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Model for measuring the impact of good pharmacovigilance practices of COVID-19 patients on hcp reactivity: Morocco case study

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Abstract

This paper presents a conceptual model used to evaluate how the improvement of good pharmacovigilance practices by patients during COVID-19 period influences the reactivity of the healthcare professionals (HCPs) in the Draa Tafilalet region in Morocco, concerning the reporting of adverse drug reactions (ADRs) through barriers that influence the reporting from both patients and HCPs. The empirical study is based on a survey submitted to a sample of a total of 180 HCP and on the application of latent variable structural modelling through the partial least squares (PLS) method. The 2017 version of the XL-STAT software served to perform the statistical calculations. The study investigates the reliability and validity of the proposed model. Our conclusions show that the improvement of good pharmacovigilance practices impact positively the reactivity of HCP in terms of ADRs reporting. The reliability of the measurement was > 0.7, which allowed us to test the internal and external validity of our conceptual model. 11 hypotheses were validated against two invalid derivative hypotheses. Spontaneous ADRs reporting is the cornerstone of any pharmacovigilance system aiming to maintain patient safety. Our findings indicate the necessity firstly, to initiate a training program on reporting for all HCPs, and secondly, to inform the general public about the national pharmacovigilance center, where ADRs can be reported. Both initiatives aim to keep the culture of ADR reporting perennial.

Key words: pharmacovigilance, HCP reactivity, structural equations modelling, latent variable, PLS.

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1. Introduction

The history of pharmacovigilance started 170 years ago, when a young girl died after receiving chloroform anesthetic before removal of an infected toenail (Routledge, 1998). The catalyst for the development of pharmacovigilance, was the thalidomide tragedy that occurred in the 1960s. Dr. McBride, an Australian doctor, observed that the incidence of congenital malformations of babies (1.5%) had increased up to 20% in women who had taken thalidomide during pregnancy (Yarrow, 1961). At the international level, the World Health Organization (WHO) began its pharmacovigilance operations after the discovery of the teratogenic effects of thalidomide, during the 16th WHO Assembly, the formation of the WHO Programme for International Drug Monitoring (PIDM) in 1968 (*Regulation and Prequalification*, n.d.). In Morocco, the National Pharmacovigilance Center (NCPV) was established in 1991. It gained WHO membership in 1992, becoming the first African, Arabic, and 34th international pharmacovigilance system (*CAPM Plateforme*, n.d.). According to the WHO, Pharmacovigilance is defined as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems (Mirosevic Skvrce et al., 2020). The main scope of pharmacovigilance is to improve the safe and rational use of medicines. While the medicine brings a real benefit to the human being by saving his health and suffering, its use is never without risk. These risks defined by the term "Adverse Drug Reactions" (ADRs) are a significant cause of morbidity and mortality worldwide (Joubert & Naidoo, 2016). However, we have to admit that drugs can be responsible for adverse effects (AEs), several international studies have highlighted the harmful consequences of ADR, whether in terms of morbidity and mortality, hospitalization or medical costs. In the USA, it was estimated that ADR caused about 106,000 deaths a year, representing between the fourth and sixth cause of death (Starfield, 2000). According to the European Commission, ADRs cause 197,000 deaths a year, and represent the fifth cause of death in hospitalized patients (Montané et al., 2018). In Morocco, the hospitalization costs inherent to the management of patients with ADRs incur additional expenses and represent more than 15–20% of the hospital budget (El Hamdouni et al., 2020). Amid the global COVID-19 pandemic caused by the new SARS-CoV-2 Coronavirus, countries have recommended various protocols. In Morocco as soon as the therapeutic protocol was launched, the NCPV, set up a strong monitoring system for AEs to study drugs and vaccines used for new indications, assess their benefit/risk ratio, and improve patient safety. Healthcare professionals (HCPs) have access to reporting tools, while vaccinated individuals can report ADR (*Accueil*, n.d.), patients had an important contribution to signals for ADRs related to drug. Our research proposes a conceptual model to measure the impact of Good Pharmacovigilance Practices by patient over the

COVID-19 period on the HCP's responsiveness to ADRs. This study is conducted in a south-eastern region of Morocco. This model will be tested using partial least squares structural equation modelling (PLS-SEM). This choice is motivated by its ability to build models with several variables and complex interactions in order to approach the complexity of real situations and is also based on these research (Avkiran et al., 2018) (Ali et al., 2019) (Sahaf et al., 2018) (Sebtaoui et al., 2020)

2. Literature review

2.1. Construct 1: Good Pharmacovigilance Practices over the COVID-19 period by patients.

The patient is the main stakeholder in pharmacovigilance, which is the ultimate goal of ensuring the safe use of drugs. A patient reporting of ADRs could supplement the existing reporting system and contribute to early detection of ADRs (Weigmann, 2016). A growing number of countries are involving patients in the direct reporting of ADRs (e.g., European Union countries since 2012), but little is known about what the patient reporting adds to pharmacovigilance systems (Inácio et al., 2017). Patient-reported safety information leads to a better understanding of the patient's experiences of the ADRs (Härmark et al., 2016). In the UK, the patient reporting can significantly contribute to drug safety by detecting distinct signals of disproportionate reporting that may not be identified from HCP reports (Hazell et al., 2013). In the Netherlands patients' reporting ADR offer a valuable contribution to signal detection, complementing the reports from HCP (Maguire et al., 2007). Involving pharmacists and doctors to encourage patient participation in data reporting boosts awareness of ADR significance, motivating patients and potentially reducing mortality and morbidity rates (Naoual Nchinech et al., 2020) (Hadi et al., 2017) (Awodele et al., 2011)(Toklu & Uysal,2008). A study revealed that patients report symptoms earlier and more frequently than clinicians, with interesting information (Engla & Journal, 2010). The 2000 International Conference highlighted the importance of patient ADR reporting for pharmacovigilance, recognizing its insight-providing capability. Many comparative studies found that the patient ADR reporting frequently offers more comprehensive details than HCP' report (Assanee et al., 2021)(Avery et al., 2011). Here comes our aim through those studies carrying only for good pharmacovigilance practices of HCP (including knowledge, attitude, practice and perception). The research underscores the need to include patients in pharmacovigilance efforts, especially from the viewpoint of HCPs in DRAA TAFILALET, Morocco. Four key Good Pharmacovigilance Practices, often mentioned in the literature, were implemented during the COVID-19 period, extending beyond HCPs: *Patient's Knowledge of ADR; Patient's Attitude; Patient's Practice; Patient's Notification of ADR.*

2.2. The construct 2: Factors braking to report ADR

Factors affecting patient reporting of adverse drug reactions: ADR forms a significant problem, both from a medical point of view and as an economic burden. Spontaneous reporting of ADRs is one of the methods for post-marketing surveillance of drug safety. A systematic review was made from 1964 to December 2014 in the UK, the Netherlands, and Australia. It showed that from 15 studies, there is poor awareness, confusion about who should report the ADR, difficulties with reporting procedures, lack of feedback on submitted reports, mailing costs, ADRs resolved, and prior negative reporting experiences (Al Dweik et al., 2017). In 2012, a cross-sectional study was conducted in Saudi Arabia which revealed that the public lacked awareness about ADRs and had limited knowledge on how to report them (Sales et al., 2017). In a separate study conducted in Japan, 845 citizens were found unaware of the direct patient ADR reporting system (Kitabayashi & Inoue, 2022)**.** One other concern, patients may believe that public reporting of drug-related problems may affect the physician-patient relationship, which is proven by these studies (Kitabayashi & Inoue, 2022) (Inácio et al., 2017). On the other hand, in 2018, a cross-sectional survey among 360 patients in Nigeria demonstrated a low level of awareness of pharmacovigilance and ADR reporting (Adisa & Omitogun, 2019). A statistical study in Thailand utilizing PLS-SEM showed a notable link between instrumental attitude and patients' intention to report ADRs to community pharmacists (Assanee et al., 2021). Based on a literature review, we surveyed HCPs to gather their opinions on factors influencing patient ADR reporting, considering their frequent interactions with patients.

Factors inhibiting HCP reporting ADR: Factors that made the HCP refrain from reporting a suspected ADR were similar. In northern Sweden, a study aimed to explore attitudes and main factors that refrain from reporting ADR(s): lack of time and giving priority to other matters in medical care as well as confidence that no new information will be provided by reporting and unwillingness to write a report on just suspicion of cause and effect (Bäckström et al., 2000). Finland examined the reasons why HCP do not report all suspected ADRs. The COVID-19 pandemic might be one of the contributing factors explaining why the subgroup of Finnish physicians selected then the "Lack of time" as the primary reason. Other reasons include factors such as the suspected ADR already being known ("it is not clear what is worth reporting"), the belief that someone else will report the ADR and the perception that the patient's suspicion was not credible, confidence that no new information will be provided by reporting (Sandberg et al., 2022). Also, lack of time was only the most common answer from HCP on two different occasions pre-COVID-19 (Bäckström et al., 2000)(Sandberg et al., 2022). On the other side, the most important factors were: the reaction is already well known, never suspected any ADR, forgetfulness, difficulties in reporting only on suspicion, lack of time, and uncertain of how to report and the HCP stated that they

would like a feedback letter containing the causality assessment (Ekman & Bäckström, 2009). In the Norwegian healthcare system found that HCP often focused on patient-related information such as weight and height. HCP usually reported more serious reactions that lead to hospitalization, life-threatening conditions, or death (Vaismoradi et al., 2019). Whereas other studies confirmed the same main factors for the decision to report an ADR: lack of time, motivation (Biriell & Edwards, 1997) (Hazell & Shakir, 2006) (O'Callaghan et al., 2018) (Stergiopoulos et al., 2016) (Joubert & Naidoo, 2016) (Rabba & Ain, 2015).

2.3. The construct 3: Reactivity of HCP

Physicians, dentists, pharmacists, nurses, and midwives as well as all other paramedical professionals must collaborate in the safe use of health products in Morocco. They must report to the NCPV, as soon as possible of any suspected ADR related to the use of one or more products under normal conditions of use, whether expected, unexpected, serious, or not. Any ADR appearing outside the normal conditions of use, any other reaction they judge relevant to report (Moroccan good pharmacovigilance practice) (CAPM Plateforme, n.d.). Collaborative studies with the Moroccan Pharmacovigilance Center have assessed pharmacists' knowledge, revealing a moderate understanding of pharmacovigilance, with 11.5% encountering AEs requiring mandatory intervention in their practice (N Nchinech et al., 2019). A South African study found that community pharmacists exhibited positive knowledge, perception, and attitudes toward pharmacovigilance. A global analysis of 50 countries, including Morocco, revealed that direct patient reporting systems were present in 44 countries, contributing to 9% of total reports, while the majority came from HCP (Margraff & Bertram, 2014). A systematic review examined doctors' knowledge, attitude, and practice regarding ADR and pharmacovigilance. Knowledge refers to understanding, attitude is the predisposition to respond positively or negatively, and practice involves applying knowledge practically (Abubakar et al., 2014). The practice of doctors was based on four parameters in the majority of surveys conducted. These include: "encounter with ADRs", "number of ADRs ever reported", "training on ADR reporting" and "source of information" to the doctors (Abubakar et al., 2014). In developing countries, Knowledge (understanding), Attitude (emotional and cognitive beliefs), and Practice (observable healthcare actions) collectively define the behavior and decision-making of HCP, which can be influenced by internal and external factors (Thomas & Zachariah, 2018). In Kuwait, a study found that hospital pharmacists had strong knowledge and a positive attitude towards pharmacovigilance and ADR reporting, yet most had never reported an ADR (Alsaleh et al., 2017). In a Knowledge, attitude and practice KAP study, most pharmacists in South Africa

were aware of pharmacovigilance, but fewer than half had reported ADRs (Joubert & Naidoo, 2016). The KAP of pharmacovigilance among HCP was highlighted and studied in different countries, and developing countries need improvement. The relevant professionals have poor knowledge, a positive attitude, and poor practice (Thomas & Zachariah, 2018). In Istanbul the KAP of pharmacovigilance community pharmacists have insufficient knowledge about pharmacovigilance practices (Toklu & Uysal, 2008). On behalf of Moroccan pharmacy students' knowledge and perceptions about pharmacovigilance confirmed the utility of KAP among them even if they are future pharmacists to maintain the continuity of ADR reporting (N. Nchinech et al., 2020). A study in Bosnia and Herzegovina found a gap between positive perceptions and actual ADR reporting, recommending education and training to improve reporting and engagement with pharmacovigilance (Amrain & Bečić, 2014).

3. Research method:

3.1. Fundamentals of PLS-SEM modelling (theory)

Path analysis models were first developed by Sewall Wright (1921), a biostatistician, in the early 1920s. It was not until the 1970s that structural models started being used in the social sciences, as noted by Jöreskog (1973)(Joe F. Hair et al., 2011). The main function of modelling is to understand, test, analyze, and interpret a given (real) phenomenon by measuring the various causal links between its components. It is a simplification of the reality of a given phenomenon or problem in interaction. The aim is to understand and explain the complexity of a model (system) by measuring its observed variables. LISREL is the best-known technique for causal modelling (Joreskog and Sorbom,1989); (Hagedoorn & Schakenraad, 1994)). Nevertheless, LISREL's efficiency decreases when it is faced with small data samples (Fornell & Bookstein, 1982), an alternative causal modelling approach called partial least squares (PLS) has been developed to alleviate these problems (Wold, 1985). The PLS Path modelling (PLS-PM) approach is based on partial least-squares, it was initiated by (Wetzels et al., 2009). Its aim is to estimate the score of the various latent variables by an iterative procedure based on simple regressions using the ordinary least squares (OLS) method. Over the past two decades, the number of studies using the PLS-SEM method has increased. Which demonstrates its growing importance in research (Law & Fong, 2020). While Structural Equation Modelling (SEM) is a broad term that includes various statistical models, one of its specific approaches is covariance-based SEM (CB-SEM) (Jöreskog, 1978). Variance-based SEM techniques, like PLS-SEM (Avkiran et al., 2018) (Hair carole l. Hollingswoth, Chong, Jeo, 2017) (Cheah et al., 2018). As (Chin, 1998) points out "To many social science researchers, the covariance-based

procedure is tautologically synonymous with the term SEM". Furthermore, PLS-SEM presents advantageous attributes when handling intricate models, non-normal data, and small sample sizes (Joseph F. Hair et al., 2019). Indeed, PLS-SEM has gained widespread application in various social science disciplines: organizational management (Sosik et al., 2009), international management (Richter et al., 2016), human resource management (Ringle et al., 2019), supply chain management (Kaufmann & Gaeckler, 2015), the impact of quality practices on firm performance (Ali et al., 2019), the transmission of systemic risk (Avkiran et al., 2018), the relationship between future time perspective, wisdom, hospitality management discipline (Faizan et al., 2018), performance of fit indexes in Generalized structured component analysis (Cho et al., 2020), quality management (Magno et al., 2022), business marketing research (Guenther et al., 2023), IT research models (Robert & Brown, 2004). After reviewing the PLS-SEM literature, we are fortunate to find that the application of PLS-SEM in pharmacovigilance has been reported once in the existing literature reviews. It was used to determine the influencing factors with intention to report ADRs to community pharmacists in Thailand (Assanee et al., 2021). As a result, our article will be the first to present a PLS-SEM analysis in the field of pharmacovigilance.

3.2. Assessment of the PLS-SEM model

For the first time in the field of pharmacovigilance studies, we use the iterative OLS regression-based (PLS-SEM) ((Kroonenberg & Lohmoller, 1990); Wold, 1982).The goal of our research is predicting key target constructs. The research aims to explore the existing structural theory. The formative constructs are part of the structural model**.** Note that this approach is recommended when the theory is more approximate.

Reliability: Measurement reliability reflects the consistency in repeated measurements, crucial for obtaining consistent and close results. This process involves assessing internal consistency**,** we follow Hair et al.'s (2017a) recommendation of utilizing both Cronbach's alpha as the lower boundary and composite reliability as the upper boundary. The formulas for calculating Cronbach's alpha and composite reliability are provided in Hair et al.'s work.

Measurement models: In PLS-SEM, there are two types of measurement models: reflective indicators represent variations in the latent construct, while formative indicators are influenced by changes in the indicator variables, contributing to the formation of the latent construct (Joe F. Hair et al., 2011). The evaluation of (external) measurement models depends on the nature of the chosen diagram (formative, reflective or MIMEC) (Jacobowicz, 2007). The same author confirms that the reflective diagram (Figure 1) is the most suitable for most uses of latent variable structural

equation models and that this choice is based mainly on the researcher's subjectivity. Each manifest variable is related to its latent variable by a simple regression:

ξ: Latent variable

X : Manifest variable

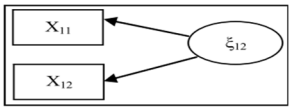

Figure 1: Reflective pattern (Joe F. Hair et al., 2011).

The relationship between the latent variable and the set of manifest variables that are associated with it can be written in the following form $\boldsymbol{X_{kj} = \pi_{kj} * \xi_{kj} + \varepsilon_{kj}}$

With: $\boldsymbol{X_{kj}}$: vector associated with the j[th] manifest variable of the latent variable ξ_k

$\boldsymbol{\xi}$: latent variable

K: index of latent variables

$\mathbf{k_j}$: index of manifest variables of the k bloc

π: loading associated with x_{kj}

$\boldsymbol{\varepsilon_{kj}}$: error term (measurement errors of manifest variables).

Convergent validity: For assessing validity, researchers should use the AVE (average variance extracted) to evaluate convergent validity. An AVE value of 0.50 or higher suggests adequate convergent validity, meaning a construct explains at least half of its items' variance, with the AVE of each latent construct exceeding the squared correlation with any other latent construct (Joe F. Hair et al., 2011) Chin et al. (2010). We calculate the AVE relating to each latent construct:

$$\boldsymbol{AVE = \frac{\sum[\gamma_i^2]var(VL)}{\sum[\gamma_i^2]var(VL) + \sum[var(\varepsilon_i)]}}$$

Along with: **VL:** latent variable

$\boldsymbol{\gamma_i^2}$ factorial contributions (loadings)

$\boldsymbol{\varepsilon_i}$: variance of errors.

Discriminating validity (divergent): Fornell and Larcker (1981) criterion: each construct's AVE should be higher than its squared correlation with any other construct. (e.g. Chin, 1998b).

Validation of the structural model:

The structural model explains connections between latent variables, and for PLS analysis, there are no fit adjustment indices. Model evaluation depends on the predictive relevance of measures, and validation of model adjustments is based on specific conditions :

- **Goodness of fit index (GoF):** This index takes into account both the performances of the structural model and of the measurement model (Wetzels et al., 2009). It is defined by the geometric mean of the average of the communities (or AVE) on all the latent variables $\overline{H^2}$ and the average of R^2 associated with the endogenous latent variables.

$$GOF = \sqrt{\overline{H^2} * \overline{R^2}}$$

- **The coefficient of determination (R^2):** used to judge the quality of a linear, single or multiple regression. It measures the adequacy between the model and the observed data. The value of $\mathbf{R^2}$ must be at least greater than 0.1 (Fricker et al., 2012).

$$R^2 = \frac{SCR}{SCT} = \sum_{i=1}^{n} (Y_i - \hat{Y}_i)^2 \Big/ \sum_{i=1}^{n} (Y_i - \overline{Y})^2$$

With: **SCR**: corresponds to the sum of the squares of the residues (residual variance);

SCT: corresponds to the sum of the total squares (total variance explained);

Y_i: the measurement values;

$\widehat{Y_i}$: the predicted values

$\overline{Y}$: The average of the measurements.

Similarly, referring to the guidelines of Croutsche (2002), and Falk and Miller (1992), the structural model can be retained ($R^2 > 0.1$). (Chin, 1998) articulated the values of 0.67, 0.33 and 0.19 are respectively considered as substantial, moderate and low.

- **Structural equations of the conceptual model:** The internal model is defined by linear equations connecting the latent variables between them. For all endogenous ξ_k, we have:

$$\xi_k = \sum_{i:\, \xi_i \to \xi_k} \beta_{ki}\, \xi_i + \zeta_k$$

where β_{ki} represents the coefficient associated with the relation between the variables ζ_k and ξ_i . $\zeta_k$in an error term and ξi → ξ_i . ζ_k explains ζ_k.

- **Hypothesis tests:** Confirmatory research aims to establish causal relationships using path models and fit indices. In PLS-SEM for explanation, the focus is on

understanding a dependent variable, achieved by maximizing explained variance (R^2) and analysing the significance, size, and direction of path coefficients to test model assumptions.

- **Effect size** (f^2): is an index that brings assessment of the effect size allowing the researchers to observe the effect of each exogenous construct on endogenous constructs. The f^2 can be evaluated using Cohen's f^2 (Cohen, 1988). f^2 0.02 represent small; 0.15 medium; 0.35 strong (large effect of the exogenous latent variable). The effect size is:

$$f^2 = \frac{R^2_{AB} - R^2_A}{1 - R^2_{AB}}$$

In PLS structural modelling, path coefficients standardized beta coefficients in ordinary least squares regressions and are evaluated for significance through bootstrapping. Non-significant or opposing paths undermine the initial hypothesis, while significant paths in the hypothesized direction offer empirical support for the proposed causal relationship. (Kroonenberg & Lohmoller, 1990). It explains whether the fact that a coefficient is significant depends on its standard errors that are obtained by bootstrapping to enable computing the empirical T values, P values. Most of researchers use P value to assess significance levels (Faizan et al., 2018).

3.3. Database and model specification

The methodology of this study consists of four steps dealt with in the following sections:

Preparation of the methodological framework of research: Our study, conducted from March to December 2021 in southeast Morocco, used a questionnaire distributed face-to-face and via Google Forms due to COVID-19 restrictions. We obtained 180 surveys with an impressive 90% response rate, despite the region's limited HCP and smaller cities.

Questionnaire design and judge validation: Based on the literature review to identify each latent variable, an item. Items related to good pharmacovigilance practices were collected on a Likert scale of 5 degrees ranging from very poor to very good, while factors breaking reporting ADRs were collected on a Likert scale of 5 degrees ranging from disagree to strongly agree, HCP practices were collected on a Likert scale of 5 degrees ranging from strongly satisfied to unsatisfied and HCP perception was collected on a Likert scale of 5 degrees ranging from strongly agree to disagree. Note that the total number of items is 53 (items/questions).

Research model: We seek, through our causal model, to measure the relationship between Patients' Good Pharmacovigilance Practices during the COVID-19 period toward ADR Reporting and HCP's reactivity toward ADR Reporting through barriers affecting ADR Reporting by Patients and HCP (Figure 2 and Table 1). To do this, an

overall hypothesis (OH) was formulated: '**The good pharmacovigilance practices of reporting ADR by patients positively influence the reactivity of HCP for reporting ADRs**'. For each causal relationship, we have formulated a derivative hypothesis (total: 13 derivative hypotheses), in Table 2.

Data gathering and validating of the instruments: After collecting survey data using SPSS 21, the data purification process follows Churchill's paradigm. It begins by defining the item list, setting boundaries for what to include in the measurement. Then, the proposed items are aligned with the model's dimensions. Purification steps are executed for pharmacovigilance practices, ADR reporting factors, and HCP reactivity, involving data summarization and potential item modification or deletion. Depending on results, adjustments may be made in steps 2 and 3. If items are retained, steps 6 and 7 evaluate scale reliability and validity. If these criteria are unmet, a revision of the item list is necessary (Churchill, 1979).

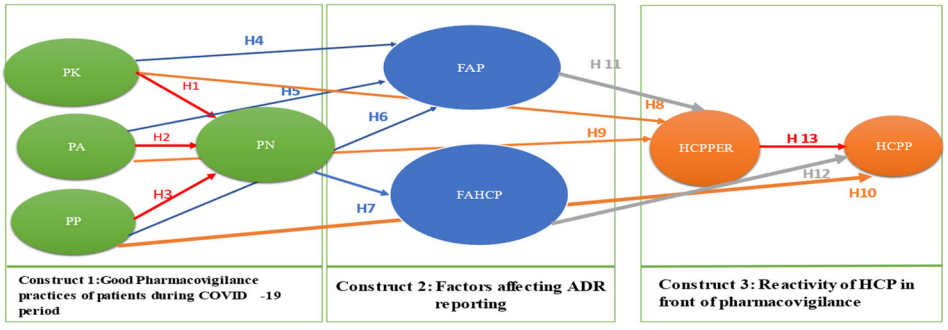

Figure 2: Proposed model

Table 1: Code used in the causal model

Constructs of the proposed model	Code of the construct's components	The components
Good Pharmacovigilance Practices over the COVID-19 period	PK	Patient's Knowledge of ADR
	PA	Patient's Attitude
	PP	Patients' practices
	PN	Patient's Notification of ADR
Factors affecting ADRs reporting	FAP	Factors affecting patients of reporting ADRs
	FAHCP	Factors affecting HCP of reporting ADRs
The reactivity of HCP	HCPP	HCP's Practices
	HCPPE	HCP's Perception

Table 2: List of hypotheses

Hypothesis Number	Causal relationship	Hypothesis Formulated
H1	PK >>> PN	We suppose that PK has a strong impact on PN
H2	PA >>>PN	We suppose that PA has a strong impact on PN
H3	PP>>>PN	We suppose that PP has a strong impact on PN
H4	PK>>>FAP	We suppose that PK has a strong impact on FAP
H5	PA>>>FAP	We suppose that PA has a strong impact on FAP
H6	PP>>>FAP	We suppose that PP has a strong impact on FAP
H7	PN>>>FAHCP	We suppose that PN has a strong impact on FAHCP
H8	PK>>>HCPPER	We suppose that PK has a strong impact on HCPPER
H9	PA>>>HCPPER	We suppose that PA has a strong impact on HCPPER
H10	PP>>>HCPP	We suppose that PP has a strong impact on HCPP
H11	FAP >HCPPER	We suppose that FAP has a strong impact on HCPPER
H12	FAHCP > HCPP	We suppose that FAHCP has a strong impact on HCPP
H13	HCPPER >HCPP	We suppose that HCPPER has a strong impact on HCPP

4. Results and discussion

4.1. Reliability

As mentioned in the methodology, the first step involves assessing **the reliability** of our measurements. Reliability ≥0.7 was considered acceptable. According to the results in Table 3, Cronbach's alpha and Rhô.D.G indexes calculated for each latent variable are above 0.7 and with reference to the recommendations of Nunnally and Bernstein (1994) (MERLEN, 2017), Fornell and Larker (1981) these results are satisfactory (reliable) according to (Kline, 1999).

4.2. Evaluation of external model (Measurement Model):

Note that the manifest variables form the blocks **around latent variables**. Since the measurement models are of the reflective type, the blocks must be one-dimensional to ensure that the obvious variables reflect their latent variable. The first eigenvalue for each block must represent at least 50% of the sum of all values in the same block. This is the case for the results depicted in **Table 4**. This confirms the one-dimensionality of the blocks.

Table 3: Reliability of measurements

Latent Variable	Items	Cronbach's alpha	Rho D. G
PK	5	0.6332	0.601
PA	5	0.7656	0.8434
PP	5	0.7737	0.8480
PN	4	0.8028	0.8715
FAP	8	0.784	0.826
FAHCP	10	0.9131	0.9781
HCPPER	8	0.9113	0.9293
HCPP	8	0.8023	0.8543

**Extracted from XL-stat software (2017 version).*

Table 4: Eigenvalues of the latent variables of the model

PK	PA	PP	PN	FAP	FAHCP	HCPPER	HCPP
2.0351	2.7389	2.6619	2.5190	3.1561	5.6848	5.0059	3.4516
1.5115	1.3235	0.8764	0.6099	1.4491	1.3188	1.1492	1.3622
0.8266	0.5445	0.7680	0.4870	1.0780	0.7598	0.5241	1.0797
0.4271	0.2193	0.4141	0.3841	0.7669	0.6556	0.3637	0.6448
0.1996	0.1739	0.2796		0.6920	0.5029	0.2943	0.5384
				0.4861	0.4129	0.2643	0.3857
				0.2460	0.2151	0.2526	0.3189
				0.1258	0.1900	0.1459	0.2187
					0.1558		
					0.1043		

Table 5: Quality index of measurement models

Latent Variable	AVE	Rho D. G
PK	0.5346	0.601
PA	0.5283	0.8434
PP	0.5109	0.8480
PN	0.6021	0.8715
FAP	0.5851	0.826
FAHCP	0.5171	0.9781
HCPPER	0.6172	0.9293
HCPP	0.6972	0.8543

**Extracted from XL-stat software (2017 version).*

Table 6: The discriminating validity (Extracted from XL-stat software (2017 version))

Latent Variable	PK	PA	PP	PN	FAP	FAHCP	HCPPER	HCPP	(AVE)
PK	0.7311*								0.5346
PA	0.4577	0.7268*							0.5283
PP	0.0861	0.1652	0.714*						0.5109
PN	0.0106	0.0874	0.183	0.7759*					0.6021
FAP	0.0732	0.0976	0.0147	0.0147	0.7649*				0.5851
FAHCP	0.0478	0.0444	0.0032	0.0315	0.3614	0.7190*			0.5171
HCPPER	0.0901	0.1414	0.0019	0.0014	0.0586	0.0340	0.7856*		0.6172
HCPP	0.0057	0.0612	0.0090	0.0446	0.0597	0.0099	0.0994	0.8349*	0.6972

** Square root of the average variance extracted (AVE).*

In our methodology, the second step involves calculating the AVE. **Table 5** demonstrates that our measurement model exhibits strong convergent validity, AVE exceed 0.5 for each latent variable, according to Fornell and Larcker's guidelines. The third phase of our methodology consists of calculating the **Square Root of AVE.** The results of **Table 6** show that the square root of the AVE of each latent variable exceeds the correlations between the latent variables (two by two). **Convergent validity and divergent validity confirm that our measurement model is valid**.

4.3. Evaluation of internal model (Structural model):

To test the internal model, we referred to Good of fit index (GoF). According to the results obtained in Table 7, the research model can be retained in terms of the threshold (GoF > 0.5), following the instructions of (Wetzels et al., 2009).

Table 7: Adjustment indices (*Extracted from XL-stat software, 2017 version)

Specification	GOF
Absolute	0.5337
Relative	0.8009
External model	0.9423
Internal model	0.8316

Chin (1998) articulated the values of 0.67, 0.33 and 0.19 are respectively considered as substantial, moderate and low. Similarly, referring to the guidelines of Croutsche (2002) and Falk and Miller (1992), the structural model can be retained ($R^2 > 0.1$). The results **of R^2 and R^2-adjusted** (**Table 8)** are substantial to moderate. The findings from our survey demonstrate the validity of both the external measurement model and the

internal structural model. This validation assures us of the credibility of the formulated hypotheses and measures the various causal links within our proposed causal model.

Table 8: R^2 Results and R^2-adjusted (*Extracted from XL-stat software, 2017 version)

Latent Variable	Type	R^2	R^2 adjusted
PK	Exogenous		
PA	Exogenous		
PP	Exogenous		
PN	Endogenous	0.2208	0.2119
FAP	Endogenous	0.2041	0.1939
FAHCP	Endogenous	0.3315	0.4153
HCPPER	Endogenous	0.1612	0.1517
HCPP	Endogenous	0.1075	0.6974

Our model holds a three **exogenous variable** , and has five endogenous variables. Each endogenous variable is explained by one or more variables and an error term. This model has five equations that were tested using the PLS approach through the XL-stat software (2017 version). The structural equations of the conceptual model are presented as follows:

$$PN = -0.1912 * PK + 0.27347 * PA + 0.37306 * PP \quad (1)$$

$$FAP = 0.10956 * PK + 0.24190 * PA - 0.00902 * PP \quad (2)$$

$$FAHCP = 0.17758 * PN \quad (3)$$

$$HCPPER = 0.06972 * PK + 0.28723 * PA + 0.13345 * FAP \quad (4)$$

$$HCPP = 0.07949 * PP + 0.03880 * FAHCP + 0.30475 * HCPPER \quad (5)$$

4.5. Hypothesis Test:

For each causal relationship, we have advanced a derived hypothesis and since we have 13 causal relationships, we have put in place 13 derived hypotheses. This assumption will also be subject to confirmation tests (Table 9).

Table 9: Research hypothesis tests

Causal relationship	Path coefficient	T*Student	Effect size	Signifi-cation	Validity	Association Degree
H1: PK > > PN	-0.194	-2.115	0.0255	0.0362	**Yes**	Small
H2:PA > > PN	0.2735	2.8834	0.0475	0.0044	**Yes**	Medium
H3: PP > >PN	0.3731	5.1062	0.159	00000	**Yes**	Strong
H4:PK >> >FAP	0.1098	1.1271	0.0073	0.2612	**Invalid**	Small
H5:PA >> >FAP	0.2419	2.3786	0.323	0.0185	Yes	Strong
H6: PP > >FAP	-0.0902	-0.1151	0.0001	0.9085	**Invalid**	Very weak
H7:PN > >FAHCP	0.1776	2.4007	0.361	0.0174	**Yes**	Strong
H8:PK > >HCPPER	0.0697	0.7390	0.0431	0.04609	**YES**	Medium
H9:PA > >HCPPER	0.2872	3.004	0.0516	0.0031	**Yes**	Small
H10: PP >> >HCPP	0.0794	1.1107	0.4570	0.0027	**Yes**	Strong
H11: FAP >HCPPER	0.13345	1.8246	0.019	0.0698	**Yes**	Small
H12: FAHCP > HCPP	0.0388	0.9333	0.216	0.0005	**Yes**	Medium
H13: HCPPER >HCPP	0.30475	4.1919	0.1004	0.0000	**Yes**	Medium

**Note: student test values are above |2.775| (|1.960|) which indicates significant parameters in the 1% (5%)*

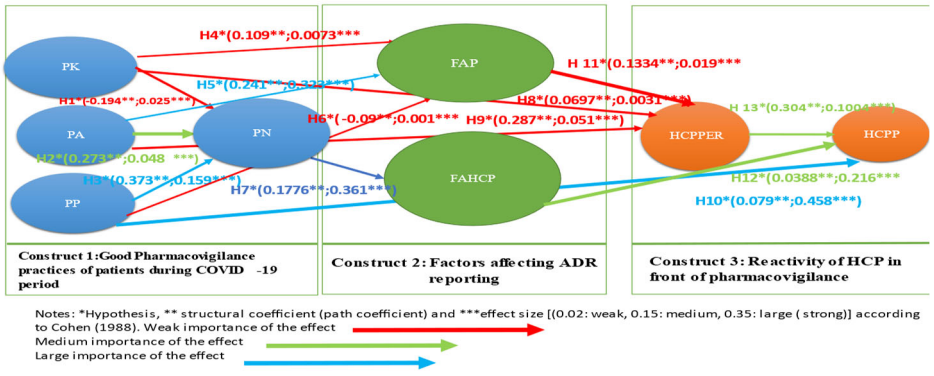

Figure 3: Final model estimated by PLS

4.6. Analysis of results:

The main goal of our empirical study is to test the impact of the good pharmacovigilance practice of patients over the COVID-19 period on the HCP's reactivity on pharmacovigilance. According to **Table 9,** we can confirm the validity of **Eleven hypotheses**: H1; H2; H3; H5; H7; H8; H9; H10; H11, and H13 (T>1.97), against two invalid derivative hypotheses H4 and H6. The final model can be represented in **Figure 3.** Based on the results in **Table 9** and **Figure 3**, we underline the following:
Direct effects: In the analysis, Patients' Knowledge negatively influences Patient's ADR notification with weak significance. Patients' attitude and Patients' practices positively influence Patient's ADR notification with strong and medium significance, respectively. Patient's attitude strongly affects factors influencing patients to report ADR. Patient's knowledge has a medium effect on HCP's perception. Patient's notification has a strong impact on factors influencing HCP to report ADR. Patient's attitude weakly influences HCP's perception to notify ADR. Patient's practices strongly affect HCP practices in pharmacovigilance. Factors influencing patient ADR reporting weakly affect HCP's perception. Factors influencing HCP reporting ADR have a medium impact on HCP's practices, and HCP's perception of reporting ADR moderately affects HCP's practices.

Table 10: Indirect effects (*Extracted from XL-stat software (2017 version))

Specification	PK	PA	PP	PN	FAP	FAHCP	HCPPER
PK							
PA	0.0000						
PP	0.0000	0.0000					
PN	0.0000	0.0000	0.0000				
FAP	0.0000	0.0000	0.0000	0.0000			
FAHCP	0.0340	0.0486	0.0662	0.0000	0.0000		
HCPPER	0.0146	0.0323	0.0012	0.0000	0.0000	0.0000	
HCPP	0.0244	0.0993	0.0022	0.0069	0.0407	0.0000	0.0000

We notice from **Table 10** that the Patient's Knowledge variable has positive and significant medium indirect effects on factors influencing HCP from reporting ADRs, "HCP's perception" and "HCP's Practices'. So, we have to improve the patient's knowledge about pharmacovigilance in order to initiate patient to report adverse drug

reaction and to maintain this culture and to improve the reactivity of HCP among reporting ADR's.

5. Conclusion

In a four-month exploratory study in the southeast region of Morocco involving HCP, it was found that spontaneous ADR reporting is an effective and low-cost method for detecting unknown AEs. The research confirmed the hypothesis that improving pharmacovigilance practices, particularly during the COVID-19 pandemic, enhances HCP reactivity in ADR reporting and reduces factors influencing reporting. However, HCP displayed varying levels of awareness and knowledge of pharmacovigilance and ADR reporting, emphasizing the need for ongoing education and training. Public awareness campaigns on ADR reporting were also recommended to boost reporting. The primary issue with spontaneous ADR reporting systems worldwide is under-reporting, acknowledged by national pharmacovigilance centers, with only 3 to 10% of ADRs being reported (OMS, 2004). Our study underscores the need for training, sustained awareness, and patient proximity to facilitate ADR reporting, suggesting awareness campaigns through social media, ADR reporting events, and maintaining post-graduate awareness for HCP via medical networks.According to this study among pharmacy student in Morocco, students expressed the desire to learn more about pharmacovigilance during their university education (N. Nchinech et al., 2020). This result led to the introduction of a system of pharmacovigilance work groups for third- and fourth-year pharmacy students for the 2018–2019 academic year. Also, from our experience in the NCPV, its proximity is of paramount importance in order to establish continuous communication with the HCP.

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