PHARMACIA

Pharmacia 72: 1–6
DOI 10.3897/pharmacia.72.e143323

Review Article

Opportunities for implementing digital applications to monitor the impact of risk-minimization measures within the pharmacovigilance process: Scoping review of published literature

Ilko Getov[1], Denitsa Panayotova[1], Stanimir Dobrev[1], Maria Dimitrova[1], Valentina Petkova[1]

1 *Faculty of Pharmacy, Medical University of Sofia, Sofia, Bulgaria*

Corresponding author: Maria Dimitrova (mia_dimitrova@yahoo.com)

Received 2 December 2024 ♦ **Accepted** 4 December 2024 ♦ **Published** 9 January 2025

Citation: Getov I, Panayotova D, Dobrev S, Dimitrova M, Petkova V (2025) Opportunities for implementing digital applications to monitor the impact of risk-minimization measures within the pharmacovigilance process: Scoping review of published literature. Pharmacia 72: 1–6. https://doi.org/10.3897/pharmacia.72.e143323

Abstract

The study provides an overview of innovative digital solutions to meet the evolving needs of drug safety monitoring and improve patient outcomes, focusing on implementing digital applications to enhance the monitoring of additional risk-minimization measures (aRMMs) for pharmacovigilance. Over the last decade, the literature has highlighted a critical unmet need for improving the efficiency and accuracy of adverse event reporting. This is crucial for identifying risks not observed during clinical trials. Digital tools offer potential benefits by providing real-time reporting, comprehensive safety data, and increased patient engagement, thus addressing the challenges of underreporting and incomplete data in pharmacovigilance. The scoping review of the literature identified current global practices and evaluated the feasibility of adopting such solutions locally. The findings suggest digital tools such as mobile applications, web-based platforms, and electronic health record integrations are effective mechanisms for the collection of real-world data, patient-reported outcomes, and patient engagement in terms of drug safety surveillance. These tools address significant challenges inherent in traditional systems, such as underreporting and data fragmentation. Integrating digital solutions into pharmacovigilance can significantly enhance the timeliness and reliability of drug safety data, supporting more informed regulatory decision-making and ultimately improving patient outcomes.

Keywords

adverse events, data accuracy, digital tools, drug safety, pharmacovigilance

Introduction

Within the past years, there has been a pressing need to enhance post-marketing surveillance, a pivotal component of the pharmaceutical lifecycle that persists beyond regulatory approval to ensure the ongoing safety and efficacy of drug products (Ghinea et al. 2021). The pharmaceutical industry is continuously evolving, driven by rapid technological advancements and the introduction of novel therapeutics. This evolution increases the complexity of managing and ensuring drug safety. Post-marketing surveillance plays a crucial role in identifying safety risks that may not emerge

during clinical trials, thereby safeguarding public health and maintaining trust in healthcare systems (Najafi 2018).

Post-marketing surveillance involves the continuous monitoring of drugs after they have been released to the market. This ongoing process is essential for identifying various safety risks that may not have been detected during clinical trials. Moreover, the importance of this surveillance cannot be overstated, as it helps in the early detection of adverse drug reactions (ADRs) and ensures that necessary safety measures are implemented promptly.

Despite its critical importance, the current system of post-marketing surveillance faces significant challenges (Ghinea et al. 2021). Key among these is the inefficiency, inaccuracy, and delay in reporting adverse events, which are central to the practice of pharmacovigilance (Alomar et al. 2020). Spontaneous reporting systems, which rely heavily on healthcare professionals and patients to report ADRs, form the backbone of pharmacovigilance activities. However, these systems are plagued by significant underreporting; it is estimated that only a fraction of ADRs are communicated to regulatory authorities, delaying the detection and response to potential safety signals (Thomas et al. 2020; Moen et al. 2022). This underreporting is further complicated by incomplete data often found in ADR reports, which can hinder a comprehensive understanding of the nature and severity of these events (Moen et al. 2022).

The fragmentation of reporting systems, especially at the national level, exacerbates these challenges by making the reporting process cumbersome and time-consuming (Kuo et al. 2018). While some countries have successfully implemented national digital reporting systems, many continue to rely on fragmented infrastructures that impede effective and efficient information flow (Yeo et al. 2021). The integration of digital applications into pharmacovigilance practices offers a promising solution to these issues, providing real-time reporting capabilities and comprehensive safety data that support more informed decision-making regarding drug use (Shen et al. 2021). Additionally, these digital platforms have the potential to significantly enhance patient engagement in pharmacovigilance processes, reduce the costs associated with drug safety monitoring, and improve overall public health outcomes.

Risk minimization measures (RMMs) are critical interventions designed to prevent or mitigate the occurrence of ADRs related to drug exposure. They are integral to risk management strategies, ensuring that the benefits of drug products outweigh their risks. While routine RMMs are generally adequate for most safety concerns, there are instances where additional measures are necessary to manage specific risks and optimize the risk-benefit profile of a drug (European Medicines Agency 2021). The landscape of risk management is evolving with an increasing emphasis on the development and implementation of innovative digital solutions (Raine et al. 2011). Web-based tools can streamline the data collection process for assessing additional RMMs (aRMMs), offering the ability to integrate real-time user behavior data to facilitate ongoing evaluations and adjustments (Banerjee 2009; Banerjee et al. 2012).

Moreover, the successful implementation of additional RMMs requires the collaboration of all stakeholders, including healthcare professionals, patients, and pharmaceutical companies. Evaluating these measures is essential to ensure that their objectives are met and that the introduced measures are proportional, considering the risk-benefit ratio of the product and the efforts required by healthcare professionals and patients (European Medicines Agency 2021).

As the approach to risk management, including the use of RMMs, continues to evolve, it is crucial to confirm that these measures do not place an undue burden on healthcare delivery systems, regulatory authorities, and, most importantly, patients (Raine et al. 2011). Innovative solutions, such as web-based tools, can facilitate the collection of data needed for evaluating aRMMs and provide timely, ongoing assessments that integrate user behavior data (Banerjee et al. 2012).

This research seeks to explore the implementation of digital applications in pharmacovigilance, addressing the limitations of current practices and providing a framework for future innovations in drug safety monitoring. By leveraging digital solutions, this study aims to enhance the safety of pharmaceutical products, support more robust regulatory decision-making, and ultimately improve the quality of life for patients worldwide.

Methods

We performed a literature search using the scoping review methodology in PubMed and the Web of Science scientific databases on predefined keywords ('adverse events' and 'data accuracy,' 'digital tools' and 'drug safety,' and 'risk-minimizing measures') for published studies evaluating current advancements and implementations of digital tools in pharmacovigilance. We applied pre-selected inclusion criteria: 1) Articles published in 2013–2024; 2) Articles matching the keywords; 3) Published abstract 4) Articles in English. We also defined the following exclusion criteria: 1) Articles published in a language other than English; 2) Articles without an abstract; 3) Articles that do not meet the purpose of the literature review.

Based on the results, we made a subsequent critical analysis that entailed a detailed examination of the effectiveness, scalability, and adaptability of these globally implemented digital applications for drug safety monitoring to evaluate their potential integration and application within the national healthcare systems, considering regional regulatory frameworks, including health strategy and legislative documents, healthcare infrastructure, and the practical challenges and opportunities that may arise in the process of adapting these digital solutions to enhance the efficacy of existing pharmacovigilance practices.

Results

Through the scoping literature review, we identified 11 articles meeting the inclusion and exclusion criteria—Fig. 1.

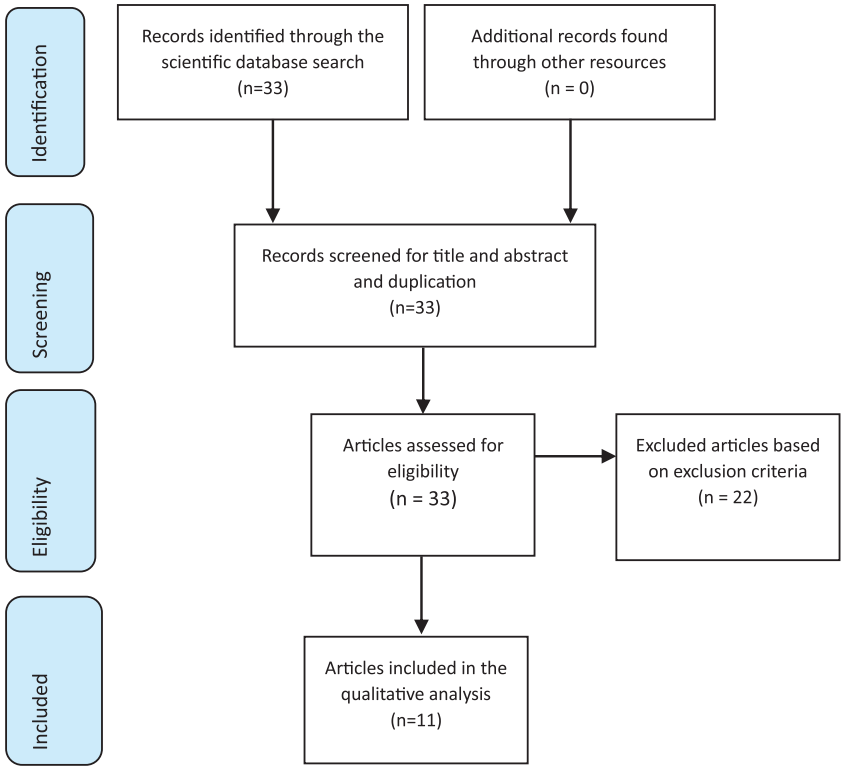

Figure 1. PRISMA flow diagram of the scoping review screening process.

The scoping review revealed a growing trend in the adoption of digital applications for pharmacovigilance, with a significant number of studies highlighting their potential to improve the timeliness and accuracy of adverse drug reaction (ADR) reporting. Specifically, digital tools such as mobile applications, web-based platforms, and electronic health record integrations were frequently cited as effective mechanisms for the collection of real-world data, patient-reported outcomes, and patient engagement—Table 1.

Table 1. Summary of scoping review results.

Article	Objectives	Conclusions
Banerjee et al. 2013	To describe the benefits and potential of the Patient-Reported Outcomes Safety Event Reporting (PROSPER) Consortium in terms of collecting PROs related to drug safety and post-marketing surveillance.	Currently, drug safety reporting is mostly dependent on healthcare professionals, but the evolvement of digital technologies can contribute to more efficient engagement of patients.
Hoppe C et al. 2016	VACC-Tool (ViVI Automated Case Classification Tool) 2.0, a mobile application enabling physicians to classify clinical cases according to 14 predefined case definitions for neuroinflammatory adverse events (NIAE).	Digital tools improve the quality of safety reporting and enhance healthcare professionals' assessment of potential adverse drug events in hospitalized patients and during follow-up.
Fuller T et al. 2020	To evaluate the role of digital health tools integrated with the EHR to engage hospitalized patients, caregivers, and their care team during hospital discharge in reducing potential adverse drug events related to poor hospital discharge organization.	The use of EHR-integrated digital health tools to engage patients, caregivers, and clinicians in discharge preparation during hospitalization was feasible, acceptable, and valuable, especially in terms of reducing the risk of adverse drug events post-discharge.
El Saghir A et al. 2021	To develop and implement an institution-specific trigger tool to detect and monitor ADEs in hospital settings.	Digital tools may reduce the time of adverse drug events assessment.
Kestler A et al. 2021	To assess the potential of a smartphone application for symptom reporting and tracking that is adjusted to the standard clinical reporting system in oncology patients.	Digital tools can improve the underreporting of paramount side effects and define the actual value of a treatment for the individual patient.
Smith MY et al. 2022	The role of digital tools in improving the effectiveness of risk minimization programs.	Regulators have acknowledged the potential value of digital tools in RMM, but still, there is no explicit regulatory guidance on their design.
Da Silva-Tillmann B et al. 2022	An exploratory study to provide initial insights on the acceptability of digital additional risk-minimizing measures (RMMs) and their efficiency compared to traditional paper sources of RMMs.	There is an interest from HCPs and patient stakeholders in digital approaches to use educational aRMMs.
Gullslet and Bergmo 2022	E-prescribing is a possible digital tool to monitor drug safety and minimize the risk related to prescribed medicines.	Challenges still exist in terms of digital competence and motivation to use digital tools among GPs.
Di Giovanni R et al. 2022	The use of advanced digital technologies in the screening of safety and efficacy data and artificial intelligence to define adverse events and support safety experts in decision-making.	Artificial intelligence may be beneficial in reducing the bias of published safety data and concentrating on the most relevant evidence.
Lim R et al. 2022	To develop a user-friendly digital tool for consumers to report medication-related adverse effects.	The web-based system for medicine adverse effects reporting is a user-friendly tool that could support patients in the adverse drug reactions reporting process.
Lang AL et al. 2024	To assess the efficiency of digital participatory surveillance tools and the potential of self-reported data for monitoring key parameters in COVID-19 patients.	Digital study web applications have the potential to support COVID-19 surveillance and continuous monitoring.

The literature search identified only two articles evaluating the role of digital technologies in developing and implementing risk-minimization measures within pharmacovigilance and post-marketing drug safety processes.

The critical analysis of the national legislative documents shows that there is an adopted framework for digital health in the digital transformation of the healthcare system, which could facilitate the implementation of digital technologies in clinical practice in Bulgaria, but further legislative considerations should be done to regulate their placement on the market and their utilization in practice, especially with a focus on pharmacovigilance—Fig. 2 and Table 2.

Discussion

The findings from this study highlight the transformative potential of digital applications in pharmacovigilance, especially in terms of adverse drug reaction reporting. Unfortunately, to date, there is little published evidence on the effectiveness of digital tools in the application of risk-minimizing measures; nevertheless, their application has been acknowledged by the regulatory authorities worldwide.

By facilitating real-time ADR reporting and improving data accuracy, these digital tools address the significant challenges of underreporting and data fragmentation, as identified in traditional pharmacovigilance systems (Ghinea et al. 2021; Alomar et al. 2020).

The success of digital applications in global implementations suggests that similar strategies could be effectively adapted for local contexts, considering regional regulatory environments and healthcare infrastructures. For example, the use of mobile health applications could be tailored to meet the specific needs of healthcare systems in developing regions, where traditional reporting mechanisms may be less effective.

In Europe, the "WEB-RADR" project has been a pioneering force in utilizing digital technology for pharmacovigilance. This project, highlighted in studies from the European Journal of Clinical Pharmacology, has developed mobile apps that facilitate direct ADR reporting to national health authorities, significantly enhancing efficiency and user engagement across several European countries (Beninger 2018). Additionally, platforms like the UK's Yellow Card Scheme have integrated mobile applications to streamline the reporting process, as documented

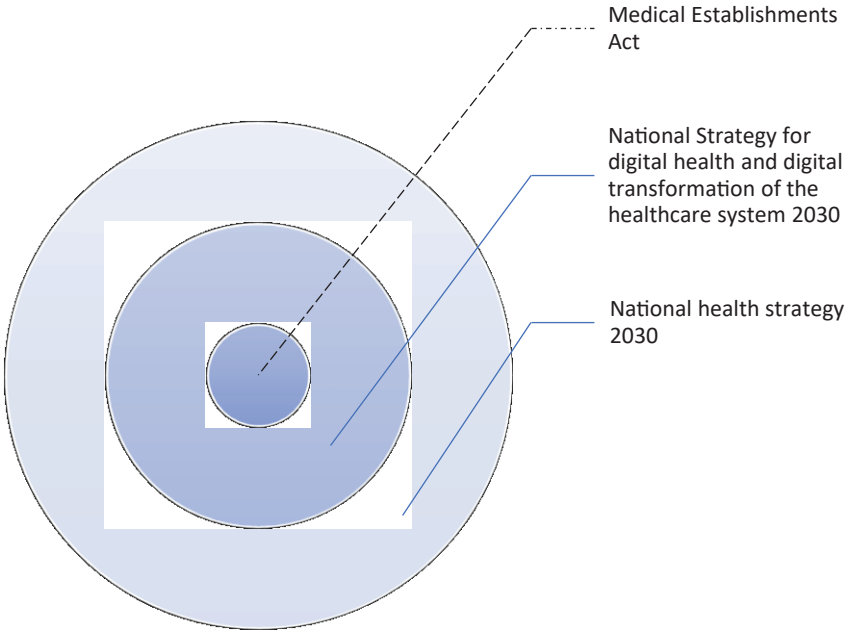

Figure 2. Health policy legislative and strategic documents with a focus on digital health in Bulgaria.

Table 2. Critical analysis of the possibilities and challenges for digital tools in pharmacovigilance based on national strategic policy documents.

Policy document	Objectives in terms of digital transformation	Possibility for pharmacovigilance	Challenge for pharmacovigilance
National Health Strategy 2030	Development of eHealth and digitalization of the healthcare system with a focus on the efficacy, quality, and safety of medical services.	Not mentioned	Lack of requirements relating digital transformation to drug safety surveillance.
National Strategy for Digital Health and Digital Transformation of the Healthcare System 2030	To develop an integrated electronic portal and application for citizens providing centralized eHealth services, including health information systems, health profiles, health records and condition monitoring, telemedicine, prescriptions, and administrative services.	E-prescriptions as a tool to monitor and minimize the risk of adverse drug reactions.	Lack of legislative requirements for the connection of the e-prescription system with the ADR reporting system.
Medical Establishments Act	Submitted proposal for draft amendment and supplement of the health law for inclusion of telemedicine.	Not mentioned	Pharmacovigilance is not in the scope of the health law.

in the British Journal of Clinical Pharmacology (Avery et al. 2019).

In North America, the "MedWatcher" app developed by the FDA exemplifies the integration of digital tools into national pharmacovigilance efforts. This application has been instrumental in improving the speed and accuracy of ADR reporting, as discussed in the Journal of the American Medical Informatics Association (Plasek et al. 2019). Furthermore, Health Canada's "MedEffect Canada" initiative has launched an online reporting tool that facilitates consumer and healthcare professional engagement, as outlined in research published in Healthcare Quarterly (Gupta et al. 2020).

Asia has seen significant advancements in digital pharmacovigilance, particularly in Japan and South Korea. In Japan, the PMDA's electronic reporting system integrates with hospital records, enhancing real-time ADR data collection, as noted in the Journal of Pharmaceutical Health Care and Sciences (Yoshida et al. 2020). South Korea's Ministry of Food and Drug Safety has developed an app-based reporting system that not only simplifies ADR reporting but also provides educational resources for healthcare professionals, as explored in the Asian Journal of Pharmaceutical Sciences (Kim et al. 2021).

In Africa, the implementation of digital platforms like the one developed by NADEMC in South Africa signifies a step forward in improving pharmacovigilance in resource-limited settings. This system has been praised for its accessibility and effectiveness in publications such as the African Journal of Pharmacy and Pharmacology (Mouton and Naidoo 2019). Nigeria's National Agency for Food and Drug Administration and Control (NAFDAC) has also introduced a mobile app to encourage ADR reporting, demonstrating significant improvements in engagement and data collection, as highlighted in the Tropical Journal of Pharmaceutical Research (Ogundele et al. 2021).

Australia's Therapeutic Goods Administration (TGA) has made notable progress with its "DAEN" online reporting tool, which supports both healthcare providers and consumers in reporting ADRs efficiently. The impact of DAEN on enhancing data transparency and regulatory decision-making is discussed in the Australian Prescriber Journal (McEwen 2020). Additionally, New Zealand's Centre for Adverse Reactions Monitoring (CARM) has integrated an electronic reporting system that allows for seamless data exchange between healthcare providers and regulatory bodies, as reported in the New Zealand Medical Journal (Simpson et al. 2019).

Comparatively, the results align with previous studies that emphasize the importance of integrating innovative technologies in pharmacovigilance to overcome existing limitations (Najafi 2018; Raine et al. 2011). However, challenges remain, particularly concerning the scalability of these solutions and the need for robust regulatory frameworks to ensure data privacy and security.

Conclusion

The findings suggest that integrating digital solutions into pharmacovigilance can significantly enhance the timeliness and reliability of drug safety data, supporting more informed regulatory decision-making and ultimately improving patient outcomes. Future efforts should focus on tailoring these digital applications to local needs while ensuring robust regulatory frameworks to safeguard data privacy and security. By doing so, the potential benefits of these innovations can be fully realized, leading to improved healthcare delivery and increased trust in pharmaceutical products worldwide.

Acknowledgements

The authors would like to express their gratitude to the Council of Medical Sciences at the Medical University of Sofia for approving and supporting this study.

Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical statements

The authors declared that no clinical trials were used in the present study.

The authors declared that no experiments on humans or human tissues were performed for the present study.

The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.

The authors declared that no experiments on animals were performed for the present study.

The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

Funding

This study is part of project D-110/2024 approved by the Council of Medical Sciences at the Medical University of Sofia. This project focuses on exploring the implementation of digital applications to monitor the effectiveness of risk-minimizing measures in the context of medicines safety monitoring.

Author contributions

DP and SD performed the scoping review and contributed to the results, revising and writing. VP, IG, and MD contributed to analyzing the survey results and writing and revising the manuscript.

Author ORCIDs

Maria Dimitrova https://orcid.org/0000-0002-4868-7775
Valentina Petkova https://orcid.org/0000-0002-6938-1054

Data availability

All of the data that support the findings of this study are available in the main text.

References

Alomar MJ, Alasmari A, Khan SA (2020) Post-marketing surveillance of suspected adverse drug reactions through spontaneous reporting: current status, challenges and the future. Therapeutic Advances in Drug Safety 11: 2042098620938592. https://doi.org/10.1177/2042098620938595

Avery AJ, Anderson C, Bond CM, Fortnum H, Taylor J (2019) Evaluation of patient reporting of adverse drug reactions to the UK 'Yellow Card Scheme': Literature review, descriptive and qualitative analyses, and questionnaire surveys. British Journal of Clinical Pharmacology 85(4): 687–697. https://doi.org/10.1111/bcp.13862

Banerjee AK (2009) Pharmacists are key to enhancing benefit-risk for medicines. Archives of Internal Medicine 169(18): 1723–1724. https://doi.org/10.1001/archinternmed.2009.342

Banerjee AK, Ingate S, Avery AJ (2012) Behavioural assessment offers an improved evaluation of risk minimisation tools (RMT). Pharmacoepidemiology and Drug Safety 21(S3): 206. https://doi.org/10.1002/pds.2333

Banjeree AK, Okun S, Edwards IR, Wicks P, Smith MY, Mayall SJ, Flamion B, Cleeland C, Basch E (2013) Patient-Reported Outcome Measures in Safety Event Reporting: PROSPER Consortium Guidance. Drug Safety 36(12): 1129–1149. https://doi.org/10.1007/s40264-013-0113-z

Beninger P (2018) Pharmacovigilance: An overview. European Journal of Clinical Pharmacology 74(10): 1251–1255.

Da Silva-Tillmann B, Wilson MC, Doshi H, Lievano F, Perrott M, Renz C (2022) Digital additional risk minimization measures: An exploratory study using qualitative feedback from healthcare professionals and patients across six countries. Pharmaceutical Medicine 36(1): 21–32. https://doi.org/10.1007/s40290-021-00415-7

Di Giovanni R, Cochrane A, Parker J, Lewis DJ (2022) Adverse events in the digital age and where to find them. Pharmacoepidemiology and Drug Safety 31(11): 1131–1139. https://doi.org/10.1002/pds.5532

El Saghir A, Dimitriou G, Scholer M, Istampoulouoglou I, Heinrich P, Baumgartl K, Schwendimann R, Bassetti S, Leuppi-Taegtmeyer A (2021) Development and Implementation of an e-Trigger Tool for Adverse Drug Events in a Swiss University Hospital. Drug, Healthcare and Patient Safety 13: 251–263. https://doi.org/10.2147/DHPS.S334987

European Medicines Agency (2021) Guideline on good pharmacovigilance practices (GVP) Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators.

Fuller TE, Pong DD, Piniella N, Pardo M, Bessa N, Yoon C, Boxer RB, Schnipper JL, Dalal AK (2020) Interactive digital health tools to engage patients and caregivers in discharge preparation: Implementation study. Journal of Medical Internet Research 22(4): e15573. https://doi.org/10.2196/15573 [PMID: 32343248]

Ghinea N, Lipworth W, Kerridge I, Day R (2021) The Importance of Post-Marketing Surveillance of Pharmaceutical Products. Journal of Clinical Medicine 10(1): 64. https://doi.org/10.3390/jcm10010064

Gullslet MK, Bergmo TS (2022) Implementation of E-prescription for multidose dispensed drugs: qualitative study of general practitioners' experiences. JMIR Human Factors 9(1): e27431. https://doi.org/10.2196/27431

Gupta A, Davies B, Mehta J (2020) Enhancing the role of consumers in pharmacovigilance: MedEffect Canada's initiative. Healthcare Quarterly 23(2): 18–25.

Hoppe C, Obermeier P, Muehlhans S, Alchikh M, Seeber L, Tief F, Karsch K, Chen X, Boettcher S, Diedrich S, Conrad T, Kisler B, Rath B (2016) Innovative digital tools and surveillance systems for the timely detection of adverse events at the point of care: A proof-of-concept study. Drug Safety 39(10): 977–988. https://doi.org/10.1007/s40264-016-0437-6

Kestler AMR, Kühlwein SD, Kraus JM, Schwab JD, Szekely R, Thiam P, Hühne R, Jahn N, Fürstberger A, Ikonomi N, Balig J, Schuler R, Kuhn P, Steger F, Seufferlein T, Kestler HA (2021) Digitalization of adverse event management in oncology to improve treatment outcome prospective study protocol. PLOS ONE 16(6): e0252493. https://doi.org/10.1371/journal.pone.0252493

Kim JH, Lee SH, Park YH (2021) Development of a mobile application for adverse drug reaction reporting in Korea. Asian Journal of Pharmaceutical Sciences 16(2): 230–237. https://doi.org/10.1016/j.ajps.2020.06.003

Kuo YF, Lee CJ, Lin HC (2018) Under-reporting of adverse events: A study of nursing aides in long-term care facilities. Journal of Patient Safety 14(2): 70–75. https://doi.org/10.1097/PTS.0000000000000364

Lang AL, Hohmuth N, Višković V, Konigorski S, Scholz S, Balzer F, Remschmidt C, Leistner R (2024) COVID-19 vaccine effectiveness and digital pandemic surveillance in Germany (eCOV Study): Web application-based prospective observational cohort study. Journal of Medical Internet Research 26: e47070. https://doi.org/10.2196/47070

Lim R, Thornton C, Stanek J, Ellett LK, Thiessen M (2022) Development of a web-based system to report medication-related adverse effects: Design and usability study. JMIR Formative Research 6(10): e37605. https://doi.org/10.2196/37605

McEwen J (2020) Enhancing patient safety: The role of DAEN in Australian pharmacovigilance. Australian Prescriber 43(1): 20–25. https://doi.org/10.18773/austprescr.2020.008

Moen J, Bjerke G, Jacobsson L (2022) Characteristics of under-reporting of adverse drug reactions to the Norwegian Yellow Card Scheme. BMC Pharmacology and Toxicology 23(1): 5.

Mouton JM, Naidoo P (2019) Improving pharmacovigilance in South Africa: The role of digital platforms. African Journal of Pharmacy and Pharmacology 13(3): 34–40.

Najafi S (2018) Importance of Pharmacovigilance and the Role of Healthcare Professionals. Journal of Pharmacovigilance 6: 252. https://doi.org/10.4172/2329-6887.1000252

National Health Strategy 2030 (2024) National Health Strategy 2030. https://old.mh.government.bg/media/filer_public/2024/05/10/rns_-_nzs_2030.pdf [Accessed on: November 2024]

National Strategy (2024) National Strategy for digital health and digital transformation of the healthcare system 2030. https://old.mh.government.bg/media/filer_public/2024/04/01/natsionalna_strategiia_ezdraveopazvane-finalen_dokument.pdf [Accessed on: November 2024]

Ogundele SO, Adeniran OA, Ojo OI (2021) Evaluation of a mobile app for adverse drug reaction reporting in Nigeria. Tropical Journal of Pharmaceutical Research 20(4): 815–822. https://doi.org/10.4314/tjpr.v20i4.18

Smith MY, Frise S, Feron J, Marshall R (2022) Improving the safety of medicines via digital technology: An assessment of the scope and quality of risk minimization websites in the United States and United Kingdom. Drug Safety 45: 259–274. https://doi.org/10.1007/s40264-022-01165-4