Philippines Pharmacovigilance Training

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SIAPS
Systems for Improved Access to Pharmaceuticals and Services

Philippines Pharmacovigilance Training

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About SIAPS

The goal of the Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Program is to assure the availability of quality pharmaceutical products and effective pharmaceutical services to achieve desired health outcomes. Toward this end, the SIAPS result areas include improving governance, building capacity for pharmaceutical management and services, addressing information needed for decision-making in the pharmaceutical sector, strengthening financing strategies and mechanisms to improve access to medicines, and increasing quality pharmaceutical services.

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Key Words

pharmacovigilance, pharmacovigilance training, Philippines, causality assessment, signal generation

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CONTENTS

ACRONYMS

aDSM	active drug safety monitoring and management
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
BDQ	bedaquiline
DOH	Department of Health
DRTB	drug-resistant tuberculosis
FDA	Food and Drug Administration
LCP	Lung Center of the Philippines
LMIC	low- and middle-income countries
MAH	Medicine Access Holder
NRA	National Regulatory Authority
NTP	National Tuberculosis Program
PD	Pharmaceutical Division
PHP	public health program
PViMS	PharmacoVigilance Monitoring System
PV	pharmacovigilance
SAE	serious adverse event
SAR	suspected adverse reaction
TB	tuberculosis
WHO	World Health Organization
USAID	US Agency for International Development

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We would like to express our gratitude to the National Tuberculosis Control Program (NTP), Food and Drug Administration (FDA), Lung Center of the Philippines (LCP), and Pharmaceutical Division (PD) for their commitment and support to the strengthening of the pharmacovigilance (PV) system of the country.

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BACKGROUND

USAID, through the Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Project, is providing technical support to the Department of Health (DOH) to implement new anti-TB medicines and novel regimens by strengthening the PV system in the Philippines.

NTP is now in the process of rolling out the standard shorter treatment regimen, which reduces the treatment duration for multidrug-resistant TB patients from 18 months to 9 months and the use of bedaquiline (BDQ) for drug-resistant TB in the Philippines. These two lifesaving treatments require active surveillance of patients in the form of active drug safety monitoring and management (aDSM) as defined by World Health Organization (WHO). In aDSM, data must be systematically collected to enable causality assessment for serious adverse events (SAEs), determine their frequency (rates) and detect signals to assess the safety of new treatments, and inform future policy on the use of these medicines.

In support of this, SIAPS conducted a training on PV to increase the capacity of NTP, LCP, PD, and FDA. Strengthening the capacity of staff in these organizations and other stakeholders in this area of PV reinforces current safe scale-up efforts and introduction of these lifesaving regimens. Furthermore, providing training for staff in data management, causality assessment, and signal detection enhances expansion of safety monitoring to other medicines used within the health system in the Philippines.

Purpose and Objectives

The purpose of this training was to build technical capacity of DOH to implement aDSM for the scale-up of new TB regimens and BDQ under program conditions, and to strengthen the DOH PV system. The objectives of the workshop were to:

- Explain the concept and principles of PV and why it is important to monitor the safety of medicines used by patients
- Know the definition of frequently used terms in PV
- Describe the different forms of PV and strategies used in PV (drug safety monitoring)
- Know how to detect and report adverse drug reactions
- Conduct causality/relationship assessment between a suspected medicine and an adverse event (AE)
- Understand the importance of data in safety monitoring and the various ways in which data can be mined to generate signals
- Use data from PV to provide feedback to reporters
- Appreciate the basics of safety communication

ACTIVITIES

Prior to the workshop, the consultant worked with the SIAPS Philippines team to set appropriate training objectives and to finalize training materials, including a facilitator's guide, participants' guide, activity exercise, case studies, and other related materials. The workshop was held at the Bayview Park Hotel Manila, October 18-20, 2017, with 10 participants in attendance. Only two participants had attended a previous PV training. All 10 participants (Annex B) from NTP, LCP, PD, and FDA play an important role in the aDSM implementation of new drugs and novel TB regimens.

The training was delivered in the form of lectures using PowerPoint presentations, guided practical exercises with case studies, and breakout sessions for group work. The three-day training concluded with a plan of action that forecasted immediate PV activities to which participants could apply lessons learned from the training.

A synopsis of key messages for the various sessions in each day of the training is presented below.

Day 1 (October 18, 2017)

- PV has now become a front-burner issue for low- and middle-income countries (LMICs) encouraged by the Global Fund requirements for many countries to include an aspect of PV in their funding proposal.

- Data is needed for policy changes, but data coming from a country's own population is more meaningful in PV, especially when advocating to in-country policy makers. One of the current challenges in PV is that many of the available statistics are from developed countries. LMICs need to collect, analyze, and use homegrown data to inform relevant decisions.

- PV is more interested in strengthening the system to prevent harm to patients rather than finding faults and apportioning blame when harm (an active failure) has occurred. This will encourage health workers to report adverse events as well as medication errors.

- There are four minimum data set requirements in order for an adverse event report to be valid, but it does not mean that these are the only important variables in PV data. The reporter's contact details cannot be anonymized when reporting adverse reactions, as some reports may need to be verified.

- PV aims to ensure safe and rational use of medicines. The focus of PV is not to take medicines out of the market, but to ensure that medicines on the market remain safe.

- Collaboration between PV and public health programs (PHPs) inspires and increases public confidence as it can provide data that may be used to reassure the public in the event of a safety concern or validate the good aspects of a PHP. PV should not be a standalone vertical program.

Session 1: Overview of the Training and Participants' Expectations

The training session began by providing the background, objectives, and methodology of the three-day PV training. Causality assessment and signal detection were emphasized as the focus of the training.

Participants were asked to share their expectations for the workshop. Most participants expressed that their expectations were to learn signal detection and causality assessment. All participants expected the training to help them perform their jobs better by providing quality care to patients and saving more lives. Participants' responses are presented in Annex 3.

Participants also completed pre- and post-training knowledge assessment tests on days one and three, respectively. Results of these assessments are presented in Annex 4.

Session 2: Why Does PV Matter?

Key objectives of this session were to sensitize participants to the fact that medicines are double-edged swords—with the ability to do good and harm—and to outline the critical role health care providers play in detecting medicine safety issues.

Session two started with a video showing the importance of reporting medicine safety issues in PV. A single case report from multiple resources can go a long way in making medicines safer. Participants were encouraged to use the video to advocate and increase awareness on PV. Topics covered under this session include the following.

- **History of PV -** Participants learned that one of the earlier documented drug safety issues that led to an era of safety was the elixir sulfanilamide experience of 1937 in the United States, and that the thalidomide disaster happened much later, in the early 1960s.

- **Aims and goals of PV –** Participants learned that PV seeks to ensure rational and safe use of medicines, as well as to educate and inform patients.

- **Importance of PV in medicine lifecycle –** During product development, only highly selected groups of people with no comorbidities participate in clinical trials. But, when medicines are registered, everyone—including the elderly, children, and pregnant women—has access to such medicines, therefore necessitating the continuous monitoring of medicines when used in "real life." Participants can advocate for the need for PV when products are released on the market.

- **Role of PV in shaping the current regulatory landscape –** Regulatory authorities depend on the vigilance and dedication of health care providers to detect medicine safety-related problems. Participants should work collaboratively with stakeholders to create awareness about the role of PV in influencing regulations.

- **Strengthening other regulatory systems** - Participants can use the experience of other countries' regulatory system strengthening approaches and implement them in the Philippines, if applicable.

Participants' Questions

1) What is the safe dosage of thalidomide to be taken by a patient?

Thalidomide is still on the market for other indications, such as treatment of certain cancers. The dose will depend on what it is being used for. However, a risk minimization plan must be in place to ensure that there is no pregnancy in female patients taking the medicine.

2) **Did thalidomide undergo pre-clinical study? Are there retrospective studies for thalidomide in pregnant subjects?**

At the time thalidomide was licensed for use in pregnant women, there may not have been a requirement to test the drug on pregnant animals and regulatory requirements may not have been that stringent. Retrospective studies on the use of thalidomide in pregnant subjects could not be confirmed.

Session 3: Key Terms in PV and What They Mean in Practice

The objective was to define some of the frequently used terms in PV and what they mean in practice. Some of the key terms in PV are used interchangeably, but there are subtle differences that affect the use of these terms. Key topics covered under this session were:

- **Key terms in PV and differences between terms –** Participants can correctly use PV terms in practice.

- **Risk factors for adverse drug reactions (ADRs) –** The various factors that may predispose patients to ADRs were enumerated to include age, gender, previous history of allergy or reaction, race and genetic factors, multiple drug therapy, and concomitant disease processes. For example, it was noted that some studies suggest that ADRs are more reported in women than in men. However, it is not clear if this is fact or artifact.

Session 4: Scope of PV

Session four looked at the growing scope of PV. It was noted that the scope of PV has broadened beyond the narrow confines of reporting ADRs to include issues related to counterfeit and substandard medicines, drug abuse and misuse, vaccinovigilance, drug interactions, lack of efficacy, and medication error.

The session also discussed the broader issue of patient safety with a focus on the issue of medication error—a preventable cause of adverse events in patients. These errors often manifest in prescribing, administration, and dispensing of medicines, and may be attributed to workload, staffing issues, and other distractions. The session included several hands-on exercises (examples listed below).

Exercise: Use of Abbreviations in Prescriptions

Participants reviewed a prescription that used a lot of abbreviations, which could lead to potential medication error. Participants were asked to suggest ways to prevent medication errors from occurring in such situations. Participants suggested that any abbreviations seen in a prescription should be clarified with the treating physician. However, it was noted that some physicians do not take kindly to their prescriptions being queried. Participants were encouraged to not be intimidated in such situations, but to always seek clarification for unclear prescriptions. Participants reported that the Philippines has a law against dispensing unclear prescriptions. It was also suggested that the use of electronic health records may be one way of minimizing prescribing and dispensing errors.

Case Study: Medication Errors Video

The session included a 17-minute video that depicted how several failures in the system could lead to medication error and eventual harm to a patient. Participants were asked to identify some of the observable errors that might have contributed to the medication error, which resulted in devastating results for the patient in the video. Participants listed the following:

- Too many distractions in the hospital environment, such as phones ringing and emergency situations that require immediate attention.

- Doctors who were not paying attention to the details of the medicine being administered, even while following the standard operating procedure. Sometimes staff can hear and repeat things without truly internalizing or actively listening to what is being said. There is a tendency to respond automatically, rather than being mindful and aware of the situation.

- Communication failure among staff members.

- Disregarding established staff verification procedures in favor of personal recommendation. Proper checks, verification, and briefing were not followed for the new doctor.

- Patient's distraction (use of ear phones) and lack of participation in the process.

Session 5: PV Methods

The objective of the session was to introduce participants to the various methods available for patient monitoring and data collection in PV. Participants were informed that two main methods are available for safety monitoring: spontaneous reporting and active surveillance. Spontaneous reporting is a quick and low-cost method for commencing safety monitoring. Active surveillance methods may be adopted to complement spontaneous reporting. There are different methods used in PV and each has their own advantages and disadvantages. Knowing these will help participants understand when and how to use each method.

Participants' Questions

1) If PV also includes failure of therapy, why is the source of the medicine not included in the minimum data required to make a valid report? How can we be sure that a suspected drug is not counterfeit?

Information on the source of a medicine may be collected at a later stage if a quality issue is suspected, but it is not information that is critical for ADR reporting. Some ADR reporting forms request the reporter to indicate if a quality issue is suspected. If so, then other details such as brand name, source of product, and batch and registration numbers (if available) may be collected. The drug would then be sampled and sent to a laboratory for testing to confirm the quality.

Session 6: Managing Data in PV

The objective of the session was to get participants to appreciate the vital role of quality data in PV and to understand how PV data can be managed. It was noted that in order to get quality data and to get the most out of the data, it is important to have clear objective(s) for data collection. Topics covered in this session included:

- **Sources of PV data** – There are many possible sources of PV data including patient charts, medical records, registries, patient interviews, medical/insurance claims, and pharmacoepidemiological studies, among others.

- **Quality of PV data –** Poor quality data can lead to drawing of wrong or delayed conclusions about a patient or a safety signal, which can in turn lead to unnecessary harm to patients.

- **Tools for managing PV data** – Two main ways are available for managing PV data: manual (paper-based) handling and electronic handling. Electronic tools such as Microsoft Excel and various software options (e.g., PharmacoVigilance Monitoring System [PViMS], VigiFlow) are available to countries for PV data management.

- **Benefit-risk analysis –** Risk perception, which is influenced by several factors, is as important as the absolute risk because people's perception of a certain risk will determine their action(s). Participants learned that benefit-risk balance must always be favorable, but benefits/risks to individuals may not be the same as benefits/risks to society. Transparency and communication are important when it comes to benefit-risk analyses for medicines. In PV, data need to be continually analyzed to detect when a shift in the balance occurs. Health care providers should appreciate that every ADR report could tilt the balance. PV should also keep an eye on known adverse reactions as detecting an increase in the frequency of known reactions may be as important as detecting unknown adverse reactions.

Participants were given three case scenarios on benefit-risk analysis to stimulate discussions and demonstrate how risks, and even benefits, are not necessarily the same for every drug and every patient.

Session 7: Integrating PV in PHP

PV keeps medicines safe and patients even safer. Session seven explored the importance of PV in public health programs. An effective medicine monitoring system is an essential and cost-effective means of maximizing the benefits of PHPs, minimizing risks to patients provided with medicines used for managing PHPs, and preventing harm to society. Topics covered in this session included:

- **PV in PHPs: Why we need to collaborate –** The survival of PHPs may depend on PV, and vice versa. Participants were shown the role of PV in PHPs to better understand the need for effective collaboration between the two.

- **PV in PHPs: How we collaborated (examples from other countries) –** Participants were shown areas where PV and PHPs had successfully collaborated in other countries.

- **Benefits of collaboration for PHPs** – The idea that PV is a luxury, affordable only in the developed world, should be replaced by the realization that a reliable system of PV is essential for the rational, safe, and cost-effective use of medicines in all countries. Participants were shown how to leverage resources between PV and PHPs.

Session 8: Let's Apply What We Have Learned

The objective of this session was to provide participants with a hands-on experience for getting information and filling out an ADR reporting form. For this session, participants were divided into two groups and asked to complete the FDA Suspected Adverse Reaction (SAR) form based on three case scenarios involving reports on lamivudine and hearing loss. After the exercise, participants shared their experiences.

All of the participants said it was their first time filling out the FDA SAR reporting form. They noted that, even though it seemed like a simple and straight forward task with minimum data required, they found it difficult to complete the form because of the limited information available. Limited available information is often a situation reporters and PV staff face in the real life practice of PV. Participants expressed that they have a better appreciation of what health care providers and PV staff go through when dealing with the issue of ADR reporting. It also helped them better understand the importance of quality data in PV.

Day 2 (October 19, 2017):

Day 2 of the training was mainly focused on sharing more about active surveillance and discussing causality assessment. The key learnings for the day were:

- The purpose of collecting data is to analyze and use the data for decision making. It is important to analyze the data from these reports. PV depends on careful analysis of data contained in reports received from health care providers.

- Causality assessment provides a logical and structured way to analyze causality/relationships between a drug-adverse reaction combination.

- Assessment of single case reports is necessary. Assessing case series is of great value in signal management.

- Active surveillance has been an entry point to public health for PV in recent times due to the recognized and growing need to monitor medicines used in PHPs, particularly with the advent of new or repurposed medicines.

- Effective and timely communication of safety issues helps health care providers provide clear, timely, and useful information to their patients and promotes patient safety and confidence in the regulatory system.

- Communicating safety information to patients and health care professionals is a public health responsibility.

Session 9: Any Active Surveillance Experience So Far?

This session aimed to share the Philippines experience with implementing any form of active surveillance in PV. Participants were asked to share any active surveillance experience they may have.

- **Nine-month treatment research and BDQ operational research –** The LCP-National Center for Pulmonary Research and FDA shared their cohort event monitoring experience for the nine-month research and BDQ research. The background, data flow, and challenges during the implementation were shared during the session. One of the major challenges was reported to be with data management due to poor internet connectivity at the collection sites.

- **Facilitator's question: How did you overcome the internet connection problem?** The central level visited the facilities on a regular basis to collect the study data.

Session 10: More on Active Surveillance

This session dealt with the topic of active surveillance in more detail covering the 5Ws and 1H (i.e., what, why, when, where, who, and how) of active surveillance. Participants learned the critical importance of clearly defining the purpose and objective of any active surveillance effort before embarking on it, as it requires a lot of resources for effective implementation. The various methods available for active surveillance were enumerated with their benefits and limitations. Participants were informed that the choice of method would depend largely on the objective(s) to be achieved.

Participants' Questions/Input

1) Does it mean that all new drugs should already have a black triangle?

No. The system would be overwhelmed if all new drugs automatically had a black triangle warning. The black triangle warning is imposed by a National Regulatory Authority (NRA) based on identified and potential risks identified during clinical trials.

2) Is aDSM a form of targeted spontaneous reporting?

The programmatic implementation of aDSM proposed for implementation by the Philippines—whereby only SAEs and selected adverse events of special interest (AESIs) will be monitored using the FDA SAR reporting form—is a form of targeted spontaneous reporting.

3) How long will aDSM last for BDQ?

If the length of implementation of the programmatic aDSM was not established in the protocol originally establishing the program, then it will likely depend on the analysis of the data obtained from BDQ operational research.

4) Is pharmacogenetics a form of active surveillance?

Pharmacogenetics is not active surveillance.

5) Among all methods discussed, which is a more applicable method?

For monitoring all medicines, spontaneous reporting is usually the first method to employ, especially if there is no specific objective in mind, beyond monitoring safety. Next steps would depend on a number of factors, including findings from data obtained from the spontaneous reporting system.

6) Who will do the analysis? What sorts of analysis need to be done?

Typically, the national PV center analyzes PV data. Where such capacity is not available in the PV center, the expertise of other stakeholders, such as members of the safety advisory committee, experts in the field of interest, and/or biostatisticians, could be called upon. Data analysis generally involves aggregating data to look for trends, determining relative or absolute risks, looking for associations and the strength of such associations, and looking for risk factors (e.g., by demographics, drug exposures).

Session 11: Causality Assessment

Session 11 aimed to acquaint participants with the principles of causality assessment and to provide them with a hands-on exercise for conducting causality assessment.

Causality assessment is evaluation of the likelihood that a medicine was the causative agent of an observed adverse reaction. Causality assessment is vital to ADR reporting and signal management and helps to determine whether the drug caused the reaction, identify possible risk factors, and determine how to reduce risk(s). Topics covered included:

- **Reporting of adverse events in PV –** PV is relatively new in many LMICs and to build a reporting culture, many national PV centers require health care providers to report all suspected reactions or clinical events, whether serious or not, and whether expected or unexpected.

- **Methods for causality assessment** – Several methods are available, but the WHO and Naranjo methods are the most commonly used. Causality assessment methods differ in many respects but share certain common features. Participants can use these methods when performing causality assessment. Causality assessment may be done on single case reports as well as on case series.

- **Basic principles of causality assessment –** Causality assessment in PV involves making a decision based on information regarding the temporal relationship between a drug exposure and the occurrence of a suspected ADR. Decisions on causality are also based on examining the extrinsic (i.e., data supporting involvement or otherwise of the drug) and intrinsic (i.e., data about the disease or patient) imputability. Thus, the following elements are typically evaluated during causality assessment: drug, patient, event, chronology, and re-challenge/de-challenge.

- **Required data elements** – For a report to be considered valid, four minimum data elements are required: an identifiable patient, a suspected medicine, an event, and an identifiable reporter. However, good quality adverse event reports containing more than the minimum required data elements will facilitate proper assessment of causality. Participants were taught to appreciate the value of good quality data in PV.

Causality Assessment Group Work Exercise

Participants worked in their previously assigned groups for this exercise. Each group was asked to conduct causality assessment of the previously discussed lamivudine and hearing loss cases, as well as the BDQ cases, using both the Naranjo and WHO scales.

After the breakout session, the groups presented their findings during a plenary session. Based on their presentations, the facilitator provided feedback to each group and made the following general comments.

- When conducting causality assessment, participants were urged not to make assumptions about data they do not have, and to never underestimate the value of the data they do have. Lab test results are objective evidence that should be used when available during causality assessment. Patient medical history is also important.

- Causality assessment cannot be done in a group of reactions. Assessment should be done for each ADR-drug combination.

- When assessing case series, the facilitator advised participants to look for similar reports from different countries, but not to be distracted by what cannot be found in the literature, as it might be an unexpected/undocumented reaction There may be a report where such a drug-ADR combination may have been mentioned even though the report may be inconclusive at the time.

- The aim of the exercise was not about getting the right answer, but rather exposing participants to important considerations when conducting causality assessments.

Day 3 (October 20, 2017)

Training on Day 3 was focused on signal management. Key take-away points were:

- Health care providers should always see PV as part of their professional, moral, and ethical responsibilities to their patients, and not something extra curricula.

- Detecting a signal is not confirmation that the medicine caused the reaction.

- Signals are hypotheses that need to be evaluated. Thus, accessing and assessing more information will help to either confirm or refute the hypotheses.

- More than one report is required to detect a signal.

- Clinical assessment of ADR case reports, either as individual case reports or case series, is the sine qua non of successful signal management.

- Confirmed signals should be shared with relevant stakeholders, including the marketing authorization holder.

Session 12: Providing Feedback to Reporters and Creating an ADR Reporting Culture

This session highlighted the importance of feedback as a stimulus for creating and nurturing an ADR reporting culture among health care providers. A reporting culture is not well developed among health care providers and consumers/patients, particularly in LMICs. PV centers must take great effort to cultivate a reporting culture among health care providers and consumers/patients for PV efforts to be successful.

This session kickstarted activities for Day 3 of the training. Participants reflected on and brainstormed the basic guidelines necessary for establishing and sustaining a positive reporting culture, including creative and effective ways for influencing improved health care practices and encouraging reporting of ADRs by health care providers. This included putting good and

workable policies in place, having the required structures to support the system, establishing an incentive scheme to reward and motivate reporters, and having regular feedback and communication.

Session 13: Communicating Safety Issues

Session 13 focused on communication as a means to building strong relationships between PV practitioners and their stakeholders. PV must creatively utilize this channel to foster strong relationships with stakeholders. While PV may not be the same as the business world, it must borrow communication tools that businesses have successfully employed to capture their audiences. PV is of immense importance to society, so those involved in PV must continually promote its importance through effective communication. Participants were shown various methods and basic principles of effective communication. They were also shown how these principles should be applied when communicating safety issues.

Exercises on Communication – Participants had guided discussions on how modern communication methods, particularly social media, are either hampering or enhancing effective communication. Participants were also asked to reflect on and discuss how PV in the Philippines can use modern communication methods/channels to make communicating safety issues more effective.

Session 14: Signal Detection/Signal Assessment

Session 14 covered signal management. In this session, participants learned that a statistical association is not a signal. Rather, signals are hypotheses that need to be tested, and identified signals should be shared with relevant stakeholders. Signals may need to be further assessed with appropriate pharmacoepidemiological studies and data. Regulatory action(s) should be taken only after signal confirmation. The topics covered in this session included:

- **Introduction to signals** – A signal is a possible causal relationship between an adverse event and a drug, which is previously unknown or incompletely documented. A signal management system involves signal generation, signal assessment, and risk management.

- **Signal detection/generation** – The process of searching spontaneous ADR data to identify hazards is known as signal generation. Signal generation can be done either quantitatively or qualitatively. Clinical assessment of ADR reports is sine qua non to signal generation.

- **Signal triaging** – Triaging is a method used to prioritize identified signals that should be investigated further. Signals are strengthened using clinical assessment of individual cases, assessment of aggregated data, and review of other data sources.

- **Number of reports required for generating signals** – More than one report is needed to generate a signal depending on quality of the information and seriousness of the event. However, there is no minimum on the number of reports required before a drug-related problem can be investigated.

- **Signal testing/analysis/assessment** – All generated signals must be subjected to further testing/assessment to confirm or refute the hypothesis that a possible causal relationship exists between the suspected medicine and the adverse event of interest.

Participants' Questions

1) Has there been legal action taken against Medicine Access Holders (MAHs) upon confirmation of signals? For any criminal case to stick, it must be established beyond reasonable doubt that there was deliberate intention on the part of the MAH to cause harm to people. It is highly unlikely that any MAH will deliberately set out to harm people with its products. Furthermore, NRA is also expected to perform due diligence and ensure that products are safe before they are licensed. However, MAHs and NRA may be charged for negligence if they are aware of a safety concern but do not take prompt action to prevent harm to patients, as was the case with Benfluorex (Mediator®) and the defunct French regulatory authority.

Session 15: Group Work on Signal Detection

Participants were provided several cases on decreased hearing with lamivudine and were asked to work in their respective groups to review the cases for the purpose of signal detection. Participants were also provided with an article from a WHO newsletter related to the cases and were advised to search for further information on lamivudine and hearing loss. The purpose of the exercise was to get participants to appreciate the level of information, clinical data assessment, and literature searching required to confirm a potential signal.

One participant from each group presented their group work along with their findings and recommendations. At the end of the session, the following general points were noted:

- Confirmed signals must be followed with risk minimization plans and prompt communication to relevant stakeholders.

- Reports that are assessed as being unlikely at the time of assessment should not be discarded, but should be archived for future references as new information that may preempt another look at such reports may become available in the future.

- Some potential signals may have potential public health impact(s) that require immediate action to forestall any harm to patients. In such case, conducting lengthy epidemiological studies may not be the ideal action to take. Alternative methods should be employed to obtain additional information to confirm or refute the signal.

Session 16: Wrap Up and Action Plan

The last session focused on wrapping up the training and drafting an action plan. The group felt that the preferred direction was to develop a joint action plan that would delineate activities to be undertaken after the training in order to address key issues in implementing active surveillance.

The action plan will also serve as guide for the facilitators to determine how far they have come in active surveillance implementation. Consequently, the group drafted and presented an action plan (Annex 5) for moving forward with active surveillance. The facilitator made some corrections and asked the group to share the corrected action plan to facilitate follow-up.

The facilitator shared a link to free online courses from Uppsala Monitoring Center-WHO on causality assessment and signal detection. She thanked the participants for their active participation and encouraged them to reach out to her with any questions or clarifications that may arise in the course of implementing PV in PHPs.

Key Facilitator's Observations

- Timely analysis of data collection through the PV system is essential for timely decision-making, including clinical/regulatory interventions, where indicated.

- Participants have a better understanding of the principles and scientific basis for several PV activities.

- Participants had first-hand experience on how to report ADRs and conduct causality assessment. They also understand the basics of signal generation.

- Participants feel more positive about their ability to carry out PV activities. They look forward to commencing full implementation, which will offer them the opportunity to learn more on the job.

All presentations for the training may be accessed from the Google drive at http://bit.ly/PVWorkshop2017. A Google account is required to access the files.

WORKSHOP EVALUATION

Instructor Evaluation summary gave the instructor a 4.8 rating out of the maximum of 5. This is a score of 96% on a scale of 100%. None of the participants gave an evaluation response of poor, very poor, or fair.

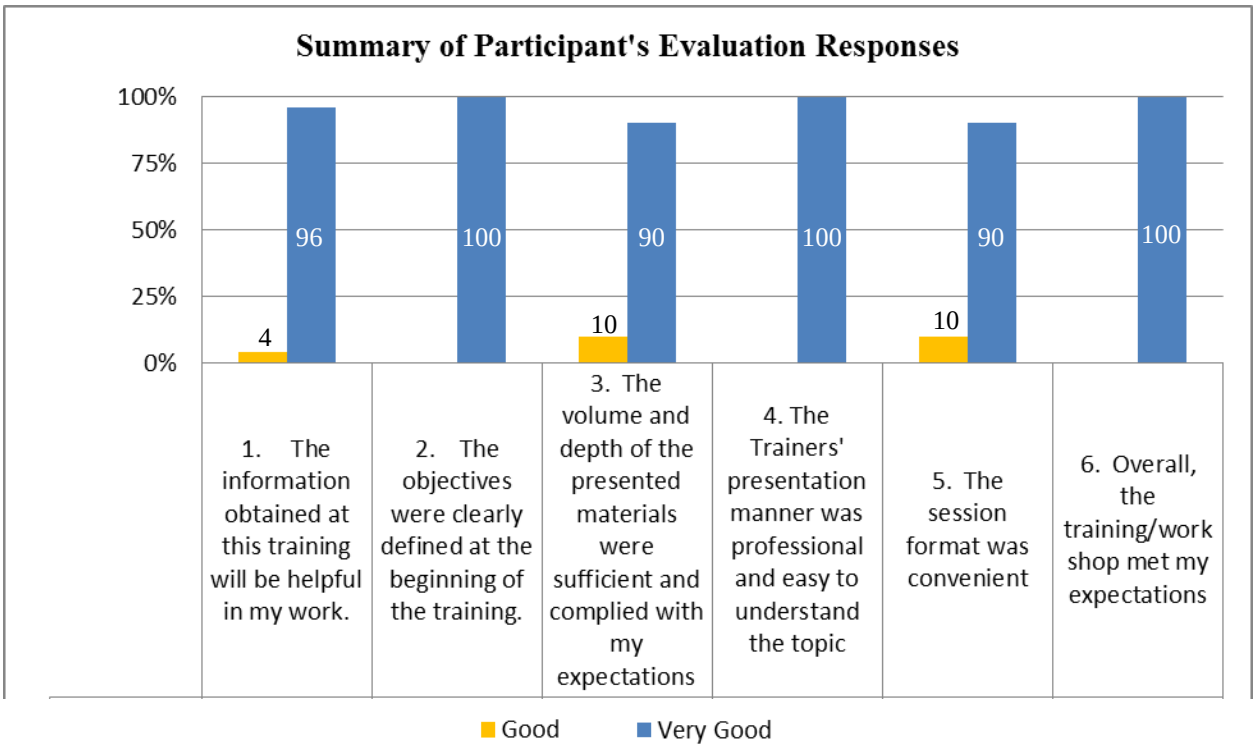

Figure 1. Summary of participants' evaluation responses

Participants' Observations

- The set up was good. Suggestively, a big room to maneuver and move would be nicer, but generally the workshop was informative.
- The training was very informative and not boring.
- I recommend the facilitator. She's very good. Three thumbs up!
- The facilitators and support are very good, too.
- Very informative. Great training!

RECOMMENDATIONS FOR NEXT STEPS

- Support the PD to effectively integrate PV in the TB program through one-on-one mentoring as a first step. This will prepare them for subsequent upscaling to other public health programs.

- FDA and PD will need to routinely assess all reports received in PV in order to detect signals.

- Provide support to central PD, NTP, and FDA to analyze data and share with the National PV Committee for review.

- Support PD and FDA to rejuvenate and capacitate their drug safety advisory committees to undertake causality assessment, which is critical to PV work.

- Develop mobile application to be used by health care providers and patients to alert them of SAE/AESI occurrences.

PHOTO GALLERY

The PV Training Participants and Facilitators during the second day of the training

ANNEX 1. WORKSHOP SESSIONS

Session 1: Overview of the Training and Participants' Expectations

Session 2: Why Does PV Matter?

- History of PV
- Aims and goals of PV
- Importance of PV in medicine lifecycle
- Role of PV in shaping the current regulatory landscape
- Strengthening other regulatory systems

Session 3: Key Terms in PV and What They Mean in Practice

- Key terms in PV and differences between some of the terms
- Know the risk factors for ADRs

Session 4: Scope of PV

- Exercise: Use of abbreviation in prescriptions
- Case Study: Medication errors video

Session 5: PV Methods

Session 6: Managing Data in PV

- Sources of PV data
- Quality of PV data
- Tools for managing PV data
- Benefit-risk analysis case study

Session 7: Integrating PV in PHP

- PV in PHPs: Why we need to collaborate
- PV in PHPs: How we collaborated (examples from other countries)
- Benefits of collaboration for PHPs

Session 8: Let's Apply What We Have Learned

Session 9: Any Active Surveillance So Far?

- 9 month treatment research and BDQ operational research

Session 10: More on Active Surveillance

Session 11: Causality Assessment

- Reporting of adverse events in PV
- Methods for causality assessment
- Basic principles of causality assessment
- Required data elements
- Causality assessment group work

Session 12: Developing an ADR Reporting Culture

Session 13: Communicating Safety Issues

- Exercises on communication

Session 14: Signal Detection/Signal Assessment

- Introduction to signals
- Signal detection/generation
- Signal triaging
- Number of reports required for generating signals
- Signal testing/analysis/assessment

Session 15: Group Work on Signal Detection

Session 16: Wrap Up and Action Plan

ANNEX 2. PARTICIPANTS LIST

Name	Organization
Patrice Jamie Cabasis	LCP
Maria Rhoda Cervas	LCP
Jo-an Tuy	LCP
Jeric Perey	NTP
Michael Junsay	PD
Jansen Lester Chan	PD
Julius Jocson	PD
Peter Emmans Palma	PD
Karina Sison	PD
Irene Florentino-Fariñas	PD
Leslee Lorna Ann De Jesus	FDA
Comfort Ogar	SIAPS
Chesa Desano	SIAPS
Kimmy Wee	SIAPS

ANNEX 3. EXPECTATIONS

What topics of special interest do you want to be discussed?	What would success look like after the training?	Why am I here? How will it help me in my daily tasks and responsibilities?
Signal detection and methods of surveillance	Going home with a smile and a bag full of knowledge in terms of PV.	I am here to learn and spearhead change in the current system of the country. This endeavor is meant to help the patients and health care providers in saving more lives through PV. It will help us better equip ourselves in preparing for change.
Causality assessment and signal detection	To make sure that the drugs downloaded in health facilities are safe and effective. As one of the PD staff, we will monitor all adverse events experienced by the patients, so this training is very crucial to execute the PD's function in PV.	I will be able to know how to do signal detection and causality assessment.
All about PV • Data gathering • Benefit-risk analysis • Spontaneous and active surveillance reporting • Causality • Signal detection and assessment • ADR, SAE, adverse events	Because, by agreement, PViMS will be transferred to PD and I will be the one who will manage the software/system. It is important for me to have the knowledge about PV.	We can do causality, signal detection, and others that I can't do before the training.
• Case studies on causality • Communicating safety issues • Signal assessment	Successful "back to work" application of all this lectures to our operation.	As part of our mandate in improving access to medicines. Monitoring the medicines being distributed to health facilities includes safety surveillance.
Conducting assessment	Participants will have more knowledge and confidence on conducting causality assessment.	I am here to learn and understand more about conducting causality assessment, because as a member of the research team, I am tasked to do initial assessment.
The specific activities done in practicing PV	We are here to learn more about PV. We want to improve the current practice of PV here in our country. This will help me because I can learn new things that I can apply in my actual work as a DSM officer.	If I have learned about the proper and right way of practicing PV and to apply it is my current work.
Know about drug safety monitoring	We learn more about PV as a newbie.	As part of the research team, it helps me in identifying AEs reported by the sites. Share knowledge on what I have learned in this training.

ANNEX 4. PRE- AND POST-ASSESSMENT RESULTS

	Pre (n=10)		**Post (n=10)**	
Mean	23	66%	28	80%
Median	23	66%	28	80%
Mode	20, 24, 26		26, 28, 30	
Range	16-29		23-32	

ANNEX 5. ACTION PLAN

#	Activity Description	Location	Person Responsible	Resources/Technical Support Needed	Timeline	Method of Verification of Completion (include targets where applicable)	Potential Barriers
1	Policy development for phamacovigilance for public health programs	PD	Mr. Michael Junsay	Funding for the writeshop and technical assistance provided by partner	March 2018	Approved administrative order	Change in leadership, political will
2	Policy dissemination and capacity building	Department of Health (NTP, LCP, and other DOH Programs) and FDA	Mr. Michael Junsay	-Technical assistance by DOH personnel -Printing of modules for monitoring and reporting tools	December 2019	Printout of modules; trained personnel	Insufficient manpower, conflict in schedule, fast turnover of health care providers
3	Data management and analysis	PD & FDA	PD- Program Implementation and Monitoring Unit Group & FDA	-Template for standardized data analysis for programmatic use -Internet connection for the respective offices -Dedicated server for PViMS -Technical assistance in first months of PV implementation	March 2018	Analyzed PV data reports	Variation of data set requirement for each public health programs, lack of manpower, no internet connection
4	Information Awareness (Information, Education and Communication (IEC) Campaign) of PV for public health pharmacist	PD & Regional Offices	RDs of respective RO and Director of PD	Funding for the production and placement of IEC materials	December 2018	IEC distributed to target sites	
5	Inclusion of PV in the curriculum of senior HS and allied health professional courses	PD, Department of Education (DepED), Commission on Higher Education (CHED), School/University Associations	PD Director and assigned staff, Secretary DepEd, CHED commissioner	Conduct of meetings	December 2018	PV included in the school curriculum	Increase in tuition fees
6	Require all hospitals to have an active PV system	PD, Health Facilities and Services Regulatory Bureau (HFSRB), Public Health Associate	All medical center chiefs, HFSRB Director, PD Director	PV report forms	December 2018	PV is included in the Regulatory Requirements; at least five PV report forms submitted	Non-compliance, violent reactions
7	Tap international development partners for sustainable funding of PV program implementation	PD, Bureau of International Health Cooperation	Mr. Michael Junsay	Terms of Reference for technical assistance	December 2018	TA provided; PV program implemented	Might not get approval

ANNEX 6. EVALUATION FORM

Criteria	Rating				
	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
1. The information obtained at this training will be helpful in my work.					
Comment:					
2. The objectives were clearly defined at the beginning of the training.					
Comment:					
3. The volume and depth of the presented materials were sufficient and complied with my expectations.					
Comment:					
4. The trainers' presentation manner was professional and easy to understand the topic.					
Comment:					
5. The session format was convenient.					
Comment:					
6. Overall, the training/workshop met my expectations.					
Comment:					