**J Young Pharm, 2021; 13(4) : 335-341**
A multifaceted peer reviewed journal in the field of Pharmacy
www.jyoungpharm.org | www.phcog.net

*Review Article*

# Introducing Modern Computing Methods to the Moroccan Pharmacovigilance System

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## ABSTRACT

The long experience of the pharmacovigilance in Morocco was initiated since 1991 with the launch of the national centre of Pharmacovigilance (NCPV). In 1992, the NCPV acquired the world health organization (WHO) membership and thus the departure of the first African, Arabic and the 34th international pharmacovigilance system (PVS) in the world, in 2011 it was designed as the WHO collaborator. Today, and despite these achievements, the entire system is facing new challenges posed by the epidemiological and demographic transitions, where the cardiovascular diseases are the leading cause of mortality and morbidity, the expansion of the Moroccan pharmaceutical industry with the national policy for promoting the market of generics and a healthcare system inadequately distributed in the country with an acute shortage among health professionals and lack of Computerization. Modern computing methods based on advanced statistical technics applied in artificial intelligence such as; machine learning, deep learning and related technologies are already in place in many other industries. They represent an opening door for the Moroccan pharmacovigilance system to progress from conventional system based on individual initiative to report cases to smart system capable of managing an active surveillance of drug side effect in real time, analysing big data coming from various data sources and consolidating a correct drug safety ecosystem. In this paper we present the Moroccan PVS in the context of the healthcare system, epidemiological and pharmaceutical industry characteristics and we discuss strategies of introducing modern computing methods to the system.

**Key words:** Pharmacovigilance, Morocco, Artificial intelligence, Computing methods, Drug safety.

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**DOI:** 10.5530/jyp.2021.13.86

## INTRODUCTION

According to the World Health Organization (WHO), the pharmacovigilance (PV) is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug related problems in the general population. The effective starting of PV was in United States of America (USA) in 1962 following the scandal of Thalidomide, a teratogenic medication which was used as sedative without any contraindication for pregnant or breastfeeding women. And the results were the born of thousands of babies with malformed limbs.[1] Since 1978, the Uppsala Monitoring Centre (UMC) in Sweden has become the global coordinator of PV in partnership with WHO and full 134 countries members around the world, managing one of the largest safety data; VigiBase, that is based on gathering individual case safety reports (ICSR) from the regulatory authorities of countries member. The most recognized data bases of ICSR are; the European data; EudraVigilance, the American base; FAERS and the international vaccines adverse event reporting system (VAERS).

Today, the PV industry concern goes beyond the classical surveillance of "drugs" to a large concept of pharmaceutical products (PP) which include; drugs, biologics, vaccines, medical devices, combination products and *in-vitro* diagnostic reagents. The main objectives of the modern PV include the protection of the public health when using PP, the construction of the medical information, risk minimization, and as an interface with industries to control PP quality.[2] According to WHO (2019), the average global frequency of the adverse drug reaction (ADR) recorded in hospitals is 134 million ADR every year, responsible for almost 2.6 million deaths, making the ADR one of the top 10 leading causes of mortality and morbidity worldwide. Hospitalization caused by ADR represent 13% in France, 16% in United Kingdome (UK) and 11.5% in Norway.

The epidemiological profile of ADR varies according to the population characteristics and the system used to detect safety signals; it is directly affected by the demographic and the epidemiological transitions, the health care system organization and the pharmacovigilance system (PVS) of each country.

Advanced countries have benefited from the technological progress made in terms of computing technics including; machine learning, deep learning, robotics, big data and which has revolutionized many sectors in the healthcare industry such as; the tasks of elaborating electronic health records (EHR) of patients by transcriptions (EHR) of patients by transcriptions of data through Neuro- linguistic programing through Neuro-linguistic programing (NLP) algorithms, the telemedicine, where patients can use artificial intelligence to put their vital signs to assess if there is a need to see a doctor or no, reducing the workflow on hospitals and passing the transfer of only critical cases and other applications in assistance of diagnosis, surgery and microsurgery. The application of these modern technologies in drug safety have delivered substantial time and cost savings, reduced the risk and ensured the technological transition of the PVS by eliminating a huge wasting time on manual and routine tasks. Intelligent systems of drug safety use algorithms to speed up the literature researches for particular information, scan social medias, analyse audio calls, translate large data of information to many languages, transfer documents on ADR into actionable information, process cases with minimal human guidance, determine whether any

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patterns in ADR are new or previously unrealized information and automated cases follow-up to improve the capture and analysis of ADR.[3]

Conventional systems in developing countries[4] are inefficient to detect ADR because the surveillance is mainly, depending on the individual initiative from health professionals to report cases who may lack the adequate training to deal with unsuspected events or simply lack the interest to do so.

In this paper, we review the Moroccan pharmacovigilance system in the context of epidemiological transition, the pharmaceutical industry and the health care system organization, we discuss the most advanced computing technics used for signal detection and strategies to introduce these methods to the system.

## THE EPIDEMIOLOGICAL TRANSITION IN MOROCCO

Over the last three decades, Morocco, as many other developing countries in the Euro-Mediterranean region (EMR) is undergoing rapid epidemiological transition as the result of immense socio-economic changes. The Moroccan population has growth from 24.81 million in 1990 to 35.11 million in 2020 with an average population growth rate of 1.33% [1990 -2020].[5] This population growth was promoted by the economic progress and the health care improvements particularly, the generalization of the basic health care insurance and the national program of immunization where the childhood mortality rate was dropped from 150‰ in 1960 to 47.9‰ in 2004. Also, life expectancy of Moroccan population has progressed from an average of 43 years in 1962 to 71 years in 2004 increasing the prevalence of non-communicable diseases (NCD) as the leading cause of mortality and morbidity. Today, 80% of mortality in Morocco is generated by NCD with primary cause of death; the cardiovascular diseases (CVD) by 34%, followed by diabetes (12%), cancers (11%) and respiratory chronic diseases by (4%).[6] Over the last 10 years between 2007 to 2017, ischemic heart disease was the first cause of death with a progression of +22.1%, followed by strokes with a progression of +15%. And during the same period diabetes mortality has progressed from the 9$^{th}$ to 4$^{th}$ position (progression of +35.4%) and hypertension heart mortality from 10$^{th}$ to 6$^{th}$ position (progression of +27.6%).[7] The rapid infiltration of NCD is explained by the increasing of their risk factors prevalence, witnessing the displacement of the Moroccan society toward the urbanization and the industrialization. According to the results of STEP study (2017),[8] the prevalence of tobacco use (all forms of smoking) was 13.45% and the percentage of the population who do not match the WHO recommendation for physical activity (at least 150 min of moderate physical activity per week) was 21.1%. The prevalence of obesity and overweight were respectively; 20% and 53%, the global prevalence of hypertension was 29.3% and the national prevalence of diabetes was 10.6%. (Figure 1).

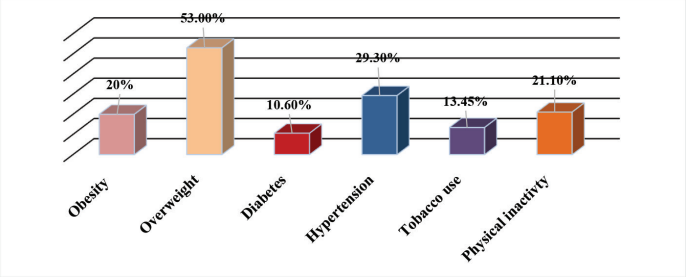


**Figure 1:** Distribution of risk factors of CVD as the leading cause of mortality and morbidity in Morocco.

This epidemiological transition has imposed changes on the health care system and the pharmaceutical industries.

## THE MOROCCAN HEALTH CARE SYSTEM

The Moroccan health care system is composed of two major sectors: the public sector including structured military health system and the private sector.[9] The system is inadequately distributed within the country, with centralization on the Atlantic coast following big cities and urban areas, while the rest of the country endures a penury especially among physicians and specialists.[10] The country counts for 149 public hospitals, 6 university hospital centres (UHC) and 12,034 physicians in public sector. The private sector includes more than 360 private clinics with a capacity of 10,346 beds and 13,545 physicians with centralization on Casablanca – Kenitra line (170 private clinics).[11] According to the Moroccan ministry of health the inter-regional dispersion of physicians was 21% and the average physician density operating in the public sector is 2.5/10,000 persons less than the average recorded for the EMR with 11.4/10,000 persons.[12]

The healthcare system endures several weaknesses in order to catch up with the epidemiological transition; the system is overloaded by the chronic disease affections, with long duration, heavy pharmacological treatment usually ended with polypharmacy, comorbidities as complications, psychological dimension where the patients lack of the psychological adjustment and important socio-economic disabilities where; the family become destabilized after the head develops a chronic condition. Most health professionals lack profound training in terms of chronic diseases, multiple morbidities and geriatric management. They may express disinterest to link any clinical manifestation to a medication use or report that.

On the central level, the system lacks an inter-departmental coordination and communication, which simply, can create confusion, technical disorders, delay to answer any emergency and low efficiency. Except some university hospital centres (UHC), most hospital centres are paper based and use classical medical registers as work archives.

## THE MOROCCAN PHARMACEUTICAL MARKET

After phosphates, the Moroccan pharmaceutical industry constitutes the second largest chemical industry and ranks the second in Africa. With an experience of more than 50 years, Moroccan pharmaceutical industries produce pharmaceuticals with a capacity of 350 million unites per 8-hr shift, covering more than 80% of the Moroccan market needs. In 2016, the prescribed medicine represented 70.9% of the total Moroccan pharmaceutical market with a value of 993 million American Dollars, and in which 41.2% were considered branded medicines.[13] Currently, the national policy of promoting generics contributed in the expansion use of these medicines, covering between 80 and 90% in public sector versus 25% in the private sector of the health care system. This market draws more than 45 million American dollars each year and thousands of direct and indirect jobs.

Moroccan pharmaceutical industry produces pharmaceuticals with good quality, accepted for export in 33 countries including European countries, African and Middle East countries (8%[14] of the total production capacity). Most Moroccan companies maintain quality assurance system in their production departments which ensure the respect of good manufacturing practices during the manufacturing process. Samples from different stages of production (semi-final and final products) of each batch are tested by internal quality control laboratory beside, external controls and audits which can be proceeded by external organisations and supplier of licences to ensure pharmaceutical quality.[15] Ministry of health proceed by two major tools of controlling the quality of drugs; the

national laboratory of control of drugs[16] and programmed unannounced inspections to production sites.

## THE MOROCCAN PHARMACOVIGILANCE SYSTEM

Since 1988, a major effort was made to introduce PV to the national health care system, starting by the academic level (science of pharmacovigilance) and the establishment of national centre of pharmacovigilance (NCPV). In 1991, a Ministerial circular organizing the PVS in Morocco and the launch of the NCPV, and after one year (1992), it acquired the WHO membership and thus the departure of the first African, Arabic and the 34th international PVS in the world. In the following years, group of legislations were adopted to improve the organization and the functioning of the system, until 2003, when the first edition of pharmacovigilance good practices (PVGP) were produced and validated by 2006. In 2011, the NCPV was designated as WHO- collaborator (Table 1).

Today, the NCPV is the central core of the Moroccan PVS, transmitting the ICSR to UMC via Vigiflow and composed of 11 different sections: The Materiovigilance, Pharmacovigilance in Oncology, the Pharmacogenetics, the Phytovigilance, the Teratovigilance, Pharmacovigilance of anti-Tuberculosis drugs, Medication errors, Cosmetovigilance, Vaccinovigilance, pharmacovigilance of HIV (human immunodeficiency virus) drugs and the section of signals management.

**Table 1: History of pharmacovigilance in Morocco.**

| Activities | Years |
|---|---|
| -Introducing Pharmacovigilance to the academia<br>-Development of the national centre of pharmacovigilance | 1984-1989 |
| -Participation in international meetings of PV | 1990 |
| -Communications with WHO<br>-First notifications of ADR transmitted to WHO<br>-Ministerial circular (N°2 DR/10): establishing the NCPV<br>-Program of teratovigilance surveillance | 1991 |
| -Recognition of NCPV as the 34th international centre of PV and the first in Africa and Arabic countries | 1992 |
| -Introducing the Pharmaco-Toxicology as a medical residency in Morocco | 1994 |
| -Program of phytovigilance surveillance | 1995 |
| -Ministerial circular (N°3 DMP/97): creation of national commission of Pharmaco-Toxico- Meterio-vigilance and clinical trials in Morocco | 1997 |
| -Program of vaccinovigilance | 1998 |
| -Ministerial circular encouraging health professionals to notify ADR<br>-The development of regional centres of PV | 1999 |
| -New local for NCPV<br>-Introducing of Quality system management in PV | 2001 |
| -Creation of Pharmaco-toxicology diploma in Morocco | 2002 |
| -Development of pharmacovigilance good practices | 2003 |
| -The national validation of pharmacovigilance good practices | 2006 |
| -Publishing the national law of pharmacy and drugs (law N° 17-04): article number 6 defining pharmacovigilance objectives | |
| -The WHO designates NCPV as centre of training for French speaking countries | 2007 |
| -The NCPV was designed as WHO collaborator centre | 2011 |

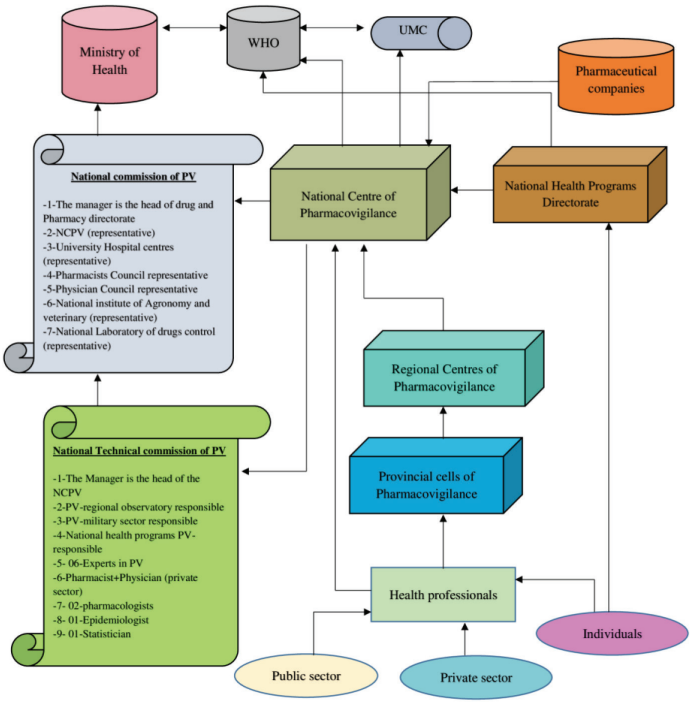


**Figure 2:** Organization of the Moroccan system of pharmacovigilance. We note that the national programs of health directorate may report directly to WHO the side effects of drugs used in specific health programs.

Notifications are collected in the provincial cell of pharmacovigilance and transmitted to the regional centres in order to be centred in the NCPV or directly from individuals and health professionals through calls centre. Signal management passes through two major phases: the first phase conducted by the national technical committee of PV, which evaluate the ICSR from spontaneous reports system, providing final technical conclusions. Based on these technical reports, the national committee of PV which is composed of experts from different sectors, provides suggestions about final decisions (Figure 2). The risk management is based on the French method of imputability, which consists of matching the chronological occurrence of events and their clinical manifestations, the final score indicates the strength of the causality. This method is not influenced by the presence of other drugs and may completed by further epidemiological investigations (cohort or case control studies) to provide solid evidences.

A retrospective analysis[17] showed that in the period between 1994 and 2004; the vast majority of notification collected in NCPV were ICSR (66.5%) versus (33.5%) of notifications generated by cross sectional studies, with a cumulative sum of 6033 notifications by an average of 431 notifications/year. A large proportion of these notifications was produced by UHC (74%), followed by notifications from the pharmaceutical companies (13.5%) and the rest from private pharmacies and public sector. Another retrospective analysis[18] [2006 to 2016] of ICSR of medication errors indicated that over the 10 years; 1618 reports of medication errors were collected by NCPV, and in which 41.1% were associated with ADR. If compare this numbers with the cumulative sum of notifications collected by EudraVigilance in the period between 2002 and 2019 (more than 2 million notifications), and considering the population and the duration, we can estimate that EudraVigilance was 20 times more efficient than NCPV in collecting notifications. Therefore, in order to increase its efficiency, the Moroccan PVS has to invest in modern computing technics.[19]

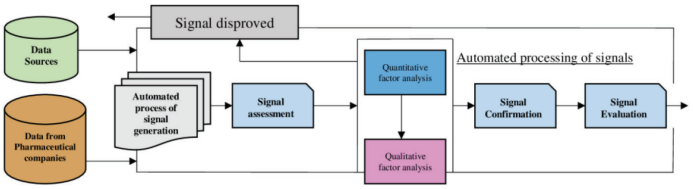


**Figure 3:** Diagram of intelligent automation pharmacovigilance system. The process of integrating multiple data sources to produce more consistence and accurate information.

## COMPUTING TECHNICS IN DRUG SAFETY

With the development of the pharmaceutical companies and the expansion of the health care industry, the need for creating high standards of information transparency and subjects' rights protection have become the brand of each PVS, and poses enormous challenges on conventional PVS which are expected to increase their efficiency in terms of drug safety and therefore adopting modern technologies.[20] To achieve the modern objectives of the PV industry, conventional PVS have to ensure a digital transition by introducing modern computing methods which are able to build solid drug safety vectors by working on big data coming from various data sources with complex dimensions in high speed (real time evidence) and providing transparent information.[21] The functionalities of the modern PVS include high efficiency of ADR captures, cases processing, combining data sources, validating signals and information distribution. They have to work on various data types including primary data source from spontaneous reporting systems (ICSR), with pharmaceutical companies, with health care structures using HER, and from other type of unstructured data which may include; phone and handwritten sources, semi-structured emails, messages from socials media (Facebook, Instagram, medical forums…), scientific peer-reviewed literature as cases and clinical narratives[22] (Figure 3).

Computing methods were used in preclinical studies and drug development to assess the toxicity of drug candidates based on molecular proprieties.[23] Several machine learning techniques have been developed to study the structural activity relationships (SAR) and estimating toxicity based on molecular structure. These techniques[24] are based on various types of regression (multivariate linear regression and rigid regression), support vector machines (SVM); performing classification using Kernel algorithms (based on clusters analysis or principal components analysis PCA) and Ensemble learning which combine several algorithms to build solid predictive models using Random forest that is based on linear discriminant analysis. Deep learning using recurrent neural network on SAR data and deep convolutional neural networks were used to study images of cells treated, to estimate the toxicity of drugs.[25]

Several post-marketing drug safety methods were developed to assess the safety profile among different populations; the most traditional technic used consists on identifying signals by inspecting individual or collective ICSR. The ICSR have to hold critical information and minimum errors to generate hypothesis which can be completed by further investigations.

Many other quantitative technics were developed and adapted to various dataset. From spontaneous reporting system, disproportionality analysis represent the most common method used to detect signals in both health care institutions and pharmaceutical industries. This method is based on analysing the statistical association between drug-event by estimating the observed to expected reporting ratio from the data. The definition of the signal detection limit is depending on the algorithms and their sensitivity. There are two major approaches; the frequentist approach[26] which is based on analysing the frequency of the association drug-event (ADR) based on tables of contingency by calculating the three statistical parameters (Table 2).

**Table 2: The 3 parameters used in the frequentist disproportionality analysis.**

| | ADR (Yes) | ADR (No) | Proportional reporting ratio : (PPR)= ((a)/(a+b))/(c/(c+d)) |
|---|---|---|---|
| Drug (Yes) | A | B | Reporting odds ratio :(ROR)= /) (a/b)/(c/d) |
| | | | Observed to expected ratio :(OE)= (a/(a+b)) [((a+c))/((a+b+c+d))] |
| Drug (No) | C | D | |

**Table 3: Probabilistic expression of disproportionality analysis.**

| The parameter | Mathematical expression |
|---|---|
| Reporting ratio | $(RR) = P[ADR(yes)]/P[drug(yes)]$ |
| Proportional reporting ratio | $(PRR) = P\left[\frac{ADR(yes)}{Drug(yes)}\right] \Big/ P\left[\frac{ADR(yes)}{Drug(no)}\right]$ |
| Reporting odds ratio | $(ROR) = \left(\frac{P\left[\frac{ADR(yes)}{Drug(yes)}\right]}{P\left[\frac{ADR(no)}{Drug(yes)}\right]}\right) \Big/ \left(\frac{P\left[\frac{ADR(yes)}{Drug(yes)}\right]}{P\left(\frac{ADR(no)}{Drug(no)}\right)}\right)$ |

**Table 4: The Mantel-Haenzel adjustment expression.**

| Exposure (s) | Outcome [Yes] | Outcome [No] | |
|---|---|---|---|
| | | | $(OR)_{Mantel-Haenzel} = \left[\sum_{i=0}^{s} a_i d_i / n_i\right] \Big/ \left[\sum_{i=0}^{s} b_i c_i / n_i\right]$ |
| [Yes] | $a_i$ | $b_i$ | $n_{ii}$ |
| [No] | $c_i$ | $d_i$ | $n_{oi}$ |
| | $m_{ii}$ | $m_{oi}$ | $n_i$ |

$(RR)_{Mantel-Haenzel} = \left[\sum_{i=0}^{s} a_i n_{0i} / n_i\right] \Big/ \left[\sum_{i=0}^{s} n_{ii} c_i / n_i\right]$

Other approaches based on Bayesian inference were developed and used; the Gamma Poisson Shrinker used by the American Food and Drug Administration (FDA), the empirical Bayesian screening and the Bayesian Confidence Propagation Neural Network used by the UMC. The estimated parameters[27] have a probabilistic (P) approaches and may expressed as shown in the Table 3.

From epidemiological and pharmacoeidemiological studies, various computed technics were applied to assess signals depending on the data design and variables implied. On cohort data, exposed subjects were compared to control group and the probability of ADR occurrence was determined using Mantel-Haenzel adjustment,[28] allowing the calculation of unconfounded and adjusted estimate of an exposure (Table 4).

The probability of ADR occurrence can be also calculated through logistic regression, propensity score or Cox-proportional hazard. On matched case-control designs[29] using retrospective data, the signal is detected using propensity score or event risk score (see equation 1, presented in additive model for two drugs).

$$\text{event risk score} = \alpha + \beta\,(\text{drug } X_1^n) + \gamma\,(\text{drug } X_2^m) + \text{Coviates}\,[N^\varphi] \quad (1)$$

On self-controlled designs[30] and crossover design; applied on retro-prospective data, the probability of ADR occurrence is determined through penalized regression or the incidence of rate ratio from the event intensity (see equation 2).

$$P\,(y_{id}/x_{id}) = e^{-\lambda_{id}} \lambda_{id}^{y_{id}} \Big/ y_{id}\,! \quad (2)$$

Where represents the rate of events for persons (i) during time (d) with represent the number of events, (P); indicates the probability and is the drug exposure.

The sequential analysis is a group of technics introduced essentially by big pharmaceutical companies to enhance vaccines safety among children. The most traditional method; the cumulative sum consists of analysing the collected data in sequential method without prior determination of sample of reports. The collected data is tested against null hypothesis (H0); if the result reject (H0) the research is ended, otherwise, further reports are added to the analysis.

The method of maximized sequential probability (MSP)[31] was developed and used to detect ADR of vaccines as early as possible. The signal is generated if the likelihood ( exceeds certain predetermined value (equation 3) and the surveillance end if it falls below certain *p*-value. In this technic there no surveillance to detect changes, the p-value are adjusted to examine the data in several tests.

$$L(R_t) = \frac{p_1\left(c_t = \frac{c_t}{H_1}\right)}{p_0\left(c_t = \frac{c_t}{H_0}\right)} = \left[\frac{e^{-RR\omega_t (RR\omega_t)^{C_t}}}{c_t!}\right] \Big/ \left[\frac{e^{-\omega t\, \omega_t^{Ct}}}{c_t!}\right] = e^{-(1-RR)\omega_t}[RR]^{c_t} \quad (3)$$

MSP is a function of likelihood ratio, where represent the number of ADR in a period [0,t] and which follow Poisson distribution with represents the mean of the population at risk (people who received the drug) and (RR) relative risk.

The conditional sequential sampling procedures[32] is another sequential method which compare the elevated risk of ADR from one drug (D) on interest compared to another drug (C) of control. This method is suitable prospective data, for drug without history such as drugs newly introduced or drugs of rare diseases. The data is uploaded periodically, stratified according to many variables (age, gender…) and using semi-parametric Poisson regression (equation 4) the relative risk ($e^{\beta}$) is determined and tested [($H_0$: $\beta=0$ against $H_1$: $\beta>1$)], where (E) is the number of incident (ADR) for drug (D) in the period of time (d), (θ) is the exposure, (I) is the indicator function, and;  is the base line event rate for drug (D) in stratum {m.k}, where m∈ {1,2,…M} and k∈{1,2,…K}.

$$\log[E(E^i_{m,k})] = \log(\theta^i_{m.k}) + \beta I_d + \sum_{v=1}^{m} \alpha I \quad (4)$$

The sequential symmetry analysis (SSA)[33] was developed to analyse the drug prescriptions trends (health insurance data) in sequence of events after initiating the first medication. The sequence ratio is derived from the average probability ($P_a$) to indicate the asymmetry of the sequence and estimating the incidence rate ratio of the outcome in the exposure period (equation 5).

$$P_a = \sum_{n=X+1}^{X+d} \Psi_n \Big/ \sum_{X-d}^{X-1} \Psi_n + \sum_{n=X+1}^{X+d} \Psi_n \quad (5)$$

($P_a$) indicates the average probability of incidence of the patient to have first prescription after (X) days in a time window, (n) the study duration in days, ($\Psi_n$)) is the number of patients receiving their first medication and (d) the specified number of days for the observation in time window. This method has high specificity (93%) and good sensitivity (61%) and can be used in complementary with traditional PV technics where the rate of ADR capture increases by 21% after adding (SSA).

Three temporal rules mining technics[34] were used in safety signal detection; the MUTARA algorithms applied on filtered data. It considers a period of time before the exposure to the drug of interest, and each event occurred during this period has a few chances to be linked to the drug through a score of correlation between time of exposure and the probability of ADR occurrence.

The temporal pattern discovery algorithms applied on HER and consider several control periods prior to the exposure to adjust the event rate over time. It calculates the logarithm of the observed to expected ratio of ADR occurrence. The third method[35] is a combination between temporal rules mining and Fuzzy logic to assess and score the causality between the drug and the ADR.

Natural language processing (NLP)[36] applied on both structured and unstructured data was used to extract potential (ADR) from big data. (NLP) perform syntactic processing, extract information by converting unstructured texts into structured format, words capture and relationships. The algorithms can be linguistic rules based (grammatical patterns) or probabilistic rules based[37] and presented as supervised machine learning or deep learning, and use various methods of classification; conditional random filed, support vector machines, neural network and the logistic regression. Other forms are based on unsupervised machine learning which use of clustering algorithms and semi-supervised machine learning (Noisy-labelling) applied HER.

## Strategies for automating the pharmacovigilance system

Introducing modern computing technics to the Moroccan PVS must follow two major theories;[38]

- A complete process of epidemiological surveillance;
- A complete process of information analysis.

Morocco is persuading crucial efforts to bring digitalization in various economical strategic sectors, where the big data analysis is already applied, and this includes; banking, business, marketing, transport and logistics. The key success of implementing computing technics has to be approached as collaborative work between various stakeholders including pharmaceutical industries.

The human capital is the cornerstone of the entire process; an independent committee has to be established, made by specialists from various fields and which has to define clear objectives on the methodology of instilling the modern computing technics to the PVS with the financial plan. This committee has to be composed of experts with different backgrounds; computer scientists, data scientists, epidemiologist and other bio-medical researchers. The leader of this committee is a pharmacoepidemiologist; a specialist who have to guide the team to the realization of the objectives and who combines different technical skills between data analysis, the clinical and the pharmaceutical significances. The first methodological step of the committee is establishing important strategic partnerships with Ministry of health, university hospital centres, private companies, experts, particularly, universities which can supply the theoretical framework.

Except the standard ICH-E2B (R3)[39] which specify the manner of ICSR transmission, there are no international guidelines on implementing and validating computing technics in PV, therefor, the selection of the appropriate algorithms should consider empirical characteristics; type of available data, drugs concerned, extrapolations, and other parameters. The validation of the algorithm and the entire system have to follow internal procedures and under the supervision of trained pharmacoepidemiologist.

If we consider the epidemiological profile of the country, a large proportion of patients (and from the general population) are followed for cardiac diseases and or for one of their chronic risk factors such as; hypertension, diabetes, dyslipidaemia.[40] Under the national health policy, essential pharmacological treatment of such chronic diseases is delivered for free in various public hospitals where most patients hold

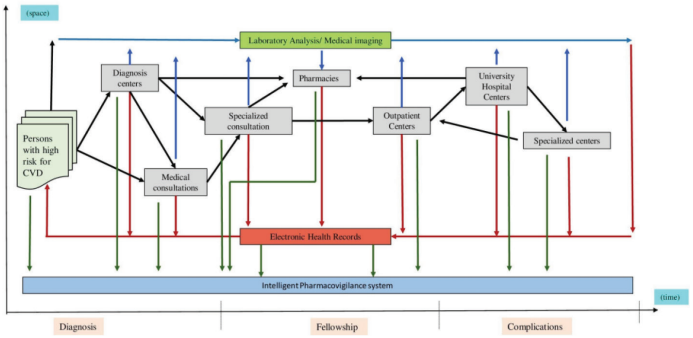


**Figure 4:** Diagram indicating the interactions of information flow of cardiac subjects within the Moroccan healthcare system. The red and green cursors are used to collect information about drug safety. The black and blue cursors is the naturel paths of patients.

medical paper based registers.[41] Establishing EHR for these patients will serve multiple purposes; for the national health programs directorate which manage chronic diseases and the national PVS to collect and analyse signals (see Figure 4).

There are 4 major important steps for the implementation of modern computing technics;

The technical development; the main objective of the digitalization is to increase ADR capture via the combination of various technics and data sources; for example; individuals can report any drug event using mobile applications linked to the intelligent system. Data from EHR can be transferred and analysed in real time to detect any event. All stakeholders can bring ideas and provide their own concept for the new technology, and the result of early stages should be a prototype that undergo heavy experimentations and analysis before providing final product.[42]

Data training; in this stage, the system learns from various data types; with cases sources or as annotated data. The ADR are identified and evaluated from the data-experiment.

The step of testing the system; using various data sources, the system is tested to determine its accuracy thought tables of true; positive and negative signals, and false; positive and negative signals. Thus, the precision defined as the ratio of correctly predicted positive signals to the total positive observation and the sensitivity (recall) as the ratio of correctly predicted positive observations to the total observations are determined. Precisely, the -score is a sensible parameter to be analysed for the system and which reflect the weighted average between the precision and the recall of the system (see equation 6).

$$F_1 - \text{score} = 2 * (\text{Sensitivity} * \text{Precision})/(\text{Sensitivity} + \text{Precision}) \quad (6)$$

This step could be achieved through defined data, real data, cross sectional studies and cycles comparison.[43]

The validation; signed by a trained pharmacoepidemiologist, the validation, including internal quality control of the entire system, indicates that the process is adhering to the standards and can generate reproducible results. The system has to be efficient on 4 major critical points; The ADR capture, the putative causality, the subject (patient or PP user) and the reporter (the source).

The technological transition of drug safety system will impose enormous challenges, especially in terms of ethics and acceptability; where some individuals will not be prepared for "the complexity" of such system or simply, for the change. In the early stages, vast media campaigns to raise the awareness among the population and health professionals, can reduce the time for the acceptance of such technological transition.

Undoubtedly, the next step required is a scientific study to impose the theoretical framework of the intelligent system to link different health departments managing chronic diseases in Morocco.

## CONCLUSION

Signal management is a complicated process with time consuming and high risk of errors. Modern technologies can accelerate the process of signal detection and management, they increase the efficiency by reducing time, cost and errors. Many pharmacovigilance systems are undergoing transitions by adopting automation technologies and improving the drug safety process. Considering the long history, experience and organization of the Moroccan pharmacovigilance system, the transition toward modern technologies represent an urgent need to improve PV practices and medication safety. Policy makers have to take important steps toward improving medication safety through legislations and health care professionals' engagement. Among various modern technics, the selection of the appropriate ones has to consider the health care system characteristics, the epidemiological profile of the country and the pharmacovigilance system features.

## CONFLICT OF INTEREST

The authors report no conflicts of interest in this work.

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**Article History:** Received: 12-07-2021; Revised: 29-09-2021; Accepted: 23-10-2021.
**Cite this article:** Elyamani R, Soulaymani A, Hami H, Abdelrhani M. Introducing Modern Computing Methods to the Moroccan Pharmacovigilance System. J Young Pharm. 2021;13(4):335-41.