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Design and Validation of a Questionnaire in Pharmacovigilance.

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Abstract: Introduction: The pharmacovigilance system collects adverse events registered by physicians in their clinical practice. However, there is a low index of reports in this regard. There are various publications at international level oriented to determine causes for this low notification. In this respect, it would be valuable to count with an instrument that would diagnose the situation prevailing for México. The objective was to develop and validate a questionnaire reliable and sensible for measuring causes of low reports.

Material and Methods: Experts validated the questionnaire and the final instrument was applied to 124 physician subjects that responded to the 30 final questions, and their answers were tabulated and categorized for measuring confidence and internal congruence. Alfa of Cronbach and "t" student tests were applied for the validation and test-posttest application.

Results: The internal consistency value was 1.097. The different answers and scores were calculated, where the final global average in points for responses for the pilot group studied was 100.72, that translated to percentage resulted in 67% (S.D. 8). The final Cronbach alpha value obtained was 0.7.

Conclusions: The validated questionnaire meets the objectives for which it was designed, and proved to be useful, reflecting the state of knowledge, abilities and attitudes.

I. INTRODUCTION

The pharmacovigilance program (FV) on a global scale is a program that was developed for the timely detection of security problems that are inherent to the prescription drugs and to the medical technologies. Mexico is part of this program since 1998, when it became a member of the world association based in Uppsala, Sweden [1,2]. The above-mentioned membership entails rights and advantages, but also obligations, like making periodical reports of the results summaries of the management of the FV from the reports sent by the physicians to the national system to further contribute with the international vigilance. The Mexican Official NORM NOM-220-SSA1-2022, "Installation and Operation of the Pharmacovigilance" [3] mentions the obligatory nature of the report of such adverse events by the practicing physicians, in this case called spontaneous report, which is the most appropriate report known to detect the so-called signs that serve as guide in the detection of the drugs security problems (López-González, 2009) [4].

Such important reports are known in the international literature and the most relevant identified causes of the low global report rate have been detected and classified.

Worldwide, there are a number of diverse studies geared towards the determination of limitations of this report by the participants of the system (report generators), as well as their causes, to increase the number of reports in the national gathering systems [4-10].

In his review, López-González [4] mentions that the adverse reactions are a public health problem in terms of mortality, morbidity and costs. It is also mentioned that the low report rate is a major-limiting factor of the system, documenting that it is estimated (on an international level) that only 6% of all adverse reactions are reported. He then continues to elaborate a theoretical model, known

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as the one of "the 7 deadly sins" that was originally proposed by Inman [5-7] that explains the main reasons of the low report rate amongst physicians. He concludes that the identification of the knowledge and the attitudes in relation with the report allow, amongst other things, to build educational strategies geared towards changing those habits and stimulate the report of suspected adverse reactions.

The systematic review of the literature by López-González [4] tried to determine the influence of the personal and professional characteristics in relation to the report and identified the related knowledge and attitudes of the physicians. These attitudes, originally proposed by Inman, are: 1. Complacency: the belief that only safe drugs are approved for sale. 2. Fear of a possible involvement of litigation or an investigation of the prescription costs by the related departments. 3. The guilt of having given a treatment that could have harmed a patient. 4. The ambition of compiling and publishing a series of personal cases. 5. Lack of knowledge of the requirements of the report. 6. Diffidence of the possibility of appearing ridiculous by reporting adverse drug reactions that are merely suspicious. 7. Indifference of some physician of his essential role as clinical investigator that should contribute with medical knowledge. 8. Lethargy. A combination of procrastination, lack of interest or time to find a report format and other excuses. 9. Financial incentives to report. 10. Insecurity, (originally not proposed by Inman, quoted by López-González, [4]).

Therefore, the low report rate by physicians is a reality for many of the systems at an international level and has been reviewed for some time. Many instruments have been developed to the study of this phenomenon, for example the addressed questionnaires, self-administered, that are applied to large groups of physicians to define the situation and contribute with their possible solutions [11].

The participants of the national system (intern and extern) are conscious of the difficulties that exist in our medium to have a participation with enough reports, and one of the objectives of the development of the present instrument that we have undertaken to validate, is that of contributing as far as possible with the solution to this problem, which has not been studied deeply enough in our country.

An investigation about the problem of the low report rate of pharmacovigilance has not been described in the national literature and this is why we have set ourselves as an objective to develop a valid instrument that is reliable and sensible to self-administrate for its application.

We are interested in contributing as possible with the corresponding solutions by identifying in our country causes of the low report rate that could be general as well as specifically local. This has been initially presented from the investigation of diverse representative groups of Mexico City, aimed subsequently at extending the casuistry, to other areas of the whole country. The chosen methodology in the design and validation of the instrument [12-14] was applied to the majority of the relevant aspects of its development, for a useful and appropriate questionnaire.

II. MATERIAL AND METHODS

Study subjects and methods: The health system personnel in the (initial) validating study of the questionnaire consists of medical professionals with and without specialty from a number of hospitals, public and private, clinicians with more than a year of patient care in Mexico City.

The study protocol was previously submitted to the corresponding ethics committee. All the data was encrypted and kept by the investigators of this study according to the Good Documentation Practice to keep complete confidentiality.

The self-administrating questionnaire was designed to explore the knowledge and relevant attitudes in the application of the pharmacovigilance guidelines that were established by the authorities of the Ministry of Health (through the Federal Commission of Health Risks Protection _COFEPRIS) for physicians in our territory (NOM-220-SSA1-2002 §5) [1].

Initial outline and selection of questions

Three physicians that are experts in the FV system provided the first questions that took into account the above-mentioned Inman factors to determine the knowledge and attitudes of the physicians towards the national pharmacovigilance system. As a guide to outline the questions, the experts were based on their knowledge and professional experience and on what is found in the international literature about the common attitudes towards the system [4, 7-10]. Each question was registered on paper and coded with a number. The questions were formed according with the Likert scale model [12-14], with a total of 5 answer options, including a central neutral answer, a "not agreeing nor disagreeing" answer. Questions that were hypothetical, vague, ambiguous, double, charged with emotive language, that summarize facts or questions that make allusion to events that happened a long time ago were avoided. Likewise, threatening questions and questions that were too sensitive were avoided [15].

A. Scale, classification and question score

The questionnaire explored a construct (the operation of the FV from the point of view of the clinician) that was divided in three complementary areas: knowledge of the system, attitudes towards the report and ways to improve the report. The answers were scored from 1 to 5, 5 being 'totally agree,' 4 'agree,' 3 'not agree nor disagree,' 2 'disagree' and 1 being 'totally disagree.' The questions were arranged in such a way, that the answers of an expert would allow for a general optimum answer. This optimum answer was then determined for every question with the help of the experts. A possible maximum score (150) for the total of elaborated questions (30) was set. In this way, an answer index for the whole questionnaire could be calculated (for the 150 answer options- 30 multiplied for every one of their 5 possible answers) and this index can be transformed for every participant in a final percentage of "right" answers, which progressively approaches 100% for the optimum of answer (final score scale from 0 to 100). The questionnaire was initially applied in diverse occasions (up to 3, in different subjects) and in each occasion, the content of the question was refined (coherence, consistency, logic, univocality) with every consecutive step (a total of 4 tests with a population of around 35 subjects). The phrasing of the questions in a positive or negative sense was adjusted to achieve the above-mentioned maximum score and the questions that on an optimum way were answered with a 'totally agree' were reversed (for the score analysis) when the answer optimum determined by the authors was 'totally disagree', so that the maximum score (optimum) for the questionnaire were the 150 reachable points.

B. Depuration, adjustments to the questions and initial application

The questions were selected for their final version using two methods: a) by experts' consensus, according to their recommendations and feedback and b) applying the questionnaire to groups of physicians with adjustments and corrections of the questions according to the answers (and requested recommendations) of the participants of this pilot testing. As mentioned, in a first version, the preliminary versions were applied to 3 small groups (from about 5 and 10 physicians), then to a first pilot group (with test tabulation), applied to 22 medical specialists, after this, new adjustments were made to the questions. The answers and their mentioned corresponding tabulation were discarded for the tabulation of definite validation. The resulting final version was then applied to 124 medical specialists and generalist subjects (the final pilot group) that answered the 30 selected questions preliminarily as final. These answers were tabulated and categorized for its application by statisticians for its validation.

C. Statistical analysis

The data for the questionnaires were uploaded on a SPSS database (13.0) on which the

corresponding descriptive statistics were performed. Confidence tests were run using Cronbach alpha[15] for the complete questionnaire.

The gender distribution was reported as absolute and relative frequency. The demographical variables of the respondents were described through averages and standard deviations (age and years of medical experience) and with averages and maximum values and minimums (in the case of qualitative variables like number of attended patients per day). The concordance was made comparing the answers 9 and 19, which were designed specially as repetition. The relation or ratio of 1 would indicate excellent concordance. The factors with a specific importance were detected by absolute values of answer; the identification of the social and cultural variables of answer through qualitative analysis, through the identification of repeated words amongst questionnaires. For the pilot group, the answers were arranged according to each one of the dimensions mentioned by Inman [6] and they were assigned, according to Likert's 5-level system, with the maximum possible score (totally agree). These values were tabulated against the maximum possible value (ideal) and were contrasted with the paired t-test between pre and post intervention evaluations. The probability values (p) lower than 0.05 were considered as statistically significant.

D. Methods and analysis models of the data according to the type of variables

An Excel for Windows database was generated to look for the internal coherence. The generation of calculi to score the questionnaires was generated with specific formulas. The influence of factors was analyzed with the general lineal model for multivariate interaction.

The items eliminated from the confidence analysis include those questions not related with the dimensions of the report which comprised the (repeated) question for internal consistency (#19) and two questions related with previous reports explored (#10 and #20) After this exclusions, we started the analysis with 27 items.

III. RESULTS

During the development, 25 questions were initially gathered, which related to three large groups of content: knowledge of the pharmacovigilance system, reasons not to report (taking Inman's rasons in account) and ways to improve the pharmacovigilance system. The validity of the content of these questions was established through the consulted experts' consensus. They were asked to fill the questionnaire and to comment on the content of the questions and about the complimentary questions.

After three consecutive applications to diverse groups of final users (a total of approximately 15 answering physicians), changes and adjustments were made, and then, the questionnaire was applied to a group of 22 (subsequent) subjects, sessions, in which further adjustments were made.

A preliminary version was later determined, which was now applied to 124 physicians, it was tabulated and the statistical calculi and results check were made.

The characteristics of the 124 participant physicians for the final validation of the questionnaire are shown in table 1. 30 questions were finally selected (5 more were added after a thorough review) to build the final definite version according with the selection of the consultants.

E. Determination of the reliability and consistency of the questionnaire

The final definite pilot application consisted in the application of the questionnaire to 124 general doctors and specialists (the calculus of the sample is contained between 100 y 200 subjects [12], whose demographic general data can be appreciated in table 1.

Table 1. Demographic characteristics of the studied group for questionnaire validation.

	Calculi	Min/max	S.D.
N	124		
Men/women	63/61		
Age (years) average	44.35	26/65	10.50
Experience (years) average	16.4 years/professionals	1/35	(S.D. ±9.85)
Nr of patients/day(average)	17.54 patients/day	3/40	(S.D. 7.36) (N= 122)

Due to the nature of the questionnaire being survey-like, consistency tests that are applied to specialized (i.e. medical) questionnaires were not made, e.g. in the case of the questionnaires for patients, in which the same is applied repeatedly to the same respondents to reach an optimum answer in the end. Likewise, for example, the sensitivity of the change is applied to determine scores in scales of state of health or scales of life quality when they are designed to detect a long-term change. This measurement was not necessary for our instrument. A test that was applied was the one of intern consistency (Table 2), a kind of reliability that refers to the degree in which diverse parts of the questionnaire are measuring all of the same attributes or dimensions.

The number of "correct" answers and the possible errors (unanswered questions and their frequencies) were used to analyze the reliability of the questionnaire and its sensibility, which was measured in terms of percentage result. The answers of each participant were combined in a global percentage and the congruency of the results was analyzed and interpreted.

The questionnaire provided the framework to give a score per participant and a global score. The final global average obtained by the studied pilot group was 100.72 (S.D. ±8) of a possible total maximum of 150 points, (67%). By contrast, the qualified expert respondents practically reached 150 points (100%).

Table 2. Results from the studied group for questionnaire validation.

Item	Calculus	S.D.
N	124	
Men/women	63/61	
Added points average / score (in%) of respondents	100.72 / 67 %	(S.D. ±8)
Intern consistency (Concordance)	1.097	(0.00 for the paired t-test)

F. Before-after testing of the questionnaire and reliability analysis

Another test (final) that was made in relation with the validation, was the application of the questionnaire to another group of physicians (250 respondents), first in a preliminary way, before a non-specific educational intervention (non-specific with regard to the correct answers of the questionnaire), and, subsequently, a new application after that. The demographic data of this group and its result in terms of an increase in the performance score, are listed in tables 3 and 4.

Table 3. Demographic characteristics of the studied intervention before-after group for questionnaire validation.

N=239	Value
Women (%)	147 (61.5)
Age (years)*	25.97 ± 2.44
Medical experience (years)*	1.94 ± 1.90
Referendum density (patients /day)**	15 (1-80)

*Average ± standard deviation **Medium (minimum-maximum)

Table 4. Answers to the questionnaire grouped together according with Inman (5), and combining the 30 questions in categories that show a significant increase in score, post intervention.

Dimension	Maximum score	Baseline value *	Final value	P*
Ignorance	13.33	6.56 ± 1.97	9.74 ± 1.81	<0.001
Diffidence	3.33	2.02 ± 0.79	2.58 ± 0.75	<0.001
Complacency	6.67	3.79 ± 1.28	5.20 ± 1.14	<0.001
Fear	6.67	4.88 ± 1.00	5.49 ± 0.94	<0.001
Indifference	6.67	5.54 ± 1.03	5.98 ± 0.94	<0.001
Insecurity	3.33	2.07 ± 0.71	1.80 ± 0.74	<0.001
Lethargy	23.33	13.67 ± 2.20	17.78 ± 2.50	<0.001

Out of 250 questionnaires that were captured, 233 cases were useful for the reliability analysis. The questions related with the dimensions of ignorance (ítems 11, 26, 27 and 30), diffidence (12), complacency (13 and 25), fear (9, 21), indifference (14, 24), insecurity (15), lethargy (1, 6, 8, 16, 17, 18, 22), solutions and incentives for reporting (23 and 28), and importance of the system (2, 3, 4, 5, 7, 29) for a total of 27 questions were contrasted through a Cronbach alpha analysis [16], obtaining a value of 0.604. After review of the corrected correlation for each item, negative values were found for questions 1, 5 and 30, as well as redundancy on the information obtained on each of them. Therefore, these were dropped from the instrument, and the confidence analysis was repeated, with a new and final Cronbach alpha for the standardization of items of 0.7. The complete 30 initial- and the remaining definitive 24 questions for the finished questionnaire can be found at the end of this article.

IV. Conclusions and Discussion

The qualities of a wide-used questionnaire for determining a construct requires validity and reliability. It has to be easy to apply and the results have to be easy to codify and interpret. Finally it is necessary that the instrument of data gathering is “friendly.” According to the proposed objective (construct), we developed a questionnaire to test general and basic knowledge and attitudes in relation with the pharmacovigilance system that is carried out in our country. Basically, the questionnaire covered three interrelated aspects like the knowledge of the system itself, the reason for the low report rate and the ways of improving the report in the future. The questionnaire proved to be useful by reflecting the state of the knowledge and attitudes that were calculated from the information that we have from the literature and the results that came out from the pilot population that was analyzed. The pharmacovigilance system as applied by the corresponding authorities, as well as the postures (attitudes) from the side of the physicians that are related with the system, rely heavily on the (resulting) volume of the periodic report.

From the possible biases of almost any questionnaire, and with the goal of reducing them, the one named “acquiescence answer,” that consists in the people’s tendency to agree with all the contents irrespective of the phrasing of the questions. The phrasing in a positive and in a negative sense was used alternately, randomly intercalated, which may signify a decrease of this bias. In this case, the score of the question was inverted. However, not every bias can be eliminated [12].

The increase in the post educational score after an educational intervention shows the sensitivity of the questionnaire directed towards improvement in the final score towards a better performance after applying this intentional intervention in the educational field.

In conclusion, the questionnaire meets with the objectives for which it was designed, which are to test the knowledge in the usage of the pharmacovigilance system, as well as the postures (attitudes) that are related to the system, and it can now be applied to a large population for purposes of carrying out an open survey.

Annex I

Questions
Selections: Totally agree / Agree / Not agree nor disagree / Disagree / Totally disagree.
X1. The national report system facilitates the report of adverse reactions.
2. There is a need of more compromise/obligation from the physicians to report adverse reactions.
3. The pharmacovigilance report system does not have any importance or transcendence for my work.
4. The pharmacovigilance report does not have any importance or transcendence for the country.

X5. When I encounter an adverse reaction, I immediately think about reporting it.
6. There are many other issues in the medical practice that are more important to attend to.
7. The pharmacovigilance report is something that has to do more with the authorities than with us, the physicians.
8. I can't find a good reason to make a routine report.
9. The report makes me expose my clinical practice in an unnecessary way.
X10. I have detected adverse drug reactions, but I have not reported them.
11. I really don't know how to make a spontaneous adverse reactions report.
12. Only those adverse drug reactions that show a cause-effect relation must be reported.
13. The adverse drug reactions are already known when the drug reaches the market, because only safe medication can be commercialized.

14. Physicians should contribute to the general advance of medical knowledge trough the adverse drug reactions report.
15. In fact, it is very difficult to determine if a drug is the responsible of an adverse reaction.
16. The adverse drug reactions report requires a lot of time and attention.
17. I don't know where to find the Adverse Drug Reactions format.
18. The report is complicated and bureaucratic.

X19. The report makes me expose my clinical practice in an unnecessary way.
X20. I have reported adverse drug reactions to the pharmacovigilance system.
21. I consider the report to be valuable in some cases of legal controversy.
22. The report format should be friendlier in its design. 23. Only a punishment-reward system will make the physicians to report the adverse drug reactions.
24. Through the report, one can contribute to the medical knowledge.
25. One must only report when there is an evident relation between the drug and the reaction.
26. The severity of the reaction is the one that decides if we must report the adverse drug reaction or not.
27. Only previously unknown adverse drug reactions must be reported.
28. Everything that is related to the report should be taught at the faculty to make it work.
29. I really don't know the scope of the report before the authorities.
X30. I know the report format to the detail.
X: *Eliminated*

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