporting ADRs. The methodological quality of the studies was assessed according to principles of Grading of Recommendations, Assessment, Development and Evaluations (GRADE). Patients are becoming an increasingly important source of information about the safety of drugs. By using patients as a source, the information comes first hand from those who have experienced the adverse drug reactions. These experiences are richer in context and information of the impact of an ADR as compared to information from healthcare professionals. New technologies (i.e., Internet) have made the collection of patients reported information (PRI) easier and also more affordable.
3. **Wearable Devices and Sensor Technologies:** Due to their potential to provide continuous, real-time physiological information in a variety of healthcare-related applications through dynamic, non-invasive measurements of chemical markers in biofluids, such as sweat, tears, saliva, and interstitial fluid (ISF), wearable biosensors are generating a lot of interest. Major advancements in the non-invasive monitoring of new biomarkers, ranging from metabolites to bacteria and hormones, have been made recently in this field, with recent breakthroughs concentrating on electrochemical and optical biosensors. These include the development of microfluidic sampling and transport systems and multiplexed biosensing techniques, as well as system integration, downsizing, and flexible materials for improved wearability and ease of use. Modern wearable biosensing technologies' greater accuracy, efficacy, and utility are increasing their reliability and economic impact. For increased sensor reliability, additional advancements in biosensor precision, stability in uncontrolled environments, and reproducible sample conveyance will be necessary. Overall, significant large-population validation of wearable biosensor performance through interdisciplinary collaboration across the technical, biological, and clinical disciplines will be necessary in order for wearable biosensors to be widely accepted by the medical and commercial worlds. Overall, wearable biosensing technologies hold great promise for improving personal healthcare and performance monitoring, with the potential to have a big impact on our daily lives. These technologies enable real-time body sensing and transfer of full physiological information. Since the introduction of smartphones and other mobile devices, wearable sensors have drawn a lot of attention due to their capacity to offer helpful insights regarding the performance and health of individuals. Early research in this field concentrated on physical sensors that tracked movement and vital indications like heart rate, steps taken, and calories burned. Researchers have moved away from tracking physical activity to concentrate on addressing significant problems in healthcare applications, such as the treatment of diabetes or remote monitoring of the elderly, changing the face of wearable technology quickly in recent years. A typical biosensor is made up of two basic functional components: a 'bioreceptor' (such as an enzyme, antibody, or DNA) that recognizes the target analyte with specificity and a physico-chemical transducer (such as an electrochemical, optical, or mechanical device) that converts this biorecognition event into a useful signal. Such devices were initially created for single-use home testing (like blood glucose test strips) or for in vitro measurements in regulated (laboratory or point-of-care) environments. Due to their high specificity, speed, mobility, low cost, and low power needs, biosensors have a lot of potential for wearable applications. In fact, cutting-edge biosensor platforms for non-invasive chemical analysis of biofluids, like sweat, tears, saliva, or interstitial fluid (ISF), have already been widely used to a variety of head to toe, on-body application sites, targeting a variety of significant analytes in proof-of-concept demonstrations.
4. **Mobile Health Applications For Drug Safety Monitoring:** Mobile technology enables health-care organizations to extend health-care services by providing a suitable environment to achieve mobile health (mHealth) goals, making some health-care services accessible anywhere and anytime. Introducing mHealth could change the business processes in delivering services to patients. mHealth could empower patients as it becomes necessary for them to become involved in the health-care processes related to them. This includes the ability for patients to manage their personal information and interact with health-care staff as well as among patients themselves. The study proposes a new position to supervise mHealth services: the online health educator (OHE). The OHE should be occupied by special health-care staffs who are trained in managing online services. A survey was conducted in Brunei and Indonesia to discover the roles of OHE in managing mHealth services, followed by a focus group discussion with participants who interacted with OHE in a real online health scenario. Data analysis showed that OHE could improve patients confidence and satisfaction in health-care services. The increasing availability of mobile devices and corresponding applications, both for providers and patients, often leads to speculation that mHealth, as the combination of mobile devices and health services is often called, would revolutionize the use of information technology (IT) in healthcare. On the other hand users, providers and operators providing such solutions are often confronted with completely new challenges. This article assesses the options and potential of mHealth and also takes a critical look at potential obstacles. As this field is very broad this critical analysis is illustrated by means of three exemplary application areas: mHealth in radiology, the influence of mHealth on research and mHealth as an enabler of new services, always with examples from other countries. The use of mHealth in radiology currently often develops empirically from existing applications in a relatively unstructured way and benefiting from the dynamic development of mobile technology. The possibilities range from viewing images at the bedside via mobile accessibility of radiologists up to teleradiology.   
   Creative use of new mobile and wearable health information and sensing technologies (mHealth) has the potential to reduce the cost of health care and improve well-being in numerous ways. These applications are being developed in a variety of domains, but rigorous research is needed to examine the potential, as well as the challenges, of utilizing mobile technologies to improve health outcomes. Currently, evidence is sparse for the efficacy of mHealth. Over a period of 3 years, the European Union’s Innovative Medicines Initiative WEB-RADR (Recognising Adverse Drug Reaction project explored the value of two digital tools for pharmacovigilance (PV): mobile applications (apps) for reporting the adverse effects of drugs and social media data for its contribution to safety signalling. The ultimate intent of WEB-RADR was to provide policy, technical and ethical recommendations on how to develop and implement such digital tools to enhance patient safety. Recommendations relating to the use of mobile apps for PV are summarised in this paper.
5. **Artificial Intelligence and Machine Learning in Pharmacovigilance:** The most well-known technologies at the moment are machine learning (ML) and artificial intelligence (AI). They are advancing pharmacovigilance while having a wide variety of uses. Here, we'll look into the Pharmacovigilance (PV) phenomenon. We can see how artificial intelligence and machine learning in pharmacovigilance are revolutionizing the field and adding more value through use cases and prospects. As a result, patients will receive better care, better medicine, and new revenue streams. The Benefits of Machine Learning and Artificial Intelligence in Healthcare AI is a field of study that aims to replicate human intelligence. It can aid in the management of complicated and multidimensional data. In response, ML makes use of both conventional and deep learning techniques. It enables the creation of precise classifications of data points and the ability to make precise predictions. Combining AI and ML is ideal for making sense of massive amounts of data. Businesses can use AI and ML in a variety of sectors and industries. Implementations of AI and ML are also apparent in the healthcare sector as their use accelerates. According to USM Systems research, half of all healthcare organizations worldwide intend to use AI by 2025.
6. **AI and ML in Pharmaceuticals:** Drug discovery requires working with a vast amount of data. ML and AI can help in this situation. Here is an example of how the pharmaceutical industry is prepared for further AI implementation. According to Statista, 59 startups are utilizing AI to produce new drug development ideas. The leading application for AI and ML is still drug development, but there are other noteworthy fields as well. Key factors are its potential for growth and profitability. According to this study, the worldwide AI industry for drug development would grow from $259 million in 2019 to $1,434 billion by 2024. The predicted yearly growth rate is 40.8%. More details about digitalization in drug discovery can be found here.
7. **Automated Signal Detection and Analysis:** Modern culture is dominated by medications, yet in addition to their medicinal benefits, drugs can have side effects that range from minor to morbid. Pharmacovigilance is the process of gathering, detecting, evaluating, monitoring, and preventing adverse medication occurrences during clinical trials as well as after a product has been put on the market. The need to create an optimal system for monitoring and timely signal detection has increased due to current trends in the rise of unforeseen bad events, also known as signals. The procedures used to systematically detect individual case safety reports are part of the signal management process. The data mining of spontaneous reporting systems, such as reports from medical professionals, observational studies, medical literature, or social media, is a major foundation for automated signal detection. If a signal is not handled properly, it can develop into a risk similar to that of the medicine, which can be dangerous for patient safety and result in fatalities, which could have a negative effect on the health care system. A signal might be further processed by the signal management team for the qualitative analysis and subsequent evaluations once it has been quantitatively recognized. Data extraction, data acquisition, data selection, data analysis, and data assessment are the essential elements of automated signal detection. This system needs to be designed in the appropriate context and format, which emphasizes the caliber of data gathered and ultimately results in the best decisions based on scientific analysis.
8. **Natural Language Processing for ADR Detection:** Hospitals require a system to assist them in frequently, quickly, and broadly monitoring the occurrence of adverse drug events (ADEs) in order to decrease them. For the goal of ADE identification in the context of pharmacovigilance, natural language processing (NLP), a computerized way to examine text data, has demonstrated promising results. However, there is a dearth of a thorough qualitative evaluation and critical assessment of NLP techniques for ADE identification in the context of ADE monitoring in hospitals. In order to fill this knowledge gap and offer recommendations for future research and practice, we conducted a scoping review. We incorporated studies that used NLP to identify ADEs in clinical narratives found in inpatients' electronic health records. NLP-related quantitative and qualitative data items were extracted and evaluated rigorously. 29 articles that were evaluated for eligibility out of 1,065 articles satisfied the requirements for inclusion. Named entity recognition (n = 17; 58.6%) and relation extraction/classification (n = 15; 51.7%) were the activities that were performed the most frequently. Nine studies (31%) reported clinical involvement. Numerous NLP modeling strategies appear appropriate, with Conditional Random Field and Long ShortTerm Memory techniques being the most frequently utilized ones. Although the systems' claimed overall performance was strong, this impression is overstated given a sharp decline in performance when predicting the ADE entity or ADE connection class. The optimal method when annotating corpora appears to be to treat an ADE as a relation between a drug and non-drug object. Future studies should study how to implement NLP techniques in real-world settings and concentrate on semi-automated techniques to lessen the manual annotation work.
9. **Predictive Analytics and risk Assessment Models:** Predictive analysis and the creation of predictive models are beginning to replace simple descriptive analysis as drug safety and pharmacovigilance organizations gain more advanced data analytics skills. In many facets of medicine and health care, predictive analytics makes forecasts of future outcomes or trends using present data1. The framework of signal detection and the identification and characterization of people with a particular risk for developing an adverse event after being exposed to a medicine, both in clinical development2,3, and in post-marketing settings4, illustrate the importance of being one step ahead of (adverse) events the most clearly.

**Identifying dangers from unprompted reports**

In pharmacovigilance reports, predictive modeling can be used to find previously undiscovered drug dangers. VigiRank, a data-driven predictive model for emerging safety signals, is a good illustration of this use since it has been demonstrated to outperform disproportionality analysis alone in real-world pharmacovigilance signal detection5. In VigiBase, where predictive models have been shown to be helpful in identifying safety signals that were ultimately verified, VigiRank is to be used in pediatric populations.6

**An analysis of an unanticipated rise in reporting frequency**

Similar to this, the European Medicines Agency created an algorithm to identify sudden spikes in the number of reports, particularly about quality issues, pharmaceutical errors, and abuse or misuse instances. Results from the method used on the EudraVigilance database were encouraging7.

**Risk assessment for negative effects following medication exposure**

The association between exposure to an investigational pharmaceutical product and the likelihood of adverse events has also been predicted using predictive algorithms. Niebecker8, for instance, described the connections between afatinib exposure and the trajectories of diarrhea and rash/acne adverse events with the ultimate goal of creating a modeling framework that would allow prospective comparison of dosage approaches and trial designs with regard to safety. Another instance is the use of predictive algorithms to anticipate adverse effects following the treatment of rituximab to patients with hematologic malignancies9.

Depending on the machine learning technique used, many approaches to predictive analysis have been used. Using a neural network model, machine learning has been used to forecast the likelihood that an adverse event would occur when a medicine is prescribed.10

Clinical development and postmarket signal detection using predictive models

To determine if safety signals found in first-in-human studies were more likely the product of chance or the drug under study, other authors created a model. Depending on the features of the individual and the study, the model estimates how likely an occurrence is to be the result of chance11.

To effectively identify signals resulting from adverse drug reactions in laboratory settings, a variety of predictive modeling techniques, including random forest, L1 regularized logistic regression, support vector machines, and neural networks, were combined. In order to create a machine learning model, the authors integrated features from each of the modeling strategies. For signal detection purposes, the deployment of this model to an environment with an electronic health record was deemed successful12.

The detection of negative drug reactions has been studied using supervised machine learning signal detection techniques. Sequence symmetry analysis (SSA) has been utilized to identify signs of adverse drug reactions in the world of medicine dispensing data. This thorough study demonstrates how SSA13 is well-complemented by a gradient boost classifier.

**Specific subpopulations like hospitalized patients**

Predictive analysis and model development shows interesting uses in the evaluation of risks as in this case, where the authors used mathematical models to determine the probability of adverse drug experiences in the surgical setting at the time of hospital admission, identifying the patients that are at a higher risk of an adverse drug experience during the hospital stay14

. In another study focused on drug safety in hospitals, the authors perform a systematic review of predictive risk models for adverse drug events during hospitalization15.

**Prediction of hepatotoxicity and interactions**

To predict drug-induced hepatotoxicity based on gene expression and toxicology data, by means of a multi-dose computational model16.

Use of predictive models for the prediction of adverse drug reactions induced by drug-drug interactions17

**Predictive models for comparative safety**

Leonard CE et al. utilized a Cox proportional hazard model to identify comparative safety differences among 3 sulfonylureas and the risk of sudden cardiac arrest and ventricular arrhythmia18.

Healthcare professionals (doctors, pharmacists, dentists) can inform the BCPH via the [“yellow card”](https://www.famhp.be/sites/default/files/downloads/fiche-jaune-FR-2009-03-24.pdf) about any suspicion they have concerning adverse effects of medicines they come across in daily practice.

It is nevertheless particularly important to report in the following situations:

* • Serious side effects include those that have resulted in hospitalization or a lengthened hospital stay, that were life-threatening or fatal, that have resulted in permanent or major disability or the incapacity to work, or that have caused a congenital disease or malformation.
* • Unexpected adverse effects: side effects whose origin, severity, and/or progression differ from those listed in the Summary of Product Characteristics (SPC).
* • Suspected adverse reactions: reactions that are known to occur but whose frequency, severity, or outcome is unusual.
* Adverse effects occurring in the following particular situations:

It is also important to report adverse effects with the so-called “Black triangle drugs”. These include the medicines that contain a new active substance and the new biological medicines. The clinical studies conducted for marketing authorisation are mainly intended to show the efficacy of the medicine and have limitations in detecting adverse effects:

* the number of patients included in the studies is usually too low to detect rare adverse effects;
* the duration of the studies is not long enough to detect adverse effects that appear later on;
* the studies usually do not include patients that present a high risk of adverse effects (e.g. pediatric or elderly patients, patients with important comorbidity or polymedication, patients with kidney and liver failure).

# Storage Of Data Collection

Pharmacovigilance is a crucial procedure for pharmaceutical companies and other regulatory agencies since it enables them to keep track on a drug's safety. It is often carried out after a medicine has completed all of the clinical trial stages and been given the green light for usage by the general public. By offering a platform for consumers to share information about their experiences with the medications, one method of gathering data for pharmacovigilance purposes. This could take the shape of a unique website that is simple to find and utilize. It might be challenging to persuade all drug users to record unpleasant drug experiences on the web portal, but the information gathered from the few who do may be helpful.

Pharmacovigilance can also benefit from input from primary care doctors. When a doctor prescribes such a drug, it is typically their duty to check in on the patient and assess how they are doing. Bringing a side effect to the attention of the party conducting pharmacovigilance is possible if it is noticed and linked to the medicine in question. The primary care doctors must be made aware of the importance of this information, what to watch out for, and how to record it if this is to be successful.

Data on pharmacovigilance can also be obtained directly from patients who are getting hospital-dispensed medications. This works especially well with IV medications, which must be administered inside of a hospital for patient safety. The task of gathering information about the side effects that patients have experienced as a result of using the medication can subsequently be assigned to a specific person.

Data mining drug safety report databases, the medical literature, and other digital resources could play an important role in augmenting the information about ADEs that is obtained during short-term clinical trials.[3](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5969211/#b3-ptj4306340) Data mining for pharmacovigilance purposes may also provide an “early warning system” that could detect drug safety issues more promptly than traditional methods. For these reasons, data mining these sources for ADEs is of great interest to the FDA, the pharmaceutical industry, and drug safety researchers.[3](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5969211/#b3-ptj4306340)

Digital Pharmacovigilance in Regulatory Frameworks

* Since it involves important domains like operations, surveillance, systems, and qualified individuals for pharmacovigilance, pharmacovigilance has established itself as a significant and dynamic working field for health-related personnel. Each discipline plays a complicated but connected role. Since the number of clinical trials is growing daily and there are more and more safety concerns about medications, pharmacovigilance is a necessity for the modern era. For the following reasons, pharmacovigilance is an immediate requirement for every nation:

The frequency of drug recall incidents is increasing.

• Preclinical and clinical study safety data are insufficient to support empirical proof.

• Because the sample size of clinical trial stages is so small, it might be quite difficult to detect the most uncommon adverse effects.

• Lack of understanding regarding vulnerable populations that are left out of clinical trials, including infants, children, the elderly, pregnant women, nursing mothers, and lactating women.

• The practice of polypharmacy.

• Failure to take into account factors affecting the patient, such as comorbidities, drug-drug interactions, and drug-food interactions.

• Noncompliance with prescribed treatment.

• Lack of knowledge about problems with PV and medication safety among patients, medical professionals, pharmaceutical corporations, and regulatory organizations.

The aforementioned factors increase the importance of PV because there is a lot of data that needs to be reported, gathered, and analyzed. This calls for a team of subject matter experts who can efficiently identify drug-related risks and support keeping a drug on the market throughout its lifecycle by regularly updating their risk management strategies for patients' safety and wellbeing.

A variety of cultural, geographic, and medical practices can be found across the continent of Asia. Consequently, pharmacovigilance in Asia needs to be unified and standardised. In terms of the idea of pharmacovigilance, the West has made greater progress than Asia. Since clinical trials and clinical research activities are rapidly increasing throughout Asia, there is a tremendous need to determine and put into action efficient pharmacovigilance procedures.

South Korea's regulatory framework for pharmacovigilance

The Korea Ministry of Food and Drug Safety (MFDS) established the spontaneous reporting mechanism for ADR in 1988. Korea joined the WHO-UMC in 1992 and has participated in global drug surveillance ever since. Korea started post marketing surveillance, a re-examination of the security of recently approved medications, in 1995. The web-based reporting system was made available for reporting adverse events in the year 2000. Since 2003, it has been mandatory for all manufacturers and pharmacists to notify the MFDS of any adverse drug reactions (ADRs) within 15 days of the ADR's occurrence.

In order to encourage spontaneous ADR coverage, the Ministry of Food and Drug Safety (MFDS) designated three university hospitals as Korean Regional PV Centers (RPVCs) in 2006. RPPVs were made necessary for all pharmaceutical companies to designate in 2007. In 2009, a well-established PV network with 15 RPVCs was built in Korea. A national concurrent medication use review system was created in 2010 for both doctors and pharmacists. It covers drug-drug interactions, drug-age contraindications, and is a real-time screening system. According to Article 68-3 of the Pharmaceutical Affairs Law, the Korea Institute of Drug Safety and Risk Management (KIDS) was established under the MFDS in April 2012.

The Adverse Drug Reaction Reporting System was introduced in Korea by Korea MFDS in 1988. Since that time, both healthcare professionals and patients have reported spontaneous ADRs. Despite lower reporting rates over the first ten years, Korea has been able to speed up the process after the founding of KIDS (Korea Institute of Drug Safety and Risk Management) in 2012. As a result, KIDS has significantly aided Korean Pharmacovigilance.

KIDS uses the WHO-UMC scale to identify signals. Additionally, it makes use of a variety of data mining methods, such as Bayesian Confidence Propagation Neural Networks. Specific regulatory actions, such label changes, can be made as a result of the detection of possible signals. The HIRA database and hospital electronic medical record (EMR) databases are being used in data mining methodologies for a more thorough investigation of drug use and disease recurrence. The task of assessing causation is also handled by KIDS, which use a range of algorithms based on decision criteria including challenge, dechallenge, and rechallenge data, as well as prior bibliographic information and other aetiologic alternatives. Pharmacoepidemiologic methods like cross-sectional, case-crossover, case-control, and other cohort studies are employed for causality evaluation and signal confirmation. An authorized, planned, and ongoing program that examines, analyzes, and interprets drug usage trends in a specific health care delivery system in comparison to set standards is what is meant by a data utilization review, according to well-established definitions.

The Drug Utilization Review (DUR) was developed to lower prescription errors and raise the standard of pharmaceutical care. A DUR notifies physicians and pharmacists of the potential side effects that patients may experience after taking their drugs.

**Singapore's pharmacovigilance regulatory framework**

The organization joined the WHO International Drug Monitoring Program in 1994, becoming its forty-first participant. Singapore's Health Science Authority, a drug regulatory body, monitors adverse events related to therapeutic items there. Patients, healthcare professionals, and industry can all voluntarily report adverse events involving therapeutic products, vaccines, complementary therapeutic goods, such as traditional medicines, Chinese proprietary medicines, dietary supplements, cell tissue gene therapy products, cosmetics, and medical devices to the HSA. The following adverse occurrences are suitable for reporting:

Any negative impacts connected to the usage of new health products, which are ones that have been available in Singapore's market for under five years.

Despite the fact that they are well-known, all grave unfavorable incidents.

consequences that are unanticipated and may not match the product's label or box insert.

Healthcare professionals (HCPs) have two options for reporting adverse events: they can do so manually by filling out specific color-coded forms and mailing them to the HSA's Vigilance and Compliance Branch, Health Product Regulation Group, or by emailing HSA productsafety@hsa.gov.sg.

YELLOW FORM: medicinal substances and supplementary therapeutic items.

Vaccines are in BLUE FORM.

Advanced therapeutic products are GREEN FORM.

Importers, distributors, retailers, and registrants of therapeutic products are all required to declare all material adverse effects related to their products. The initial report submission requires the following details:

a recognized journalist or healthcare professional.

a patient who can be identified.

unfavorable outcome.

a potential item.

Thailand's pharmacovigilance regulatory framework

The pharmacovigilance system in Thailand was created in 1983. The national center was established by the Food and Drug Administration, and its main objective is the ADR monitoring program. The number of reports has increased to more than 50,000 annually from the initial 176 reports from numerous tertiary hospitals in the first year, with pharmacists acting as the principal reporter. The sphere of work also includes consumers, market authorization holders, and health services including pharmacies, doctors' offices, private hospitals, and all varieties of public hospitals, from community hospitals to tertiary hospitals to university and research hospitals. The United States Agency for International Development (USAID) and other Asian countries have taken the initiative to evaluate Thailand's pharmacovigilance system. The project's expertise and learning experiences can serve as a foundation and guiding principles for the pharmacovigilance systems of other nations in addition to helping the countries under study. The following laws apply to pharmacovigilance activities:

Thailand's drug laws and policies are governed by the Drug Act of 1967.

National Drug Policy (2011): A Strategy for the Development of the National Drug System, 2012–2016.

Thailand formally enrolled in the WHO program in 1984. It employs the E2B compliance INTDIS format for ICSR documentation. ATC codes for medications, ICD-10 for indications, and WHO-ART (Adverse Reaction language) were all utilized in medical language.

* The PV database has the following types of reports:
* Unplanned reports,
* adverse event reports following immunization,
* Active surveillance reports,
* Product quality reports,
* PURR, and
* information from PHPS.

Enhancing Adverse Event Reporting and Monitoring

When a new drug or therapy is being tested, an adverse event is a sudden issue that arises. It can range from mild to severe and may be brought on by the medicine itself or something else, according to the National Cancer Institute. Here, we examine the reasons behind the persistently low rate of adverse event reporting and how technology and better protocols might streamline the procedure.

Insufficient AE Reporting

Reporting of AEs is not only subject to biases, but it also frequently goes unreported. For significant adverse events (SAEs), in particular. According to clinical trial standards, researchers are required to immediately report SAEs to the sponsor, who then notifies the FDA within 15 days. Neuer claims that reporting is still troublesome and frequently does not appear at all in articles that are published.

Intervention to Promote AE Reporting

Poor AE reporting rates necessitate the use of appropriate interventions and training. In a study that was published in the journal Frontiers in Pharmacology, researchers argue that frequent interventions and encouragement to report adverse events are crucial.

They put their idea to the test in a children's hospital in Israel, where they developed an interventional program and compared it to a control period to ascertain which medications cause adverse effects (AEs). Over the course of three months, the intervention study gathered data. After that, they made a comparison using data acquired for 12 months prior to and following the study. The 12-month period before to intervention displayed a 0% AE report rate, according to the researchers. During the intervention, it rose to 46 reports, but in the year following, it sharply dropped.

Consequently, it is concluded that frequent interventions and training are necessary.

Even in countries with official mechanisms for reporting adverse drug reactions (ADRs), a more recent study indicated that reporting rates are low. ADR reporting did, however, increase as a result of initiatives to inform healthcare professionals and hospital teams about when and how to report ADRs.

Collaboration and Stakeholder Engagement

This resource book seeks to assist practitioners and stakeholders in gaining a deeper understanding of how to approach and structure a collaborative process by outlining the fundamentals of collaboration, offering a variety of tools, and reporting on a number of case studies from across the world. Stakeholders are urged to make use of the concepts and knowledge presented here to forge fresh and inventive connections with the people and organizations that can support the realization of collaboration. The process of stakeholder collaboration will go through several revisions.

Whatever the outcome, the stakeholder collaboration process can aid a variety of stakeholders, including allies and opponents, the public and private sector, communities, and individuals, in better understanding the problems and difficulties associated with achieving conservation goals and objectives at various scales. Any individual, team, or organization that influences or is impacted by a certain problem or result is referred to as a stakeholder. In this book, "stakeholders" refers to individuals, organizations, or social groups that participate in or are impacted by decisions about biodiversity conservation-related issues. Despite the seeming simplicity of this concept, it might be challenging to provide a clear response to questions like these: "The people" are who? What exactly is a "institution"? What exactly constitutes a "social group"? But in order to find and engage the appropriate stakeholders, these questions must be addressed.

Exist several kinds of stakeholders?

Depending on how they use and have historically interacted with resources, different interest groups will have varying stakes in their management.

Primary stakeholders are those who are at the center of any conservation movement due to their positions of power, authority, responsibility, or claim to the resources. They must participate in any action because the result will immediately touch them. Local community-level organizations, interests from the commercial sector, and regional and federal government organizations can all be considered primary stakeholders. By virtue of the influence they have, this category of stakeholder also include those who have the potential to effect collaborative results even though they might not personally be impacted.

Those with a secondary stake in the result are those who are not directly interested. The consumer, who cares about a product's continued availability, the employee of a company, who worries about job security, or the tour operator, who wants to know if a destination for ecotourism will still be reachable by tourists, are a few examples of secondary stakeholders depending on the issue. These stakeholders might need to be included in cooperation processes, but because of how minor their function is in comparison to the key stakeholders', they might only need to be involved occasionally.

Due to their power and resources, opposing stakeholders may be able to have a negative impact on the results. It is critical to engage them in open communication despite the fact that they may adversely affect various parts of conservation planning, especially in the beginning. Even Women, indigenous peoples, and other disadvantaged and disenfranchised groups are examples of marginalized stakeholders who may really be primary, secondary, or opposition stakeholders but who may not have the recognition or ability to take part in collaborative initiatives equally. Always make an extra effort to assure their engagement. Determining the amount of time and assistance needed to enable them to arrange themselves and take part in a collaborative process requires strategic forethought. Though conservation organizations are becoming more aware of how crucial it is to work with their opponents, they have little practical experience in this area. If conservation is to be successful, this will undoubtedly change over time.

Future Perspectives and Innovations

Global pharmacovigilance systems are undergoing considerable change as a result of technology improvements, an increase in the amount of data that authorities and businesses have access to, and a rise in patient involvement in healthcare decision-making. Pharma firms continually contend with a rising number of changes in pharmacovigilance and regulatory compliance: more data from more sources, more products in more places, and constantly shifting reporting requirements.

The need to analyze more data as rapidly as feasible, to monitor risks more thoroughly, and to appropriately report unfavorable events globally increases as a result of these changes.

We think that increased communication between regulators, patients, and medical practitioners, as well as more intelligent data gathering and reporting of potential adverse events, will be crucial components of pharmacovigilance in the future.

In accordance with the laws of the relevant country, our pharmacovigilance department is made up of highly educated, competent, and compliant professionals with the required organizational and technical assistance to satisfy the particular demands of customers.

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