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# EFFECT OF COVID-19 ON PHARMACOVIGILANCE

Clinical Research

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## ABSTRACT

COVID-19 is one of the most disruptive events in modern history with the restriction on physical contact, travel and free movements, isolation, quarantine, and substantial clinical workload during the pandemic, traditional pharmacovigilance approaches of spontaneous reporting, and causality assessment will be more challenging. They have been unexpected opportunities recognized by innovators, researchers, and healthcare professionals. The key health authorities have released guidance for stakeholders, providing information and guidance on the conduct of clinical trials and post-marketing surveillance during the COVID-19 pandemic. To start a clinical trial a sponsor designs a research protocol. This protocol is designed according to the guidelines handed by the regulatory authority. The guidelines describe in detail how sponsors can ensure that trials or studies contain the mandatory pharmacovigilance regulations. The Pandemic affected the work of pharmacovigilance professionals, which made it work from home so it affected such processes as case submission and audits, and also it makes the biggest impact on vaccines. They are incremental changes on a large scale. The COVID-19 pandemic teaches the importance of electronic reporting, the importance of robust and responsive intelligence processes, and the need for centralized systems for submission oversight.

## KEYWORDS

Safety reporting, electronic reporting, robust and responsive intelligence, centralized systems, COVID-19 clinical operations, and AI technologies.

## 1.0. INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was recognized in late December 2019 in Wuhan, China, and is responsible for the COVID-19 disease. The COVID-19 pandemic is one of the most disruptive events in modern history, affecting public health on a truly global scale, (1) societal and political instability, and economic disruption. However, there have been unexpected opportunities recognized by researchers, innovators, and healthcare professionals. (2)

Pharmacovigilance is the science and activities where it is involved in the detection, assessment, understanding, and prevention of ADR and thus monitors the safety profile of medicines. However because of the COVID-19 pandemic pharmacovigilance too will be the beneficiary of unexpected opportunities. The history of pharmacovigilance was established 169 years ago with the death of a 15-year-old girl, Hannah Greener. During the past 1 to 2 decades, PV has taken shape as it has settled into three core disciplines i.e. case management, signal management, and benefit-risk management which is supported by healthcare professionals. With the current restriction on physical contact, travel and free movements, isolation, quarantine, and substantial clinical workload during a pandemic, traditional pharmacovigilance approaches of spontaneous reporting, and causality assessment will be more challenging. It may not capture details of all adverse events, thereby affecting the completeness and quality of safety reports. (4) A web search term for COVID-19 clinical trials revealed the ever-increasing number of clinical trials registered across the globe.

The regulators need information on a near real-time point. So the key health authorities, including the US FDA, EMA, and MHRA have released guidance for stakeholders, providing information and guidance on the conduct of clinical trials and post-marketing surveillance during the COVID-19 pandemic. This rapidly changing situation has meant that sponsors need to be more vigilant and proactive in determining the effects of the pandemic and changes in authority expectations to minimize the impact on safety reporting and to maintain patient safety. (3)

### 1.1. Impact of the pandemic on pharmacovigilance

Pharmacovigilance centers has to adapt their organization and workflow to the needs of the COVID-19 pandemic. For better coverage of pharmacoepidemiologic surveillance of COVID-19 drugs implementation of active pharmacovigilance, approaches are necessary. Effective communication strategies on drug safety promote greater awareness for reporting suspected adverse reactions related to COVID-19 vaccines and other drugs. There is a need for pharmacovigilance centers to better link drug safety data with actual effectiveness in clinical practice.

Historically driven by innovative new technologies and regulatory pressures, large-scale change has generally occurred incrementally. (2) they are effective on strategic priorities, a shift in product focus, workload changes, changes in sourcing model, effect on case reporting compliance, effect on business continuity, changes in pharmacovigilance technology strategy, the impact of interactions with health authorities, effect on resource capacity, and impact on recruitment. (6)

### 1.2. The role of pharmacovigilance in the pandemic

Pharmacovigilance teams worldwide are involved in collecting and analyzing the data from the clinical trial and the post-marketing system to monitor the safety of the drugs and vaccines used against COVID-19.

On the other hand, there is no acceptable gold standard study design to determine true drug safety. Hence there is a process of drug repurposing. In 2020 many companies launched targeted research to explore new potential uses of their drugs by various heterogeneous sources such as randomized controlled clinical trials, and spontaneous adverse event reports are used for safety assessment. PV plays a big role in this research and EMA has also drawn additional attention to it. In June 2020, EMA added nine additional active substances (chloroquine, darunavir, emtricitabine-tenofovir, filgrastim, ivermectin, nitric oxide, oseltamivir, prednisone, and ritonavir) which are being investigated as a potential treatment for COVID-19. This will help the policymakers to decide whether to continue or discontinue the use of the proposed drug in clinical care and research. (5)(1)

COVID-19 affected the work of pharmacovigilance professionals, who were made to work from home so it affected such processes as case submission and audits. However, regulatory bodies have considered this, allowing us to carry out some tasks digitally. EMA has updated the "Questions and Answers on Regulatory Expectations for Medical Products for Human Use During the COVID-19 Pandemic" which allows conducting audits and inspections remotely because of the pandemic.

In the present situation, pharmacovigilance professionals make the biggest impact on vaccines. The pandemic affects the industry from a regulatory point of view, for example, medical device regulations postponed by one year to allow health authorities and manufacturers to

focus entirely on fighting COVID-19. (5) With the rapid development of artificial intelligence (AI) technologies and the large amount of pharmacovigilance-related data stored electronically, data-driven automatic methods need to be applied to all aspects of pharmacovigilance to help healthcare professionals. In this review, we summarize the challenges into four categories: establishing a database for an AI-based pharmacovigilance system, lack of human resources, weak AI technology, and insufficient government support. (7)

**2.0. Challenges For Safety Reporting Activities Due To The Covid-19 Pandemic**

The covid-19 epidemic presents some unusual challenges to pharmacovigilance centers. It is relatively complex to manage medicine safety issues, indeed for medicinals formerly in use, when we are faced with a new clinical suggestion for which there is genuinely little information. In correspondence, the epidemic nature of the sickness demands quick responses, which implies the soon-chasing of discovery processing and reporting of safety issues to the EMA. This is a precise problem considering pharmacovigilance centers are under-resourced for the big amplification in reviews mainly due to an overburden of pharmacovigilance professionals. Also, this overall situation associated with the COVID-19 epidemic has seen a bold creation of misinformation and dummy news. The fast spread of misinformation about the safety of the vaccine population's medicinal plan compromised, for instance, the accomplishment of group immunity. (1)

While managing the complaint outbreak for COVID-19 cases has been of high precedence, there has also been the preceding question and concern for frontline manpower, policymakers, and experiments of how the unique situational factors caused by the epidemic have impacted clinic adverse events. Throughout the field, exploration assessing the impact of COVID-19 on the safety of care has revealed several areas of concern and implicit root causes for an increase in safety events in some areas outlined below. Case safety enterprises related to COVID-19 were also addressed in a recently published analysis of data freely submitted by federally listed patient safety organizations to the patient safety organization privacy protection center. (13)

**3.0. The Key To Achieving Safety Reporting Compliance**

Measuring the compliance of a defined set of variables is crucial for functions like pharmacovigilance, where there's violent reporting to different non-supervisory and non-regulatory realities with strict regulations and high examination threats. The real idea of covering compliance but, more importantly measuring the performance of the system in its capability to describe and help unborn compliance situations. Compliance and nonstop enhancement reviews earn a specific conference in a PV association; a healthy PV association will be the result of a nonstop drive for optimal compliance. It will also be an important tool to communicate internally about best practices and additional increase the recognition of the strategic function of pharmacovigilance. (9)

One of the most important aspects of clinical research is ensuring the safety of new medicines, treatments, etc. The safety aspect is covered, enforced, and complied with in two ways. Originally, the sponsor of the clinical research generally a pharmaceutical association conducts medicine safety tests at all the stages of the clinical trials they keep where it's needed by law. The sponsor starts a clinical research study/ trial by designing a research protocol**.** This protocol is designed according to the guidelines handed by the nonsupervisory authority. The guidelines describe in detail how sponsors can ensure that their trials or studies contain the mandatory pharmacovigilance regulations. Since reporting of adverse events is set down to be the most usual exercise negotiated by sponsors regarding pharmacovigilance clinical trials the guidelines also explain how the reports of adverse events during the trial are to be handed by the sponsor to the nonsupervisory agency. (10)

**4.0. Covid-19 Clinical Operations**

The onset of a world health organization in 2020 set multiple biotech companies during a race to develop and register a vaccine effective against severe acute respiratory pattern coronavirus. High figures of vaccine trials are impacting registration and begin-up ages. . Logistics challenges affecting timelines and access to large populations may be answered by clinical trial services providers, who can give ready-to-draw in the structure including cold chain operation. The most apparent impact of the worldwide epidemic on clinical trials was the suspense of registration during times of high contagious threat. Remote monitoring was always a top discussion content but it was nothing used formally. Right now, CROs are being forced towards setting up structure and technologies needed to support effects like direct-to-case logistics. (11) On the 18th of March 2020, the US (United States) Food and Drug Administration (FDA) published substitute guidelines for clinical trials conducted during this critical situation. (12)

When the remote trial model authenticated unexpectedly and increased, meaningful changes passed to the traditional clinical force chain. Direct-to-patient approaches handed an answer to the varied logistics conditions of remote trials, with favor providers playing because of the ground between sponsors and cases. CROs are over to now with all the original conditions and are suitable not exclusively to follow the regulations, but to shape it during a particular frame to render and allow a largely better climate for decentralized clinical trials with adaptive clinical trial arrangements and remote monitoring using information technology. (11)

**5.0. Lessons Learned From The Covid-19 Pandemic To Build Strong Drug Safety Reporting Systems**

**5.1. The importance of electronic reporting:**

The pandemic underlines how electronic or paperless reporting is the most effective reporting method. Although many countries have adopted electronic reporting, such as the E2B gateway, portal entry, and email, many agencies still use traditional methods of courier or hand delivery of compact discs for non-electronic reporting or electronic reporting.

Electronic reporting and email submissions are not directly impacted due to COVID-19. The complicated nature of regulatory safety reporting requirements stipulates a high level of expertise to secure immediate access to critical intelligence. The pharmacovigilance intelligence theme specializes in the evaluation of safety reporting requirements through daily review of information from; a subscription database, legal regulations and guidelines, authority web pages, and direct established contact with regulatory bodies.

Using regulatory intelligence gathered from 80 countries, the drug safety reporting system is composed of date-stamped decision rules. So the required safety information is to be submitted and distributed automatically to all relevant stakeholders including sites, Ethic Committees, Institutional Review Board, and Competent Authorities within due dates. The safety information is reported in the instructed format in each case. The global provider of drug development solutions and services to the pharmaceutical, biotechnology, and medical device industries, announced a new drug safety reporting solution based on a cloud-based system, which has automatic and configurable business rules. Its features are reporting functionality and a dashboard that shows both individual and aggregate submissions at a study and portfolio level. The solution ensures compliance in an increasingly complex regulatory environment and provides increased transparency to monitor and manage developments and visibility into the safety profile of an investigational product throughout its lifecycle. (14)(15)

There are 136 countries in the WHO program for international drug monitoring (WHO PIDM) that share their data with vigiBase, the WHO global database of individual case study reports(ICSRs), which is maintained by the Uppsala Monitoring Center (UMC) in its role as the WHO collaborating center for International Drug Monitoring. vigiFlow is the data entry page that takes and stores in vigiBase. (16)

The result shows elevated quality, increased speed, and powerful regulatory compliance. In addition, compound-level reporting removes duplication of notifications to those sites participating in multiple studies investigating the same compound, thereby reducing the burden.

Example 1- Oracle ARGUS safety database, configure a dedicated schema for each client. The system is FDA regulation 21 CFR Part 11 compliant and has the capacity for the generation of all standard regulatory and periodic reports.

Example 2-The European Medicines Agency (EMA) continuously monitors adverse drug reaction (ADR) data through the

EudraVigilance database, a comprehensive multi-component system that facilitates data collection, data management, and analysis securely. EudraVigilance has about one million ADR reports in post-marketing surveillance modules. It is used to demonstrate new or changed risks and those risks have an impact on a medicine's overall benefit-risk balance.

Example 3- Another initiative is the WEB-RADR (Recognizing Adverse Drug Reactions), which is led by a consortium of world-leading experts from industry, regulatory agencies, and academia. The objective of an EU-wide mobile phone app is to allow users to report Adverse Drug Reactions (ADRs) directly to their National Competent Authority (NCA).

Furthermore, there is possible to use the app as a platform for patients and clinicians to access accurate, timely, and up-to-date information on PV issues and develop text-mining techniques for publicly available data on social media sites, complementing existing methods of signal detection. (17)

**5.2. Importance of robust and responsive intelligence process:-**

To fight against the COVID-19 pandemic, many countries are working actively in finding a suitable vaccine. For the months and years to come, several trials will be going on, that need to be monitored. Thus, to conclude safety there will be a rush in need of pharmacovigilance solutions in the coming years.

To avoid disruption to clinical trial or project activities there is a need for access to up-to-date regulatory intelligence is key for a sponsor or MAH, including fulfilling legal responsibilities for patient safety. A strong process for regulatory intelligence maintenance, a rapid change-implementation process and a robust system to enter rule-based decisions can contribute to ensuring compliance and quality.

The need for a robust, easy, configurable, and scalable safety pharmacovigilance solution is efficient. The COVID-19 pandemic has made people realize that there is a need to work comprehensively to fight against the deadly virus. Hence, there is a need for a single platform that collaborates in real time and works towards a common solution in a cost-effective and timely manner.

For many pharmacovigilance teams, one most significant challenges is a delay in the outcome, most of which can be avoided by technology intervention. Most of the delays occur due to manual and time-consuming reporting processes, which increases when you need to handle the post-marketing adverse events spontaneously.

Due to COVID-19, there is a rapid rise in pharmacovigilance case volumes, and there is a need to invest in a single platform that takes care of all the challenges, including risk mitigation and data analysis. A single robust platform for pharmacovigilance teams encourages a collaborative ecosystem, increases transparency, enhances compliance, and greater operational efficiency. (18)

Artificial intelligence is a rapidly growing field of technology that has a lot of potential in pharmacovigilance. As AI continues to develop, it will play a higher role in drug safety monitoring and adverse event detection. In AI machine-learning algorithms are used on large data sets. (19)

Leveraging technologies like artificial intelligence, medical coding, and automation, and introducing a robust single pharmacovigilance platform that is easy to use, minimizes human involvement, and thus eliminates the scope of human errors. Such platforms would enable operational efficiencies, clinical studies, the study of safety, and risk management programs to protect the patient population. (18)

**5.3. Centralized system for submission oversight:**

In multi-clinical research, centralized systems are the most operative way to assure patient safety, trial integrity, and data quality. Pharmacovigilance is important because clinical trials are conducted in a controlled environment so severe ADRs may be unknown. Hence in post-marketing surveillance, severe ADRs are identified by the data mining process of spontaneous reporting.

So automated systems are required to do this work. The automated AEDAMS (adverse event data management systems) forwards the AE information to individuals in designated roles (investigators, sponsors, Data Safety and Monitoring Boards) and manages subsequent communications in real-time, as the entire reporting, review, and notification are done by automatically generated emails.

The centralized systems are the automated AEDAMS (adverse event data management systems) that collects AEs in a standard way by multiple distributed users, perform automated reporting assessment, facilitate accurate and timely AE reporting (like SUSAR cases) and review it, support in generating and prioritizing the tasks, capable of sending communications to various teams, prepare aggregate reports.

Automation reduces the risk of human errors during challenging work situations like a pandemic. The system was designed in such a manner that it adheres to timelines and data requirements in compliance with GCP (International Conference on Harmonisation E6) reporting standards and US federal regulations and can be arranged to support AE management, for many types of study designs, and adhere to various domestic or international reporting requirements. (20)

Some of the centralized systems used are and their description:

- Oracle Argus Safety
- ARISg
- Oracle Adverse Event Reporting System (AERS)
- ClinTrace
- PvNET
- repClinical
- Vigilanz Dynamic Monitoring System
- PV works

**Table-1: Centralized systems used in Pharmacovigilance**

| | |
|---|---|
| Oracle Argus safety | **Ensure global regulatory compliance:** to manage the worldwide reporting obligations the system should be compliant with global regulations and guidelines. It supports reporting compliance via a comprehensive and robust reporting engine that allows users to arrange specific rules to match regulatory requirements. Then it is combined with advanced automation features such as "Auto-distribute" and "Auto-submit" it enables full compliance and lowers the cost of regulatory reporting.<br><br>**Offers better data perception and faster decision-making:**<br>it is designed for fast safety data entry, and advanced functions such as dynamic workflows, company-defined reporting rules, and extensive automation are incorporated to ensure maximum case processing efficiency. It provides a complete perception of the drug safety profiles necessary to let executives make decisions on their products and portfolios. Integrates safety and Risk Management: it has a comprehensive toolset for expedited and periodic reporting, and capability for clinical trial SAE reconciliation. It has risk management capabilities to address regulatory requirements and manage product benefit-risk profiles, including reporting automation using advanced conditions, documentation storage, and collection of information for advanced visualization. In addition, it is integrated with a signal detection and management system for the active mining of safety data.<br><br>**Industry-proven and accepted:**<br>it has been used for over a decade by many leading companies including global pharmaceuticals, Biotech, CRO, and medical device manufacturers.<br><br>**Other key features:** origination of cases, support for e-signatures, duplicate search capability, audit trials, electronic submission capabilities, query and reporting cases received and submitted, view of core documents, and global protocols. |
| ARISg | It is used by more than 300 companies that maintain their critical drug safety data. It Provides all the functions required to manage AE reporting. It helps speed up the management of ADRs with the use of its configurable workflow and advanced automation features. It allows all pharmacovigilance processes from case entry to automatic generation of submission-ready AE reports including CIOMS 1, MedWatch 3500A. |

| | |
|---|---|
| Oracle AERS | It supports the capture, management, reporting, and analysis of SAE and product compliance cases for all medical products including drugs, medical devices, vaccines, biologics, and gene therapies from all clinical and spontaneous sources. It was designed by industry professionals and the intuitive interface provides powerful functionality at the touch of a button. The AERS graphical user interface provides interactive presentations of key case information allowing users to visualize the case elements and understand the complete case picture. |
| PvNET | It is the leading software used in pharmacovigilance for AE reporting, ADR data management, and regulatory reporting of ICSR. It also provides features like workflow which support data entry, QC and medical review, global dictionary support (MedDRA), audit records for safety data management activities, duplicate case checking, centralized triage prior to full case processing, analysis, and generating various regulatory reports such as CIOMS, MedWatch and ICH approved PSURs and other annual reports (21) |

## CONCLUSION

The effects of COVID-19 on pharmacovigilance are huge and there are so many measures implemented that have been adopted. As pharmacovigilance has a large amount of data that has been stored electronically and with the rapid development of artificial intelligence (AI) technologies, the safety reporting to the regulatory authority will be performed by the data-driven automatic methods, that need to be applied to all aspects of pharmacovigilance to help healthcare professionals.

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