Implementing Active Pharmacovigilance and Cohort Event Monitoring for Multidrug-Resistant Tuberculosis Regimens in the Philippines

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About SIAPS

The goal of the Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Program is to ensure 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

active pharmacovigilance, cohort event monitoring, health systems strengthening, tuberculosis

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CONTENTS

ABBREVIATIONS AND ACRONYMS

ADR	adverse drug reaction
AE	adverse event
AO	administrative order
CDC	Centers for Disease Control and Prevention (United States)
CEM	cohort event monitoring
DCAT	Data Collection and Analysis Tool
DOH	Department of Health [Philippines]
DR-TB	drug-resistant TB
ERB	ethical review board
FDA	Food and Drug Administration [Philippines]
GDF	Global Drug Facility
Global Fund	Global Fund to Fight AIDS, Tuberculosis and Malaria
IMPACT	Innovations and Multisectoral Partnerships to Achieve Control of Tuberculosis
IRB	institutional review board
ITIS	Integrated Tuberculosis Information System
J&J	Janssen Pharmaceutical Companies of Johnson & Johnson
LCP	Lung Center of the Philippines
M&E	monitoring and evaluation
MDR-TB	multidrug-resistant tuberculosis
MSH	Management Sciences for Health
NCPAM	National Center for Pharmaceutical Access and Management
NDAC	National Drug Advisory Committee
NTP	National TB Program
NTRL	National TB Reference Laboratory
PBSP	Philippine Business for Social Progress
PIP	Policy Implementation Package
PMDT	programmatic management of DR-TB
PR	patient registry
PV	pharmacovigilance
SAE	serious adverse event
SIAPS	Systems for Improved Access to Pharmaceuticals and Services
SOP	standard operating procedure
SSASSA	Sentinel Site–Based Active Surveillance System for Anti-retroviral and Anti-TB
TASC	technical assistance support to countries
TB	tuberculosis
TRB	Technical Review Board
UMC	Uppsala Monitoring Center
USAID	United States Agency for International Development
WHO	World Health Organization
XDR	extensively drug resistant

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INTRODUCTION

The Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Program is a five-year cooperative agreement funded by the United States Agency for International Development (USAID) and implemented by Management Sciences for Health (MSH). The goal of SIAPS is to improve the availability of quality pharmaceutical products and effective pharmaceutical services through strengthening pharmaceutical systems.

In the Philippines, SIAPS supports the Philippines Department of Health (DOH) initiatives to reduce the TB disease burden through a systems approach to strengthening pharmaceutical management and services. SIAPS works with the National TB Program (NTP), National TB Reference Laboratory (NTRL), Food and Drug Administration (FDA), and other partners to build their capacity in pharmaceutical management.

As part of this support, USAID Philippines requested the technical assistance and services of SIAPS to conduct a pharmacovigilance (PV) workshop and provide technical assistance to the NTP and the FDA to strengthen their PV system.

BACKGROUND

NTP is preparing to introduce the nine-month regimen (short regimen) and use of bedaquiline for treating patients who have tuberculosis that is resistant to the first-line multidrug-resistant tuberculosis (MDR-TB) regimen, beginning with a research-oriented pilot phase. The most appropriate approach to assess the safety of these regimens is through active surveillance methods, which include cohort event monitoring (CEM) for short regimen protocols and bedaquiline-containing regimens, and a patient registry for bedaquiline use.

The recent SIAPS assessment of the Philippine Pharmacovigilance System[1] revealed that the weakest component (function) at both national pharmacovigilance (PV) unit and public health program levels relates to risk assessment and evaluation. Although safety signals of potential TB medicines may be generated through the current voluntary adverse drug reaction (ADR) reporting system, no program has experience in conducting a proactive approach for detection and evaluation of safety signals. Other weak system components involve risk management and risk communication and coordination of systems, structures, and stakeholders.

The September 2014 joint World Health Organization (WHO) and SIAPS mission[2] on the use of PV to support management of MDR-TB highlighted the need for active surveillance when implementing the short regimen and bedaquiline protocols. Currently medicine safety monitoring is done on the basis of voluntary (spontaneous) reporting of suspected ADRs, but programs have insufficient capacity for performing causality assessments of ADR reports and determining risks. Programs lack experience with proactive approaches such as CEM and patient registries, two methods that are relevant for safety monitoring during implementation of any new treatment regimen. Developing capacity to apply active surveillance methods for monitoring the safety of TB medicines is expected to result in a strengthened national PV system.

Antonia Kwiecien (SIAPS Senior Technical Advisor) and Syed Rizwanuddin Ahmad (SIAPS Consultant) traveled to Manila in March 2015. They conducted a workshop and provided technical assistance for NTP and FDA to accomplish the following:

- Strengthen the DOH and the FDA PV system.
- Build technical capacity of the DOH's NTP to conduct active surveillance of the nine-month regimen protocol and the introduction of bedaquiline-containing regimen.

[1] J. C. B. Marcelo, "Safety of Medicinal Products in the Philippines: Assessment of the Pharmacovigilance System and Its Performance" (submitted to USAID by the SIAPS program, Management Sciences for Health, Arlington, VA, January 2013).

[2] D. Lee and R. Lopert, "Pharmacovigilance to Support Management of MDR-TB in the Philippines" (trip report from Manila, Philippines, SIAPS program, Management Sciences for Health, Arlington, VA, September 15–19, 2014).

ACTIVITIES

During the first two days of the March visit, Kwiecien and Ahmad met with the FDA staff members to provide information, knowledge resources, and practical exercises to develop their medicine safety data analysis skills for effective decision making. The group also discussed approaches for strengthening the national PV system, including interdisciplinary collaboration, roles, and responsibilities and for implementing approaches and mechanisms. The proceedings agenda is attached in annex A.

During the final three days of the visit, Kwiecien and Ahmad facilitated a workshop for program managers, partners, staff members, and other stakeholders participating in the operations research studies for the nine-month regimen and introduction of bedaquiline. The workshop focused on PV activities and action planning for strengthening PV for TB treatment. The agenda is attached in annex B.

A participant list for the FDA PV system–strengthening workshop and the stakeholders' protocol-specific PV workshop is attached in annex C.

A summary of participant evaluations is attached in annex D.

Genevieve David was appointed as reporter for the week's proceedings. The week's proceedings follow.

Additionally, two parallel meetings were organized. The first meeting was Thursday evening with a group from the National Institutes of Health, University of the Philippines–Manila, to discuss the role of the National Institutes of Health in the national PV system, as well as a mobile app that can be adapted to report adverse events (AEs).

The second meeting was Friday afternoon with representatives from Janssen Pharmaceutical Companies of Johnson & Johnson (J&J) Philippines to discuss their role in the national implementation of bedaquiline.

Pharmacovigilance Systems Strengthening Proceedings

Day 1, Monday, March 16, 2015

Introduction (FDA)	Introduce nine-month regimen, including regimen and novel drugs for MDR-TB, especially bedaquiline and delamanid
	WHO requires CEM; FDA is still in the process of strengthening its capacity. It still uses spontaneous reporting and has no experience yet with active surveillance.
Objective of training (SIAPS)	Provide learning resources, practical exercises, new skills for using data for decision making that focus on TB yet are applicable to other settings, PV systems strengthening with interdisciplinary collaboration and identification of roles and responsibilities, various ways to gather and disseminate information, introduction to action planning, update on global TB conference, and presentation of Swaziland experience

Key Themes	Experts (SIAPS)	FDA and Other Responses to Experts' Input
SIAPS Global TB Conference, Bangkok Update		
	Challenges in the Philippines Need for revision of PV legislation Absence of National Drug Advisory Committee Underreporting of ADRs Gaps in links with various sectors Active surveillance that is not yet fully functional, mostly spontaneous reporting	
	Solutions Revise existing PV policies Reestablish the National Drug Advisory Committee Address underreporting Engage various sectors in PV activities Build capacity for active surveillance Establish structure and capacity of PV centers and active surveillance system	
	PV activities done in the Philippines Created National Adverse Drug Reaction Advisory Committee in 1994 Developed a National Policy and Program on Pharmacovigilance (AO 2011-0009) Institutionalized ADR reporting in 1997	

Key Themes	Experts (SIAPS)	FDA and Other Responses to Experts' Input
	<u>Approaches to address challenges</u> Strengthen governance— • Revise administrative order (AO) on PV Strengthen capacity on PV— • Reestablish the National Adverse Drug Reaction Advisory Committee (1994) • Enhance capacity for causality assessment and decision making • Strengthen risk assessment and evaluation, especially on active surveillance Increase stakeholder collaboration and engagement— • Strengthen the engagement of different sectors and stakeholders in PV activities Increase advocacy and communication strategies— • Hold public hearings and forums, publish bulletins • Publish medicine safety bulletins • Review existing reporting tools and role of FDA, explore options to improve ADR reporting and data management • Plan information reporting to prevent duplication	
	<u>PV achievements in the Philippines</u> Joined the WHO Collaborating Center for Drug Monitoring in 1995 and became the 42nd member Developed policies and structure to implement TB activities Developed a national database for ADR reports Put in place spontaneous ADR reporting Enacted communication strategies	
	<u>Way forward</u> Enact and support PV Strengthen capacity for active surveillance	

Key Themes	Experts (SIAPS)	FDA and Other Responses to Experts' Input
	Strengthen AE reporting from clinical trials conducted in the country Update existing regulations to align with international standards and practices Intensify post-market surveillance through compliance monitoring and PV	
	Other countries Perform active surveillance Perform causality assessment at health-facility level	
Reporting system	Philippines database A reporting system is important for new drugs in the market, especially with unlabled adverse events Lack of a reporting system can create problems in the long run Public can lose confidence in the system or public health program Each country is different Each product is used differently Different individuals respond differently Certain AEs can be seen only in the Philippines because of genetic characteristics, making a reporting system important With vigilance, something unique can be found in the Philippines not seen anywhere else	
	Challenges in the Philippines Use analysis, assessment, and data and reports for decision making and regulatory action Address underreporting	
	Reasons health care providers would report Enough awareness to identify and suspect AEs System in place through which physicians, pharmacists, nurses, and other health care providers can report Health facilities with access to forms Time and incentives	
	Are companies mandated to report? Are health facilities?	Yes; FDA evaluates reports to make sure they comply with the criteria of the WHO Uppsala Monitoring Center (UMC)

Key Themes	Experts (SIAPS)	FDA and Other Responses to Experts' Input
	Suggested examples for the Philippines MedWatch unit in the US FDA, with the main objective to educate and train health care professionals and consumers about the importance of reporting Use of a booth and presentations at scientific meetings of professional associations to educate about existence of reporting programs Publication in journals of various professional societies, such as Acta Medica Philippina, and in newsletters and bulletins Knowledge, awareness, and practice of health care professionals and consumers regarding ADR reporting	
PV system	Sources of information Published literature, which covers major safety issues that must be monitored, and resulting media reports and FDA responses Reports Decisions made by stringent agencies, such as US FDA, European Medicines Agency (but these have limitations for new drugs, especially to treat certain diseases like TB; for example, bedaquiline is conditionally approved by FDA, but not much is known about how it is used and its AEs) All other data streams, not just spontaneous reports	
	Many players needed for a PV system to work	
	An advisory committee, although dependent on final decision by FDA on the basis of its assessment and review of data, especially on new drugs, not just from the spontaneous reporting system	Still refining the system procedures with the use of VigiFlow
	Communication plan to accompany a spontaneous reporting system	
	Risk management plan that includes signed and informed consent about risk for AE, including AE not yet known; certain prescribers; patient criteria	Risk management plan is now a requirement for authorization holders and part of licensing requirements of FDA, but it is only beginning; FDA not yet fully trained
Elements of action planning	Map of sources of PV data, where the data goes, who collects data, where to access the reports, and how can they be obtained (streamline); other missing elements that must be added; sustainability	
	Political will and champion of PV system	
	TB point person, advisory committee for AE (a group ultimately responsible for looking at all data and making recommendations to various groups, such as a pharma company, the public, and NTP and HIV and AIDS program)	Web-based PV system for ADRs is not accessible to the PV team; accessible only to the IT person, but it was created for consumers

Key Themes	Experts (SIAPS)	FDA and Other Responses to Experts' Input
	Method for getting human resources to the FDA level Other challenges to accomplishing all the goals and activities we talk about today	
	Mechanism so that data collected in the NTP database is imported in the FDA system	Philippines FDA does not receive reports from the program; NTP is just managing reports
	A patient registry to link information from TB sites to national sites and health facilities Means to centralize information from various public health programs (HIV, diabetes, etc.) starting with TB Modification of current data collection forms to capture all AEs, not only ADRs	SIAPS (Muñez): There is a plan to transition to an electronic system in health facilities; this patient registry portion has to be streamlined; health facilities also encounter a lot of AEs, and SIAPS also has an approach for active surveillance

Day 2, Tuesday, March 17, 2015

Activities	Key Points (MSH)	FDA Responses to Experts' Input and Questions
Presentation and Discussion: Cohort Event Monitoring (CEM) (Ahmad)		None
Presentation and Discussion: CEM for TB (Kwiecien)		
	Policy Implementation Package (PIP) for new TB drug introduction; monitoring and evaluation of new drugs and regimens including PV and drug resistance surveillance; nine key steps for CEM	None
Presentation and Discussion: Patient Registries (Ahmad)		
	Emphasized that the role of FDA is important and can make things happen; Philippine FDA can have a leadership role	None
	Sample requirements for the Centers for Disease Control and Prevention (CDC) patient registry for bedaquiline can be found in clinicaltrials.gov	None
	If a pharmaceutical company maintains a registry, anything can happen; pharma companies usually maintain single-product registries; joint registries are maintained by third parties (Ahmad)	
	In the United States, patient registry will be maintained by J&J; in Philippines, it can be maintained by the Global Drug Facility (GDF), but this still has to be worked out; it will be more or less similar across countries; real-time data may be provided to J&J	
	Purpose of the registry: • Surveillance for AEs • Tracking patients Patient information includes demographics, patient outcomes, ADR, lab test results, use of	

Activities	Key Points (MSH)	FDA Responses to Experts' Input and Questions
	other medicines, and co-morbid conditions. Baseline information is important. Monitoring will include resistance to bedaquiline. No drug sensitivity testing is going on in the Philippines. GDF providing the drug will find a lab and provide means and resources to bring specimens to the lab. Objective is to prevent the recipient from developing further resistance.	
Advisory Committee (discussion)	Suggested members: NTP (leader of study), Lung Center of the Philippines (LCP), implementer of study as principal investigator, key players in CEM protocol, Technical Assistance Support to Countries (TASC), USAID; Philippine Business for Social Progress (PBSP) as funder and Global Fund as principal recipient; Research Institute and Tropical Medicine for laboratory site; SIAPS and Innovations and Multisectoral Partnerships to Achieve Control of Tuberculosis (IMPACT)	What are the systems and procedures for establishing CEM for TB?
	The advisory committee should focus on TB, with one advisory committee per project. Members of the National Advisory Committee can be selected to focus on TB.	
	How often should members meet? At the beginning of CEM, the committee should meet regularly to develop a system and procedure. Frequency depends on when the program plans to start, meeting more frequently depending on the time line. (The target date was March 2; participants are still waiting for medicine dossier.) Can be monthly, quarterly, depending on how long, then on an ad hoc basis.	
	Can reports be ongoing for X number of days if AE happens all the time, but with data entered every day? Put start and end date in forms, indicating severity during that period and including the characteristic (e.g., blood in vomitus).	Should health facilities report AEs daily?
	Forms designed by the FDA, CDC, and WHO will be modified.	
Case Discussion: Causality Assessment (Ahmad)		
	Case examples for exenatide and pancreatitis show how to deal with missing data through causality assessment, biological plausibility, any other explanations coming from other drugs or from the disease condition itself, other sources of information.	
	What kind of regulatory action can be made based on PV data? Actions include (a) publish a letter in the *New England Journal of Medicine*, (b) maintain status quo while still evaluating data and monitoring the event, (c) strengthen labeling depending on severity of event, (d) perform a risk management intervention, and (e) recommend as second line rather than first line medicines (the European Union can temporarily suspend a product but not the United States).	Is there guidance for action?
	Educate medical students about issues related to PV; use MedWatch, the FDA's safety	

Activities	**Key Points (MSH)**	**FDA Responses to Experts' Input and Questions**
	information and adverse event reporting program, and state why reporting is important. Develop a culture of reporting; people are not even aware that a system is in place.	
Final inputs from Kwiecien	Use technical assistance for development of instructor's guide for implementing pre-service and in-service curriculum on PV in Vietnam, which can be adapted in other settings (link in WHO website). http://apps.who.int/medicinedocs/en/d/Js21804en/ Components are the following— • Training for health care professionals and postgraduate students in Hanoi University of Pharmacy • Instruction in how to set up a PV system in hospital to do causality assessment for antiretroviral, TB, and malaria program	None
	Next steps: Action plan (components and mechanisms for spontaneous reporting, resources, and roles and responsibilities; CEM for nine-month regimen • Standard operating procedures (SOPs) • Practical exercises • Development of data analysis skills	
	Interdisciplinary collaboration with all stakeholders, with the message for FDA: FDA can take the lead on industry, professional societies, other public health disciplines and programs, and patient advocacy groups (Ahmad)	

Day 3, Wednesday, March 18, 2015

Introductions	
Overview of agenda (Kwiecien) 1. PV requirements of nine-month protocol 2. PV requirements for introducing bedaquiline in the Philippines 3. Accurate record keeping with practical exercise 4. Accurate and timely data collection and why it's important in CEM with practical exercise 5. Data collection and monitoring of cohort events 6. Swaziland experience 7. SOPs and action plan development and overview 8. Causality analysis 9. Data and safety monitoring 10. SOP for short regimen protocol for introducing bedaquiline in the Philippines	
Objectives: Develop CEM skills for accessing sources of information; do practical exercises.	
Outputs: SOPs and action plan	
Presentation and Discussion: "Feasibility, Effectiveness, and Safety of Nine-Month Future Regimen for MDR-TB in the Philippines, Operational Research Protocol" Section 6: Safety Monitoring (Ahmad)	
Key Point/Content	**Inputs/Questions from Participants**
<u>Main points</u> • Consider what is serious in the eyes of the patient • Be able to justify your judgment because a third party may question your causality assessment • Have baseline values for severity in causality assessment • Note possible attributions and all information in patient chart before making a judgment • Note limitations of spontaneous reporting system for ADR in Philippines: it has limited information and cannot be used solely for causality assessment • Use different criteria to classify	On criteria for seriousness of disability, seriousness depends on how patient reacts Laboratory values may fall outside the normal range, but physician judgment is not clinically significant (i.e., hypokalemia) Naranjo ADR probability scale criteria were discussed during the training with the nine-month regimen but not included in protocol.

case as serious or nonserious, a scale that is common in ADR	
Presentation and Discussion: Source Documentation (Kwiecien)	
Summary of group activity findings – Do our documents meet ALCOA requirements?	
Attributable • Signature is not dated • Not all entries are signed and source cannot be traced (because this is not required in routine program implementation), but there are entries that are supposed to be signed • Not all doctors sign their names	
Legible • Handwriting unreadable, can't be deciphered • There are erasures and superimpositions	
Contemporaneous • Rows/columns are not used correctly • The original document was not photocopied completely/part of the page is missing	
Original • Could not ascertain originality without source document	
Accuracy • Laboratory tests don't have a source document	
Presentation and Discussion: Introducing Bedaquiline (Kwiecien)	
<u>Key points</u> • Six elements of PIP (focus on Element Three)	
Element Three Part I: Pharmacovigilance	• Nine key steps for introducing bedaquiline in country • Good documentation of trainings to be conducted
<u>Part II: Drug-resistance surveillance</u> Incorporate PIP in the National Implementation Plan for bedaquiline in the Philippines— • Take drug sensitivity testing into account in planning. • Consider possible AE of other drugs, if planning to enroll co-infected participants.	On establishing a national CEM committee, consider the following— • LCP: CEM is at the level of FDA. It is different from the Scientific Committee, which is an effort of WHO, local, and national partners. • FDA: The plan is to create a National Drug Advisory Committee (NDAC) that is not necessarily focused on CEM. • LCP: Since NDAC is generic, ad hoc members from the committee can be used**.**

• Consider preexisting drug interactions; hence, develop an interactive essential medicines list.	
Bring parties together again on a specific training for PV. Put all these points, including roles and responsibilities, in the action plan and SOPs.	LCP: the forms for nine-month regimen and bedaquiline are the same. The plan needs to look at the PIP to see if changes in forms are needed. The forms for implementing the nine-month regimen are the same as the forms for the bedaquiline regiment.
Obtain ethical approval, because bedaquiline has been tested on fewer than 500 patients so data are still limited.	PBSP: Are the nine key steps standard? Is ethical approval really needed for bedaquiline when it is already part of the nine-month regimen and we are working with the same forms?
Presentation and Discussion: Good Documentation Practice (Kwiecien)	
Key points— • Signature log • SOPs on electronic records	LCP: Protocols for both TRB and ERB and documentation plan are in place. Implementation plan is not yet in place.
Group Activity on Good Documentation Practice	
ALCOA	<u>Attributable</u> Signature is not dated. Not all entries are signed and source cannot be traced (because this is not required in routine program implementation), but some entries are supposed to be signed. Not all doctors sign their names.
	<u>Legible</u> Handwriting is unreadable and can't be deciphered. The forms contain erasures and superimpositions.
	<u>Contemporaneous</u> Rows and columns are not used correctly. The original document was not photocopied completely or part of the page is missing.
	<u>Original</u> Could not ascertain originality without the source document.
	<u>Accurate</u> Laboratory tests don't have a source document.

Presentation and Discussion: Accurate and Timely Data Collection (Ahmad)	
Is there a provision that if you leave something blank, you cannot proceed?	LCP: There is a plan that if you leave something blank in the form, you cannot proceed.
If the form does not have a comments page, how do you capture the information in a database? The good option is to put in a comments section rather than use separate forms. Narrative is important in causality assessment.	AE forms are filled out by doctors and nurses. The forms do not have a comments page, but additional information can be obtained from the source document. The research committee that planned this form decided to maintain it as is and have medical staff elaborately describe the serious AEs in a separate form. For nonserious AEs, the minimum is enough. Clinicians are still expected to provide their assessment in a patient progress report.
The user should be able to indicate the number of entries in each page.	One page can accommodate only two AEs. All others are entered in a separate document in the field manual.
Because this report is a study, there are no foreign reports to rely on, so investigate how to report to FDA as well. What about pharma company?	FDA has specific forms for spontaneous reporting. It is still using that method for CEM.
	LCP: MDR-TB is expected to have many serious AEs, so the FDA spontaneous report form is difficult to use.
Recap (Mangao)	
What did you find most striking	FDA: Causality assessment, documentation practice. ALCOA was new.
Dossier will be provided. Linezolid is not yet approved by GF for procurement; there is a need to provide supporting documentation.	LCP: ALCOA was very useful and important for documentation. Forms provide latest data and keep data organized. We have a deep understanding of CEM, but our knowledge of PV is limited. With the introduction of bedaquiline to treat pre-XDR (extensively drug resistant) or XDR-TB cases, background regimens are important because an issue with FDA is they tend to use off-label drugs for XDR-TB cases. The nine steps were technically comprehensive, including ethical approval, because the plan is to introduce bedaquiline under programmatic conditions, but NTP has to decide.
	National Center for Pharmaceutical Access and Management (NCPAM): Everything is new, commenter is not sure if NCPAM has big involvement in cohort, but it has new ideas to incorporate TB in NCPAM program.
	LCP: PIP, monitoring and evaluation (M&E) for PV, and need for ethical approval for bedaquiline that was not in the original plan
	PBSP: More definite and clearer understanding of PV. Directions were validated, although without in-depth knowledge of PV yet.
	TB IMPACT: Increase objectivity in clinical trial.

End-of-Session Feedback
Training is successful. Causality assessment was especially useful. Still have a lot of things to do. Very privileged to have FDA.

Day 4, Thursday, March 19, 2015

Key Points/Content	**Inputs and Questions from Participants**
Morning Reflection and Leveling of Expectations (Mangao)	
Questions are as follows— 1. What topics of special interest do you want discussed?	Causality assessment, systematic causal analysis, presentation of the VigiFlow, Swaziland experience, application of SSASSA and Data Collection and Analysis Tool (DCAT) in Philippines
2. What do you want to do and experience in the next two days?	• Group activities, discussions, initial plans of FDA on active surveillance; discussions on each organization's (FDA, NTP, NCPAM, etc.) duties and responsibilities in CEM; specific roles and actions in cases of risk; more wake-up calls to be more meticulous, as shown by ALCOA, which was striking
3. What would success look like after training?	• Strengthened PV system in the Philippines, everyone equipped to practice PV, everyone encouraging colleagues to report AE, standardized forms for ADR/AE, strong collaboration with the FDA, integration of PV in NTP, how to do on-site CEM and causal assessment
Presentation: World TB Day Announcement—Bedaquiline Donation Program Action Planning and SOPs for CEM (Kwiecien)	
<u>Things to consider in action planning</u> • WHO and GF recommendations • National PV system • Options for risk management • Identification of problems regarding quality in medicines • National PV Advisory Committee (for short-regimen and bedaquiline introduction) • Clear communication strategy	DOH received notice from USAID that the Philippines will receive free bedaquiline from a newly announced donation program.
J&J is not insisting on full CEM because it is too complex, although WHO is still going to recommend it. However,	UMC database (VigiBase) can be manipulated as a national database to capture Philippine data.

Key Points/Content	Inputs and Questions from Participants
participants can decide whether to take it as recommendation or regulation. J&J requires only that serious AEs from bedaquiline be reported, including treatment course interruptions, life- threatening events, or death.	
Causality assessment is not required for bedaquiline but must be done for short-regimen protocol to strengthen PV skills.	
Discussion: World TB Day Announcement—Bedaquiline Donation Program Action Planning and SOPs for CEM (Muñez)	
Toxicity criteria Bedaquiline form ADR/AE form for bedaquiline	
Forms for CEM have already been agreed on, including causality assessment.	It is better, more efficient, and easier for staff if the PV form is synchronized with the bedaquiline form. There is a need to compare forms and see how they can be synchronized; the content of the forms is similar.
J&J has much to gain from a regulatory perspective. J&J's requirements and input are minimal.	The PV system in the country needs to be strengthened to have capacity in reviewing and deciding on the forms. What is the plan (i.e., memorandum of understanding, donation) in introducing bedaquiline in the country? The plan depends on the decision and commitment made by bosses in Hanoi.
Requirements are set at the global level (i.e., WHO and USAID). Everything will go through the GDF.	The cohort study depends more on determination of AE than efficacy. NTP, FDA, and WHO have different CEM requirements. FDA performs only spontaneous reporting of AE, the PV system is being strengthened through CEM, and NTP and FDA have to collaborate.
Unfortunately, SIAPS and GDF were not involved in the discussions regarding the requirements for implementing CEM and introducing new medicines. Because the FDA is the regulatory authority for the PV system, they will decide what needs to be done regarding introducing bedaquiline and new regimens for TB. It is for the country to decide what is best. WHO and J&J can recommend, but cannot overrule. Further stakeholder discussions are needed.	WHO has recommendations when introducing new first- or second-line drugs— • Strong PV system • Operations research • Independent study Draft recommendations for harmonizing the methods for collection, sharing, analysis, interpretation, and communication of information in CEM of MDR-TB are available in the Hanoi PV workshop report.

Key Points/Content	**Inputs and Questions from Participants**
Presentation and Discussion: "Active Surveillance: The Swaziland Experience" (Ahmad)	
• Developed detailed reports from the SSASSA activity reports • Developed articles on the preliminary findings compared with findings from other countries • Disseminated recommendations of the advisory committee and the implications for treatment sites Periodic meetings were held to obtain feedback and revise data collection forms. People also felt they were part of the team, which can reduce turnover rate of trained staff.	How were data used? What is the feasibility and acceptability of the system? Was the protocol followed? What is the acceptability to stakeholders?
Presentation and Discussion: Causality Assessment and Case Study: "Exenatide and Pancreatitis" (Ahmad)	
Feedback on causality assessment by Rizwan Ahmad	Case work on causality assessment per group
Group Activity: Case Causality Assessments (Ahmad)	
Can use either Niranjo or WHO scales Questions are as follows— 1. Do you have enough information to make an evidence-based causality assessment? 2. What information is missing? 3. On the basis of your assessment, will you a. stop the drug? b. continue? 4. If you continue, will you take any risk management interventions? If yes, what will those be?	Feedback is as follows— • Tools make causality assessment systematic and objective. • Many criteria are used (WHO, Bradford-Hill, Naranjo) that might lead to discrepancies. Hence, there should be agreement on the choice of one tool for standardization.
Case 1: QT prolongation in a TB patient Case 2: Hepatotoxicity in a TB patient Case 3: Hearing loss in a TB patient Case 4: Linezolid-induced pure red blood cell aplasia	
A study should use one format for data collection purposes. In Swaziland, it was found that some questions in the DCAT were not relevant in the setting, so a modified version was created.	

Key Points/Content		**Inputs and Questions from Participants**
Presentation and Discussion: Basic Concepts in Signal Detection (Ahmad)		
End-of-Day Reflection (Mangao)		
Answers to expectations	The group asked FDA to make a presentation on VigiFlow Antonia Kwiecien can make a presentation on SSASSA and DCAT. Experiences will be incorporated in action planning; roles and responsibilities will be included in SOPs. Ideas of success should be kept in mind as the outcome of training.	• VigiFlow was not presented; SSASSA and DCAT were only mentioned. • Activities provided enough experience. • SOPs by the group can be incorporated in the draft field manual of LCP.
Suggested Readings	*A Practical Handbook for the Pharmacovigilance of Medicines for the Treatment of Tuberculosis: Enhancing the Safety of the TB Patient* (WHO, 2012) Meeting report of Hanoi workshop	

Day 5, Friday, March 20, 2015

Key Points/Content	**Inputs/Questions from Participants**
Question and Answer Recap (Mangao)	
Presentation of Revised Agenda	
1. VigiFlow 2. Data and safety monitoring 3. SSASSA and DCAT 4. SOPs and action planning 5. Continuation of SOPs and action planning 6. End-of-day reflection 7. Closing	
Presentation and Discussion: VigiFlow (Lirasan, FDA)	
FDA has no experience yet in checking authenticity of reports, but it analyzes reports before information goes to VigiBase.	There might be issues of authenticity of AE reports. How does FDA validate the authenticity of reports?

Key Points/Content	Inputs/Questions from Participants
Paper and Web-based reporting occurs in collaboration with UMC, but it is not yet recommended because data are not shared by the information technology participants. Online ADR reporting can be used.	NCPAM: FDA looks only at reports. It does not look at who is reporting or at the screening committee. NCPAM suggested to help at this level.
Focusing on ADR reporting is difficult because of insufficient staff; submission to Uppsala is quarterly.	Not all physicians are aware of ADR reporting.
Who monitors data and safety in the Philippines? The Philippines has a unique situation because even the drug does not come directly from the company. Patient and FDA representatives are suggested to be included.	WHO will organize the data and safety monitoring as a scientific committee. The committee is only a discussion so far and is not a role for a pharmaceutical company.
	WHO requires that those conducting operational research on the nine-month treatment regimen must be monitored by an independent body or scientific committee (as prescribed by WHO) before implementing research. The WHO country office takes the lead in organizing, supporting, and maintaining this body. Names were proposed, but WHO will still screen, invite, and talk about arrangements (should be done by Woo-Jin Lew, of the WHO country office): how the body operates, its composition, and its functions; how to treat and analyze data; where to submit data; and how the body would relate to NTP and LCP. Expectations and terms of reference should be written clearly so those involved will be on the same page. Committee is composed of two local and four or five international experts (academic, pharmacologist, epidemiologist, private practitioner, and patient representative were not recommended). The question is how this committee's function relates to FDA.
	WHO (Woo- Jin): The body will meet once a year.
Presentation and Discussion: "PV Training: SIAPS Tools–SSASSA and DCAT" (Kwiecien)	
The current version of SSASSA and DCAT are being combined into a single web-based platform that should be ready by October 2015.	
Presentation of Rough Draft of SOP: "Active Surveillance: CEM for New Medicines and Novel Regimens in the Philippines" (Muñez)	
Refer to draft document presented in Annex G. SOP	
Develop an SOP on active surveillance and CEM for the nine-month regimen and bedaquiline, specific for TB and future research on TB medicines and regimens.	LCP: This SOP should be generic. DOH FDA probably will be constant in its role in PV, but LCP being the principal investigator for NTP may change. We may need to enter generic roles and not specify whether LCP and other institutions will still apply in the case of other researchers. Who will be the user?
This is the first time that FDA has collaborated with the program this closely to build active	The objective should be to define the SOP model specifically for the PV of the nine-month and bedaquiline regimens with the aim of later developing a generic guide for other new

Key Points/Content	Inputs/Questions from Participants
surveillance. It is a new undertaking for everyone.	medicines. If criteria are met (feasible, acceptable, and efficient) and this SOP is institutionalized, generic guidelines can be developed. Other future drugs will have a different setup. LCP can be removed later; it is currently a research arm. LCP will be one of the health care providers that report using generic guidelines; reports will no longer pass through LCP. Hence, the title must be changed. When this transition is finished, we will provide recommendations to FDA, which does not yet have CEM experience.
	Is there a regional and central consilium? Who are these people? Not all regional consilium will participate in the study. But as long as a consilium is deciding how to implement the protocols at a site, it should be oriented to the study.
They only do management of ADRs and case management.	Is a consilium of doctors and heads of treatment centers reviewing safety reports?
	Roles and responsibilities will be discussed when the process is in place.
	NDAC will be convening quarterly, and FDA submits reports to Uppsala quarterly. What then is the use of reporting within seven days if all these reports will be analyzed on a quarterly basis? (Response: Serious adverse events will be analyzed immediately. Investigation will not have to wait for quarterly meeting.) Facilities will be pressured to report immediately but will get feedback quarterly. FDA will evaluate reports for investigation or regulatory action. FDA will not wait for the advisory committee to act: action will be on the level of FDA. The advisory committee will be convened only when enough evidence has been gathered and if a need to stop the drug or to revise the label is shown.
	The outputs of health facilities need to be specified. Reporting should not stop with the program. Facilities should submit a consolidated report to LCP, not just pass on individual reports to a higher level without analysis. We propose an FDA form to provide uniform feedback. What is not clear is what happens to reports after they are submitted to FDA. The process is still being tested for FDA.
	FDA currently provides feedback through a letter.
	Causality assessments are done for both serious and nonserious AE. An advisory committee should consider both.
	Suggestion: For serious AEs (SAEs), analysis should be detailed and include final causality, especially clinical trials that involve multiple study sites. Final say on whether an AE or an SAE is associated with the drug is important. Will a copy be given to the institutional review board (IRB)? Study sites are responsible for giving a copy to their individual IRB.
	IRB wants only an annual progress report.
Action Planning	
Each group (NTP, FDA, NCPAM, and LCP partners) worked on its own specific action plans and presented them to the group in a plenary session.	Refer to action plans in Annex H.

Parallel Meeting Proceedings

National Institutes of Health

The purpose of the meeting was to discuss a potential collaboration between Dr. Hilton Lam's group and SIAPS to combine their experience in the use of a mobile device application to capture PV data.

The following topics were discussed during the meeting—

1. Muñez provided background information about the current workshops, cohort event monitoring, operations research, and PV in the Philippines.

2. Lam updated the group on a project using the application to assess the cost of medicine stock-outs and a second project using the application for a wheelchair user study conducted by JHPIEGO, an affiliate of Johns Hopkins University, Baltimore, Maryland.

3. Advantages of the application include the following—

    a. GPS functions, which can track the location of users to confirm that they are collecting data in the field
    b. No associated fees for licensing or purchasing the application
    c. User friendly
    d. Reduced paperwork
    e. Decreased time to conduct a study compared with a paper-based system
    f. Available in a desktop version

4. Disadvantages of the application include the following—

    a. Has been used only for short-term projects (less than three months)
    b. Limited experience with the application (only two studies to date)

5. The next step is as follows—

    a. Continued discussions with FDA, NTP, and SIAPS to obtain more information

A list of meeting participants is attached in Annex E.

Janssen Pharmaceutical Companies of Johnson & Johnson

The purpose of the meeting was to discuss the recently announced bedaquiline donation program and the role of J&J as a partner in the introduction of bedaquiline in the Philippines protocol.

The following topics were discussed during the meeting—

1. How do we go about PV for bedaquiline from J&J's perspective?

2. One of the challenges of introducing bedaquiline in country is the limited capacity of human resources, thus more partners are needed.
3. Bedaquiline will not be introduced commercially in the Philippines.
4. Now that it will be donated, the Certificate of Product Registration needs to be amended.
5. The order placed with the GDF is on hold, so it doesn't have to be paid before the donation memorandum of understanding is in place.
6. NTP needs to apply for the donation through the GDF.
7. The donation program was the topic of a general discussion.
8. FDA expects J&J Philippines to be involved in PV activities, including risk management.
9. The group asked what additional resources J&J could provide, in particular, human resources and equipment. Currently, J&J is able to participate in meetings, calls, and trainings to serve as advisers and provide expertise.
10. LCP will send bedaquiline reports to FDA and J&J in parallel.
11. J&J will notify the FDA regarding any global SAE reports. The FDA will in turn notify NTP, which will notify LCP. LCP will be responsible for notifying the study sites.
12. J&J will provide a quarterly global update to FDA.
13. The bedaquiline protocol is anticipated to start in the quarter after the start of the nine-month protocol.
14. Partner primary points of contact are

    - J&J—Erwin Benedicto
    - FDA—Melody Zamudio
    - LCP—Vivian Lofranco
    - NTP—To be determined

Action items—

1. J&J will provide a copy of the risk management plan.
2. Partners and stakeholders will invite J&J to future meetings, calls, and trainings regarding bedaquiline.
3. Partners will work together to obtain bedaquiline through the donation program.

A list of meeting participants is attached in Annex F.

RECOMMENDATIONS

The following recommendations were discussed with the stakeholders during the workshops—

1. Rejuvenation of the passive PV system: Augment the passive system with an active surveillance component to make it a stronger and more effective postmarketing surveillance system.

2. Active surveillance methodology: Develop and implement an active surveillance strategy initially for specific drugs and diseases, such as in the case of TB and HIV/AIDS, and in a variety of settings, then expand to other health programs.

3. Mandatory reporting: Consider having FDA require mandatory spontaneous reporting by marketing authorization holders and health care institutions (hospitals and clinics). The success of any PV system depends on the active contribution and participation of all the different stakeholders who submit spontaneous reports of adverse events to the national center, including health care professionals, consumers and patients, and the pharmaceutical industry.

4. Establishment of Drug and Therapeutic Committees or Pharmacy and Therapeutics Committee: Establish the committees' tasks to include monitoring the safe use of medicines in their facilities and encouraging reporting of suspected ADRs to FDA at all health care institutions (both government and private hospitals).

5. Culture of reporting: Incorporate PV in the curriculum of all health care professionals, including pharmacy, medical, nursing, and allied professionals, to emphasize the importance of reporting of adverse events associated with medicine.

6. Training programs: Include PV in continuing education activities offered for certification and licensing of health care professionals. The program could include sessions on how to identify suspected ADRs.

7. Publicity campaign to target the general population: Educate the general public on the importance of PV through billboards, public service announcements in the mass media, and posters in public places, including doctors' offices, hospitals and clinics, and public transportation systems. Raising awareness about the PV system is bound to increase reporting of suspected ADRs.

8. Options to report AEs: Facilitate ease of reporting through all possible avenues, such as a paper form with paid stamps, electronic, fax, e-mail, and telephone.

9. Underreporting of ADR reports: Conduct a knowledge, attitude, and practices survey to find out the reasons for underreporting and the nature of obstacles that are being faced by the health care professionals and consumers. Efforts may be made to address the reasons for low reporting rates.

10. Patient and consumer reporting of ADR reports: Encourage consumers and patients to report any suspected ADRs. Specifically designed reporting forms in nontechnical language can be developed for consumers to make reporting easier. In recent years, a number of countries have initiated programs to accept reports submitted by patients and consumers in their national PV programs.

11. Training and capacity building in PV for the staff of FDA and NTP: Establish regular program for training and capacity building of the staff of FDA and NTP in active surveillance methodologies, including CEM, causality assessment, and data for decision making.

12. Publishing a newsletter or bulletin: Launch a regular publication in the form of an ADR newsletter to showcase the results of reporting by health care professionals and patients and consumers. Such feedback will go a long way in encouraging reporters to report all suspected ADRs.

13. Treatment guidelines for TB: Include a prominent section on the importance of PV in patient safety and list the common ADRs associated with anti-TB medications, how to manage them, and where to report them.

14. Fear of liability as a barrier to reporting: Educate health care professionals and allay their fear of potential lawsuits from the pharmaceutical industry if they submit suspected ADR reports.

15. Public-private partnership: Create a partnership among FDA, NTP, and the pharmaceutical industry to enhance active surveillance methodologies to build a stronger PV system. Ensure that the partnership is fully transparent to build public confidence in the system.

The status of the recommendations from the joint WHO and SIAPS report is presented in the table below:

Joint WHO and SIAPS Report Recommendations

Recommendation	Status
Obtain ethical approval of the nine-month regimen and the bedaquiline protocols.	Nine-month regimen protocol will be submitted on X date, with a response anticipated by X date. The bedaquiline protocol is to be made final by June 2015. Submission to the ERB is expected by June.
Establish registration of, or FDA authorization to import, bedaquiline, which needs some clarification from Janssen on technical and administrative issues.	Bedaquiline was approved for registration by FDA October 2014.
Support procurement of anti-TB and ancillary drugs.	A bedaquiline procurement form has been prepared. The form submitted to GDF needs to be revised.

Recommendation	Status
Establish training for implementation of new protocols.	Under way— • Refer to the training of nine-month treatment regimen study, Muñez and Mangao, January 19–23, 2015. • Training for bedaquiline is scheduled for September 2015.
Make electronic data collection systems interoperable at both the DR-TB sites and PV unit.	We are awaiting an update from J&J and will explore use of VigiFlow by the study sites.
Obtain additional resources needed for implementation of two studies that include active PV. Conduct a task analysis to determine human resource needs, especially in the context of NTP's decentralization plans.	A research team in LCP is being strengthened. NTP provided two staff in FDA to assist in TB-related activities, including PV.
Data collection	
Improve efficiency and streamline data entry by eliminating paper-based data collection; explore feasibility of using tablets for data entry at the DR-TB sites and other levels in the health care system.	
Modify current PV data collection forms for both protocols to capture all AEs in addition to known ADRs.	Study form 7 was developed by the program. Reporting of SAEs follows the form from GDF/Janssen.
Educate and encourage treating clinicians to report all AEs of DR-TB patients enrolled in both protocols.	These steps were done during the training for the nine-month regimen study. Training on patient counseling and MDR-TB clinical management will be conducted in the third quarter of 2015 by IMPACT and the Union.
Enter data collected by the DR-TB unit into the electronic data system (Integrated Tuberculosis Information System or ITIS) in a timely fashion.	Data may or may not be entered in ITIS. A list of variables required for the study will be prepared by LCP.
• Ensure that all PV data collected in programmatic management of DR-TB (PMDT) units are promptly communicated to the PV unit.	This phase is on schedule.
• Incorporate spontaneous reporting of ADR data collected by the PMDT units into the national data collected by the PV unit and transmitted through VigiFlow to the UMC.	This recommendation requires more advocacy and training.
• Establish a comprehensive patient registry as part of the implementation of the bedaquiline protocol.	CEM will be used to capture patient safety data.
• As a matter of urgency, make data from the Web-based system at the PV unit accessible to the responsible staff, so that reports submitted can be assessed.	FDA is using VigiFlow and makes data accessible.
• Create a mechanism so the two electronic collection systems at the DR-TB (ITIS) and PV units (VigiFlow) are interoperable.	Possible options are being discussed with the SIAPS home office.
Data analysis	
• Build capacity at the PV unit to make use of the data collected for signal detection, analysis, decision making, and communication.	Addressing these recommendations is ongoing.
• Engage the DR-TB and PV consilium in the identification and analysis of safety signals emerging	

Recommendation	Status
from data recorded and reported.	
Develop human resources for PV— • Allocate or establish human resources at the FDA PV level to analyze the data, manage communications, and promote PV activities.	
Develop political will— • Encourage NTP to seek continued support from incoming FDA director.	

ANNEX A. PHARMACOVIGILANCE SYSTEMS STRENGTHENING AGENDA

Pharmacovigilance Systems Strengthening, FDA Workshop		
March 16, 2015 (Monday)		
TIME	ACTIVITY	FACILITATOR
09:00 – 09:30	Introductions	All
09:30 – 09:45	Overview of Agenda and Objectives	Antonia
09:45 – 10:00	Summary of Bangkok Global TB Conference	Antonia
10:00 – 11:00	Mapping Current PV System and Discussion	Rizwan
11:00 – 11:30	Review of WHO Mission Report Recommendations	Antonia
11:30 – 12:00	Introduction to Action Plan	
12:00 – 1:00	LUNCH	
13:00 – 13:30	PV for TB - Current Tools and Resources	Antonia
13:30 – 14:00	Overview of Three Day Training on PV: Cohort Event Monitoring	Rizwan
14:00 – 14:30	Active Surveillance – Lessons Learned from Swaziland	Rizwan
14:30 – 16:00	Action Planning	All
16:00 – 16:30	Summary of the Day, Planning for Tomorrow's Session	Antonia

March 17, 2015 (Tuesday)		
TIME	ACTIVITY	FACILITATOR
9:00 – 9:30	Morning reflection	Princess and Zaza
9:30 – 10:15	Cohort event monitoring (CEM)	Rizwan
10:15 – 11:00	Patient registry (PR)	Rizwan
11:00 – 12:00	Activities on CEM and PR	Rizwan
12:00 – 13:00	LUNCH	
13:00 – 15:00	Activities on CEM and PR continued	Rizwan
15:00 – 16:00	Revise Action Plan	Antonia
16:00 – 16: 30	Wrap-up and Adjourn	Princess and Zaza

ANNEX B. STAKEHOLDER WORKSHOP AGENDA

Pharmacovigilance Workshop, FDA, NTP, Stakeholders, and Partners		
March 18, 2015 (Wednesday)		
TIME	**ACTIVITY**	**FACILITATOR**
08:30 – 09:10	Registration and opening remarks	FDA
09:10 – 09:30	Overview of the training	Antonia
09:30 – 10:00	Review of PV requirements for 9 month protocol	Rizwan
10:00 – 10:30	PV Requirements for introducing Bedaquiline	Antonia
10:30 – 11:00	Accurate record keeping	Antonia
11:00 – 12:00	Record keeping activity	All
13:00 – 13:30	Accurate and timely data collection	Rizwan
13:30 – 14:00	Data collection activity	All
14:00 – 15:30	Cohort event monitoring	Rizwan
15:30 – 16:30	CEM Activity (e.g., missing data, monitoring forms, M&E	All
16:30 – 17:00	End of day reflection and Wrap up	Princess and Zaza

March 19, 2015 (Thursday)		
TIME	**ACTIVITY**	**FACILITATOR**
08:00 – 08:15	Registration	
08:15 – 08:30	Morning reflection	Princess and Zaza
08:30 – 09:00	Active surveillance – Swaziland Experience	Rizwan
09:00 – 11:00	Activities on cohort event monitoring (part two)	All
11:00 – 12:00	Intro to SASSA and DCAT	Antonia
13:00 – 13:30	Introduction SOP Development and Action Plan	Antonia
13:30 – 14:30	Causality analysis	Rizwan
14:30 – 16:30	Activities on causality analysis	All
16:30 – 17:00	End of day reflection and Wrap up	Princess and Zaza

March 20, 2015 (Friday)		
TIME	**ACTIVITY**	**FACILITATOR**
08:00 – 08:15	Registration	
08:15 – 09:00	Morning reflection	Princess and Zaza
09:00 – 10:00	Data and safety monitoring	Rizwan
10:00 – 12:00	SOP activity	All
13:00 – 15:00	Action plan activity	All
15:00 – 16:00	Finalize SOP and Action Plan	All
16:00 – 16:15	End of day reflection	Princess and Zaza
16:15 – 16:30	Closing remarks	NTP

ANNEX C. NATIONAL PHARMACOVIGILANCE SYSTEMS STRENGTHENING SESSION AND PROTOCOL-SPECIFIC WORKSHOP PARTICIPANTS

Management Sciences for Health / SIAPS Philippines
Training on PV for NTP, LCP, FDA and Other Partners: Cohort Event Monitoring
March 16-20, 2015

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ANNEX D. PARTICIPANT EVALUATIONS

Pharmacovigilance Systems Strengthening Session Evaluation

Day 1					
No. of respondents: 7					
	Very Poor	Poor	Fair	Good	Very Good
Content				6	1
Organization				5	2
Instructional aids				6	1
Teaching				4	3
Involvement of participants				5	2
Pace of delivery				5	2
Materials			1	4	2
Facility				2	5
Food				2	5
	Not useful	Little	Somewhat	Quite	Very useful
Extent of usefulness				1	6
	Yes	No	It depends		
Would you recommend this training	7				
	Not at all	Little bit	Some	Quite a bit	A lot
To what extent can you apply the session in your work				2	5

Day 1					
No. of respondents: 7					
	Too basic	Just right	Too advanced		
Session was_____ for my experience level		7			
	Very Poor	Poor	Fair	Good	Very Good
To what extent did instructors					
Know the subject matter				3	4
Encourage participation				4	3
Answered questions completely				3	4
Provide clear explanations				3	4
What did you find most useful/helpful					
Sharing of observation and experience from other countries					
Elaboration of PV system					
CEM					
Swaziland PV system					
Developing of action plan					
Workshop					
Swaziland experience					
What did you find least helpful/useful					
None					
Other comments					
None					

Day 2

No. of respondents: 7					
	Very Poor	Poor	Fair	Good	Very Good
Content				4	3
Organization				4	3
Instructional aids				6	1
Teaching				4	3
Involvement of participants				6	1
Pace of delivery				4	3
Materials			1	3	3
Facility				1	6
Food				1	6
	Not useful	Little	Somewhat	Quite	Very useful
Extent of usefulness				1	6
	Yes	No	It depends		
Would you recommend this training	7				
	Not at all	Little bit	Some	Quite a bit	A lot
To what extent can you apply the session in your work				1	6
	Too basic	Just right	Too advanced		
Session was_____ for my experience level		7			
	Very Poor	Poor	Fair	Good	Very Good
To what extent did instructors					
Know the subject matter				2	5
Encourage participation				3	4
Answered questions completely				4	3
Provide clear explanations				4	3
What did you find most useful/helpful					
Sharing of experience on subject matter					
Types of registry					
Causality assessment					

Day 2
No. of respondents: 7
CEM and causality assessment
In pharmacovigilance, it is important to build our capacity since PV in the Philippines is in the development stage and we have a lot to do to improve our practice setting, strengthening and how to sustain this practice is important and it was discussed in the session. CEM is a new concept and we are glad that we are enlightened a bit
Registry
What did you find least helpful/useful
None
Other comments
More trainings on PV involving surveillance for inspectors
Since we are not fully knowledgeable about CEM and patient registry, it would be helpful if additional reading materials were provided
There should be more exercises on causality assessment

Implementing Active Pharmacovigilance and CEM for Multi-Drug Resistant TB Regimens Workshop Evaluation

Day 3					
No. of respondents: 11					
	Very Poor	Poor	Fair	Good	Very Good
Content			1	7	3
Organization			1	8	2
Instructional aids			1	9	1
Teaching			1	7	3
Involvement of participants				7	4
Pace of delivery				8	2
Materials			1	8	1
Facility				6	5
Food				4	7
	Not useful	Little	Somewhat	Quite	Very useful
Extent of usefulness				2	9
	Yes	No	It depends		
Would you recommend this training	11				
Who else do you think should receive this training?	PMDT Physicians, NTP, probably study site staff				
	encoders and data officer				
	Not at all	Little bit	Some	Quite a bit	A lot
To what extent can you apply the session in your work				3	8
	Too basic	Just right	Too advanced		
Session was_____ for my experience level		8			
	Very Poor	Poor	Fair	Good	Very Good
To what extent did instructors					
Know the subject matter				6	5
Encourage participation				7	4
Answered questions completely				9	2
Provide clear explanations				9	2

Day 3		
No. of respondents: 11		
	Yes	No
Did the session meet your expectations	10	
Do you have any more expectations?		
Deeper understanding of PV		
What did you find most useful/helpful		
PIP		
CEM		
Facilitators and speakers were open-minded		
Documentation		
Mapping and doing PV and apply it in CEM		
PV requirements		
Record keeping		
Data collection		
What did you find least helpful/useful		
Review of CRF forms because the forms are already final		
Other comments		
It would be helpful to know the TOR of the consultants so we would be clear with our expectations		

Day 4					
No. of respondents: 13					
	Very Poor	Poor	Fair	Good	Very Good
Content				10	3
Organization			2	8	3
Instructional aids			1	8	4
Teaching				8	5
Involvement of participants			1	6	6
Pace of delivery			1	9	2
Materials			3	7	3
Facility				7	6
Food			1	5	7
	Not useful	Little	Somewhat	Quite	Very useful
Extent of usefulness				5	8
	Yes	No	It depends		
Would you recommend this training	13				
Who else do you think should receive this training?	study site staff, TC/STC Physicians/Nurses, other program managers				
	Not at all	Little bit	Some	Quite a bit	A lot
To what extent can you apply the session in your work			1	2	10
	Too basic	just right	Too advanced		
Session was _____ for my experience level		10			
	Very Poor	Poor	Fair	Good	Very Good
To what extent did instructors					
Know the subject matter				8	5
Encourage participation				9	4
Answered questions completely				11	2
Provide clear explanations				10	3
	Yes	No			
Did the session meet your expectations	13				
Do you have any more expectations?					
roles and responsibilities of group involved in PV especially causality analysis					

Day 4
No. of respondents: 13
Standards
defined roles and responsibilities of all stakeholders
What did you find most useful/helpful
Practical exercises
Criteria used to process of causality analysis
Causality assessment
signal detection
What did you find least helpful/useful
overview on signal management
Other comments
Thank you for accommodating our requests/comments in the evaluation
case studies are useful
we want copies of the presentation
Follow-up meeting shall be set to discuss decisions made within the training

Day 5					
No. of respondents: 15					
	Very Poor	Poor	Fair	Good	Very Good
Content				10	5
Organization			1	11	3
Instructional aids			1	10	4
Teaching				10	5
Involvement of participants			1	9	5
Pace of delivery			2	9	4
Materials			1	11	3
Facility				7	8
Food		1		6	8

Day 5					
No. of respondents: 15					
	Not useful	Little	Somewhat	Quite	Very useful
Extent of usefulness				4	11
	Yes	No	It depends		
Would you recommend this training	11	1			
Who else do you think should receive this training?	PMDT Team				
	Not at all	Little bit	Some	Quite a bit	A lot
To what extent can you apply the session in your work		1		3	11
	Too basic	Just right	Too advanced		
Session was _____ for my experience level		11	1	first time to attend PV training specifically in CEM and TB	
	Very Poor	Poor	Fair	Good	Very Good
To what extent did instructors					
Know the subject matter				7	8
Encourage participation			1	7	7
Answered questions completely				10	5
Provide clear explanations				11	4
	Yes	No			
Did the session meet your expectations	14	1			
Do you have any more expectations?					
I thought after this, we would already have a clear SOP for CEM					
Participants will be updated on the conduct of clinical trial on Bedaquiline in the Philippines					
What did you find most useful/helpful					
Drug Supply Management and Supply tools					
We were able to discuss our action plan for the implementation of PV in CEM					
Action Planning					

Day 5
No. of respondents: 15
SOP and Action Plans
Signal monitoring
VigiFlow
Causality assessment
What did you find least helpful/useful
VigiFlow
Other comments
Revise the proposed SOP
Provide participants with presentations
More practice case for causality assessment
Congratulations SIAPS team!
Good job SIAPS!

ANNEX E. NATIONAL INSTITUTES OF HEALTH PARALLEL MEETING PARTICIPANTS

SIAPS Philippines / National Institutes of Health University of the Philippines Manila March 20, 2015		
Name		Institute
1	Hilton Lam	National Institutes of Health University of the Philippines Manila
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3	Francis Capule	College of pharmacy, University of the Philippines Manila
4	Art Lagos	SIAPS
5	Nerizza Munez	SIAPS
6	Princess Christine Mangao	SIAPS
7	Chesa Desano	SIAPS
8	Antonia Kwiecien	SIAPS
9	Syed Rizwanuddin Ahmad	SIAPS Consultant

ANNEX F. JOHNSON & JOHNSON PARALLEL MEETING PARTICIPANTS

SIAPS Philippines Parallel Meeting with J&J and Partners March 20, 2015					
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ANNEX G. STANDARD OPERATING PROCEDURE

Active Surveillance: Cohort Event Monitoring for New Medicines and Novel Regimens in the Philippines

(This SOP consists of X pages (including this cover sheet and addendum).

NTP (provide details)	***Drug safety Department*** ***xxxxx Division/Function***	***SOP Nº***	
		Revision Nº	***Original document***
		Implementation Date	
Page Nº	***x of xxx***	***Last Reviewed/Update Date***	
SOP Owner		***Approval***	

Table of Contents

1 Introduction

Cohort event monitoring (CEM) is a prospective, observational, cohort study of adverse events associated with one or more medicines.

An adverse event (sometimes called an adverse experience) is defined by WHO as, "*Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment.*"

An event is any new clinical experience that occurs after commencing treatment with a medicine regardless of its severity or seriousness and without judgment on its causality. (Favorable events may be recorded as an indication of an unexpected therapeutic effect.)

Cohort event monitoring (CEM) records all clinical events and not just suspected adverse reactions.

Cohort Event Monitoring is active (or proactive) pharmacovigilance surveillance which means that active measures are taken to detect adverse events. This is managed by active follow-up after treatment and the events may be detected by asking patients directly or screening patient records. This surveillance is best done prospectively.

2 Purpose

The purpose of this standard operating procedure is to outline a step by step approach for undertaking Cohort Event Monitoring for new medicines (NM) and novel regimens (NR) for the treatment of TB.

3 Scope

The procedure applies to the 'Cohort Event Monitoring' of all new medicines and novel regimens for the treatment of TB.

It is applicable to personnel intending to establish or are running a pharmacovigilance centre.

4 Responsibilities

This section describes the roles and responsibilities in the management and coordination of active PV at facility and national levels**.**

At the level of the health facility (here: the selected site for piloting novel regimens and/or novel drugs such as bedaquiline to treat TB and MDRTB), the main activities are the detection, management and reporting of adverse events. Several persons/entities have different responsibilities with respect to Pharmacovigilance (PV):

Treatment facility clinicians/nurses and other staff have the responsibility to collect PV data during the treatment initiation visit and subsequent clinical examination appointments. The PV

data collection should be done carefully following the approved protocol. The health care provider seeing the patient should collect any information of relevance as requested on the PV forms during the interview and clinical examination of the patient.

Data entry staff (encoders) have the responsibility of checking completeness and consistency of data collected from the source document before they enter it on the forms or into an electronic system. They are also responsible for the data storage and quality, timely data transfer to the research team , and regular feedback to the clinicians. They shall notify the treatment facility clinicians if quality, quantity or timeliness of the PV data collected standards are not met. The data entry staff is also responsible for submitting the entered data to the national PV database at regular intervals, according to national regulations.

Research team will conduct preliminary causality analysis and advise the treating clinicians through the consilium on potential relationships between the drug or regimen and the adverse event reported.

5 National level

The main agencies involved in PV for new TB drugs at national level are the National Tuberculosis Program (NTP) and the Food and Drug Administration- National Pharmacovigilance Center (FDA- NPC). The FDA- NPC is also responsible for appropriate implementation of active PV.

Since the NTP has multiple responsibilities that need to be coordinated with other organizations, it is advised to install a national PV committee for TB drugs. This committee could be acting as a subgroup under the FDA National Advisory Committee for PV (NPvAC) with invited experts from TB Program.

The FDA National Advisory Committee for TB PV shall consist of representatives from the NTP, FDA-NPC, technical partners, academic, clinicians, and pharmacists. The group is responsible for preparing the introduction of novel drugs in general (i.e. adaptation of WHO guidance on new (MDR) TB drugs/regimens and development of a national plan for introduction, revision of treatment guidelines and clinical tools, etc.). In this responsibility, the NPvAC is responsible in monitoring the Research team in the implementation of PV in the study. This includes the translation of the data dictionary into the local language and adaptation of the data collection tools to the local situation where needed, preparation of the software elements within an electronic registry, and testing and piloting data collection.

The responsibilities of the different actors at the national level are outlined in Table 1.

Table 1. Responsibilities for PV implementation at the national level

Active PV component	Lead responsibility for active PV
Establishment of national PV committee for TB drugs	FDA- NPC
Planning and budgeting	NTP, LCP, FDA-NPC and partners
Protocol preparation	NTP, LCP, FDA-NPC and partners
Ethical clearance of protocols & conformity to international regulations	NTP, LCP, FDA-NPC and partners
Design and production of tools for data collection (preferably integrated into established reporting and recording systems)	LCP and FDA-NPC
Development of a training plan ensuring that all staff involved in CEM receives appropriate training and is prepared for introduction of bedaquiline	LCP
Staff training	LCP
Ascertainment of the availability that a new or existing electronic database for MDR-TB patients on treatment (adapted for the collection of PV data) is available and functioning adequately before the start of data collection Integrate data entry checks within the system according to the data dictionary	NTP, LCP, FDA-NPC and partners
SOP development the national level, to be adapted to facility level	NTP, LCP, FDA-NPC and partners
Collection of data	Treatment facility
Management and supervision of all aspects of PV data collection as outlined in the protocol*	Research team, FDA-NPC, NPVAC
Accurate processing and management of all PV data collected**	Research team, FDA-NPC
Transfer of cleaned and validated data to WHO- UMC	FDA-NPC
Causality assessment (see paragraph 6.1)	Research team and NPVAC
Development of plans for data analysis, signal identification, and communication	Research team
Data analysis and provision of feedback to health centers and clinicians‡	Research team, FDA-NPC
Signal detection (see paragraph 6.2)	Research team, FDA-NPC
Coordinate issuance of press releases for professionals and the general public on overall safety, or about particular issues that have arisen, with proper risk management to prevent unfounded mistrust in the medicine under CEM	FDA-NPC, NTP

***** This includes:

- Monitoring of data collection
- Supportive supervision of the participating sites in the form of follow-up of the quality, quantity and timeliness of data collection by email, telephone, and in-person site visits

****** This includes data checks and validation and storage data collected

† Reports on AE received by the NPVC from patients on bedaquiline who are not included in the national bedaquiline CEM, should be investigated and reported to the supranational level as well

‡ Note that these specific tasks are primary tasks of the NPVC, but may be performed initially by the national PV committee. Type and contents of the feedback that will be provided to local health facilities should be coordinated by the reporting clinicians at local health facilities, a representative from the M&E team of NTP, the NPVC and the supranational CEM expert team

6 Procedure

The basics of the CEM procedure are to:

- Establish a cohort of patients for each drug and/or drug regimen.
- Recording adverse events experienced by patients in the cohort(s) before and after medicine exposure.

6.1 Pre-Treatment Phase

6.1.1 Planning and Budgeting to ensure resources are available for CEM

6.1.2 Develop and implement a Training Plan

6.1.3 Designate a full time CEM coordinator must be appointed to oversee the study at hand.

6.1.4 Select appropriate sentinel sites, with trained teams and adequate resources to perform CEM.

6.1.5 The reporting forms need to be available in the local language(s)

6.1.6 Advocacy: Using appropriate means, all relevant stakeholders must be informed of the following

- Reasons for monitoring
- Methodology as it involves them;
- Value of safety monitoring and the advantages of CEM;
- Contribution it will make to the health of the population (improving benefit and reducing risk);
- Potential for increasing the effectiveness of public health programmes;
- Potential for reducing health costs for the community and government; CEM monitors normal clinical practice but any patient not wanting to be part of the study is free to opt-out

6.2 Establishing the Cohort

6.2.1 **Numbers of patients**[3]

6.2.1.1 A cohort of 10 000 patients is usually recommended. This gives a 95% chance of identifying a specific event that has an incidence of 1:3000 (uncommon or rare). Normally several events are needed to alert to a signal, or help evaluate a problem.

6.2.1.2 A cohort of 3000 patients gives a 95% chance of identifying a single event with an incidence of 1:1000.

6.2.1.3 If a comparator study is being undertaken, greater numbers will be needed if the background incidence in the community is high and it is desired to detect statistically significant differences between the comparators.

6.2.1.4 For concomitant medicines: larger numbers might be needed to detect differences between patients on specific medicines (e.g. anti-tuberculosis) and the other patients.

[3] Note these numbers will not apply for TB patients, it is for information only

6.3 Selection of Patients

6.3.1.1 Decisions will need to be made as to where the patients will be recruited and where the monitoring will be performed:

6.3.1.2 Patients might be recruited from all health facilities involved in treatment of specific conditions

6.3.1.3 Patients might be recruited from selected health facilities that are representative of the whole country, designated as "sentinel monitoring sites".

6.3.1.4 Children: In order to determine any risks or risk factors specific to children, the whole population will need to be monitored to enable comparison of children with the adults in the cohort.

6.3.1.5 For specific comorbidities In order to determine any risk factors specific to patients for specific comorbidities with tuberculosis or another specific comorbidity, the whole population of users will need to be monitored to enable comparison with the cohort members who do not have tuberculosis or another disease of interest.

6.3.1.6 If the only interest in monitoring was in outcomes in pregnant women, then patient selection could be restricted to women of child-bearing age.

6.4 Pre-treatment Phase

All events occurring in an assessment period (between the baseline assessment and treatment initiation) should be recorded, including those from the patient's diary. These control events will be recorded on a pre-designed "Treatment initiation questionnaire".

6.4.1 Pre-treatment assessment: Essential data elements

6.4.1.1 Patient details

6.4.1.2 Health number (if available): this may be a national identifier (preferred), hospital, clinic, or programme number.

6.4.1.3 Name: full name or initials depending on the requirements of local privacy legislation. Patient identification is important for follow-up purposes and avoidance of duplication.

6.4.1.4 Address: to allow for follow-up and accurate identification. This may take various forms depending on the location.

6.4.1.5 Sex

6.4.1.6 Date of birth (preferred) or age (add 'est' if age is estimated).

6.4.1.7 Weight and height

6.4.1.8 Patients past medical history

6.4.1.9 Pregnancy status

6.4.2 Details of medicines

6.4.2.1 Name(s): (this may be brand or generic) and formulation (e.g. tablets, syrup, injection). Mode of administration (e.g., oral, rectal, injection).

6.4.2.2 Indication(s) for use.

6.4.2.3 Dose: Size of each dose and dosage interval is preferred. If not available , recording the total daily dose is appropriate.

6.4.2.4 Date of commencement.

6.4.2.5 Date of withdrawal.

6.4.2.6 Duration of use, if dates of commencement and withdrawal are not available.

6.4.2.7 All medicines being taken at the time of consultation should be listed. Each suspect medicine can be indicated by an asterisk or any other appropriate means.

6.5 Post- Treatment Phase: Event Reporting

6.5.1.1 All adverse events (even if minor) shall be recorded and not just suspected adverse reactions. Clinicians or recorders should make no judgment regarding causality.

6.5.1.2 These events will be recorded on the "Treatment review questionnaire". The logistics of this will be described in section.

6.5.1.3 Normal clinical terms or descriptions should be used. There should be no attempt to apply the official adverse event terminology (WHO ART)

6.5.1.4 All clinical events experienced by each patient should be recorded. This includes unexpected improvement of concomitant disease (favorable event) as well as adverse events.

6.5.1.5 All events occurring in the assessment period (between the baseline assessment and treatment initiation) should be recorded, including those from the patient's diary. These control events will be recorded on the "Treatment initiation questionnaire".

6.5.1.6 At follow-up visits any new events or worsening of pre-existing conditions that have occurred since treatment began should be recorded on the "Treatment review questionnaire".

6.5.2 Recording event details

6.5.2.1 A brief description of each event should be recorded. These event descriptions should be reviewed later by a Clinical Reviewer and standard adverse event terminology will be applied. The clinician does not need to know, or refer to, the standard event terminology.

6.5.2.2 Standardized codes can be used for common events as per WHO guidelines for various disease states

6.6 Reporting forms (questionnaires)

There are three questionnaires which should be used for routine monitoring. Additional questionnaires should be developed for monitoring pregnancy. Questionnaires should be adapted for local use.

6.6.1 The baseline questionnaire

This is used to record:

- Patient details, including demographic data (these are repeated in subsequent questionnaires);
- Any current treatment;
- Past conditions of importance
- Laboratory test results.

6.6.2 The treatment initiation questionnaire

This should be used to record:

- The above details; plus

- Any events during the pre-treatment control period;
- Comorbid conditions.

6.6.3 The Treatment Review questionnaire

This is the post-treatment (or follow-up) questionnaire. It is for recording the follow-up information on events and outcomes of treatment at each review.

- A new questionnaire should be completed at each follow-up visit.

6.7 Data Management

This chapter describes data collection and data management processes and procedures at facility, national and supranational level, including:

- The overall data flow within and between these levels
- Data management
  - Facility level: data collection, data entry, and data quality and validation
  - National level: system management, monitoring of facility data including quality, and analysis and reporting
- Data security and patient confidentiality
- System requirements
- Test and pilot
- Standard operating procedures

6.7.1 Data flow

Creation or adaptation of data collection tools (e.g., paper forms) and creation or adaptation of electronic database requirements shall be in place and consistent with the NTP recording and reporting system before PV data collection starts, to facilitate the data flow.

A schematic overview describing the data flow from data collection at facility level to analysis and reporting at supranational level is shown in Figure 1. PV data is collected and entered at facility level in the (preferably electronic) reporting and recording system and transferred to the national level. Facility level data is managed and monitored at the national level by the NTP in close collaboration with FDA. If a NPVC is in place, PV data shall be sent by LCP to FDA according to national regulations. The next three paragraphs describe the guiding principles for the data management processes for each administrative level involved. Focus is on data quality and an uninterrupted and standardized flow of data among all three levels.

Recommendations will be submitted by National drug Advisory committee. FDA will release the final decision to NTP and report to Uppsala, every quarter.

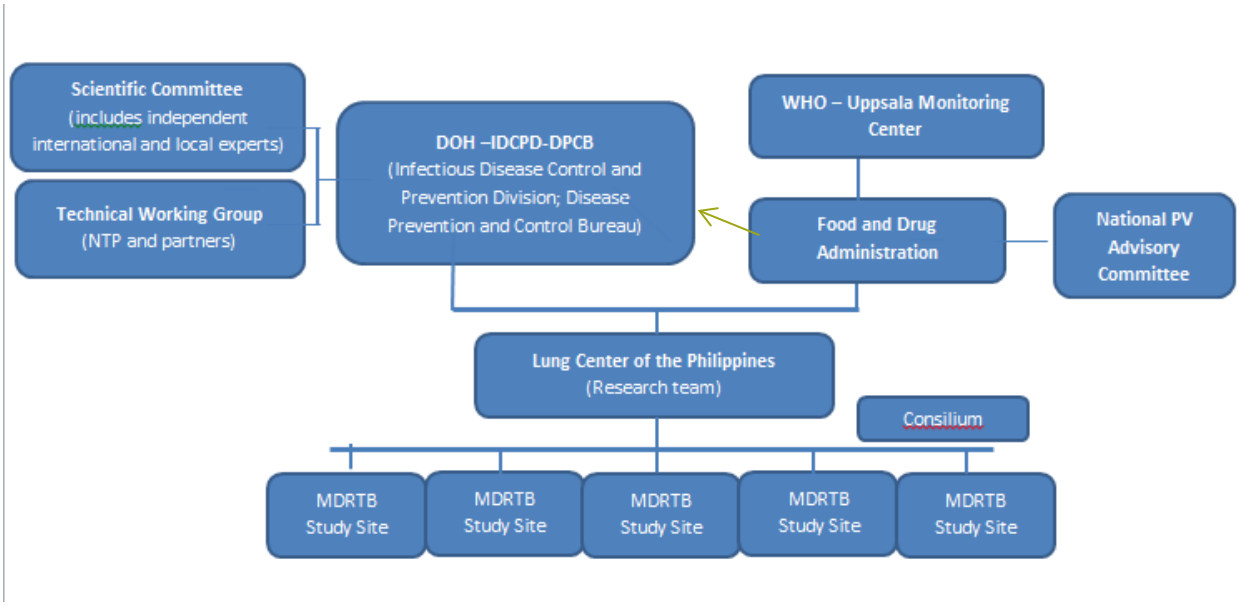

Figure 1. Data flow at facility, national and supranational level

6.8 Facility level: data collection and data entry

A data dictionary defining the minimum dataset required for CEM PV available (see Annex x), including the variable types, formats and related validation rules. It is not recommended to create full new data collection tools specifically for the collection of PV data. Data described in the data dictionary that are not yet included in existing (paper or electronic) data collection tools for MDR-TB patients should be integrated into existing data collection tools as much as possible.

PV data collection and data entry is done at facility level, where patient data are collected during clinical examination visits. By integrating PV data collection in the regular visits to the clinic, there is a minimum burden for patients and staff to collect PV data. Clinicians need to make sure that all data are completely, appropriately and consistently collected before submitting the data to the data entry staff within time lines set in the corresponding SOP.
Adverse event data that are collected later (e.g. laboratory results) should be submitted separately to the data entry staff who will include these in the database. Relevant data for patient management should also remain available in the patient's medical file.

Box 4. Immediate reporting of serious adverse events (SAE)

In case of serious adverse events (SAE, see Definitions), all relevant information about the SAE should be sent to the National Pharmacovigilance Center (NPVC) according to national regulations. See paragraph 6.4 for details.

The frequency of PV data collection is mainly dependent on the regular schedule of assessment and follow-up at the clinic. The minimum frequency of PV data collection is once per month during the initiation phase of treatment and once per quarter during the continuation phase of treatment. In addition to PV data collection during the scheduled visits, PV data should be collected during unplanned additional clinical examination visits in the occurrence of an adverse event. Because most countries already collect part of the minimum dataset for patient and treatment management, it is recommended to integrate PV data collection as much as possible within the existing data collection tools, to minimize overlap and ensure efficient data collection. Although the format of the data collection tools may be adapted to local preferences, it is a condition that the standardized format of the data fields (see data dictionary; annex x) is used in all countries. This will allow for accurate translation and back-translation of data across regions and countries, enabling valid comparison. Countries can decide to collect an additional set of PV data. As long as the minimum dataset is included, pooling can be done at supranational level.

The processes of data collection and data entry are dependent on the country specific setting and tools in place. Guiding principles for data entry and data collection in order to produce high-quality data are:

- Minimize transcription error
    - By entering data directly in the system during data collection;
    - If data are not entered directly in the system during collection, data entry is done by the same staff member that collects the data;
    - If this is not feasible, local solutions should be developed ensuring that data entry occurs timely and as close as possible to the primary data source (i.e. in the same facility);
    - Relationship assessment between drugs and adverse events is done by the treating clinician;
    -
- Minimize data entry errors (completeness and accuracy)
    - If data are collected on paper, the electronic data entry fields are fully in line with the paper forms;
    - Automatic data entry checks are in place such as mandatory fields, cross checks, follow-up question only if applicable (e.g. no question about pregnancy when gender is male);
    - A procedure for cross-checking PV data with patient's medical files is in place;
- Minimize delay between collection and entry of data
    - By entering data directly in the system (during clinical examination visits);
    - By automatic linkage of lab results to the electronic recording and reporting system;
    - By structurally adding laboratory results that are not available timely to complete the PV dataset;
    - By appointing dedicated staff for data entry;

- Optimize consistent data collection and entry

    - Data collection and entry is done by the same staff members as much as possible;
    - If data is first collected on paper, cross-checks paper and electronic records for discrepancies;
    - Training of (new) staff using (locally adapted) guidance documentation;
    - Annual refresher training for all staff
    - If data is collected on paper, paper forms are stored locally to enable retrospective cross-checking (see paragraph 4.5 on storage);

6.9 National level: monitoring and reporting

At national level, the NTP and NPVC have an important role in monitoring the data collected and reported by the facilities, and reporting national data back to the facilities. The roles and responsibilities at national level are outlined in paragraph 3.2. The specific data management processes at national level are dependent on the country specific setting and tools in place. This paragraph provides guiding principles for these national processes. These are:

- Monitoring and validation of facility level data

    - Provide frequent (to be defined) feedback on the timeliness of reporting;
    - Provide frequent feedback on the completeness of the PV reports;
    - Use standardized system-generated notifications;
    - Validate specific content of the reports (e.g. causality assessment).

- Training of facility staff

    - Make an inventory of new staff for training;
    - Use (locally adapted) guidance documentation.

- System management

    - Ensure availability of data collection and entry tools;
    - Ensure security of the system and confidentiality of the data (see paragraph 4.5);
    - Store pooled facility data (see paragraph 4.5);
    - Enable data extraction for analysis, reporting, and data transfer.

- Analysis and reporting to facilities

    - On quality (timeliness, completeness and accuracy) of data/reports;
    - On the comparison between facility data and national level data;
    - On causality assessment between AE and drugs;
    - On signals identified at national and supranational level (see paragraph 6.2).

- Transfer data to supranational level

- Extract, clean and validate national data;
- Anonymize the dataset (e.g. remove person and facility identifiers).

More on signals and provision of feedback can be found in paragraphs 6.2 and 6.3, respectively.

6.9.1 A broadband Internet connection (>1 Mb/s) is needed
6.9.2 Microsoft Access could be used for data management, but may be difficult to manage
6.9.3 Purpose-built databases can be programmed using the software, SAS. This requires a person with expertise in this software.
6.9.4 A relational database is desirable that can link separate smaller databases for analysis as required. A single database with all the data would be too big to manage.
6.9.5 Fields required in the database need to allow for entry of all the data elements included in the questionnaires.
6.9.6 It is desirable to have separate databases for the following**:**

- Cohorts with all patient data;
- Medicines with all details of use;
- Events with dates and outcomes;
- Reporters (treatment providers) with contact details.

Reporting flow for SERIOUS AEs is described below and represented in Figure 2 below.

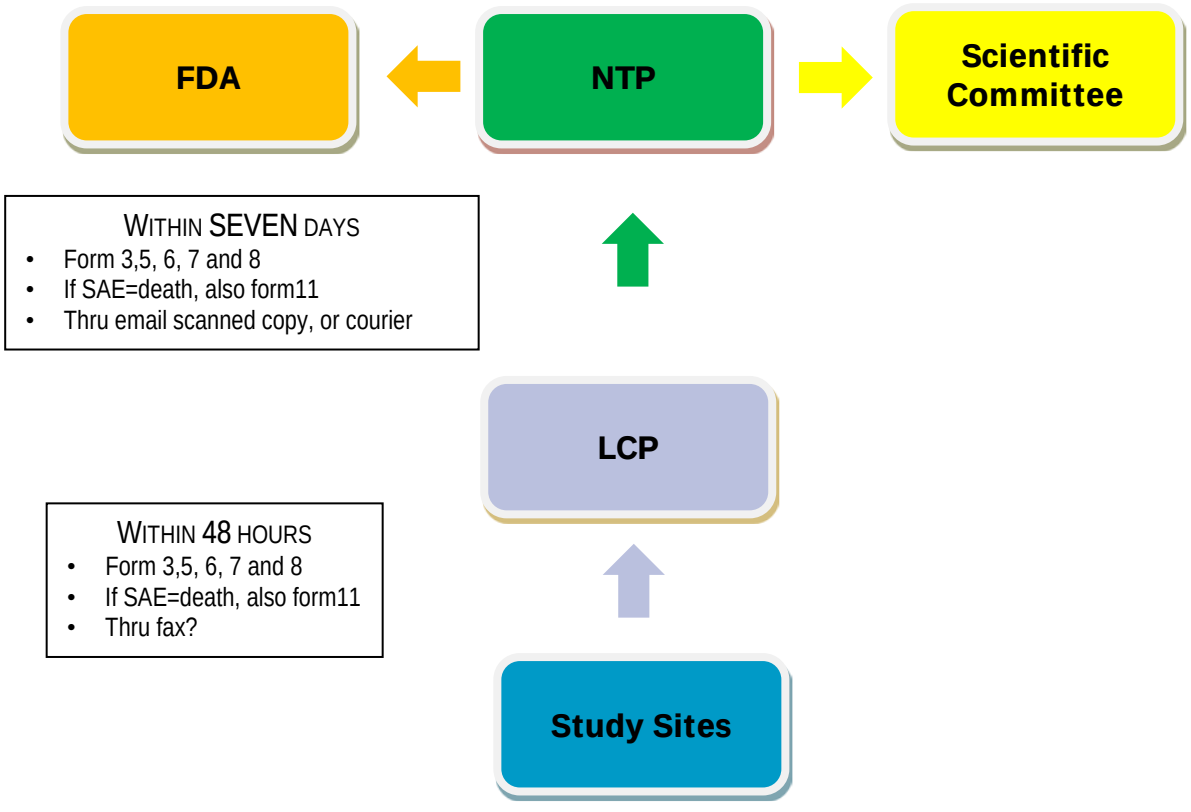

Figure 2 – Reporting Flow for SAEs

Reporting flow for SERIOUS AEs is described below and represented in Figure 3 below.

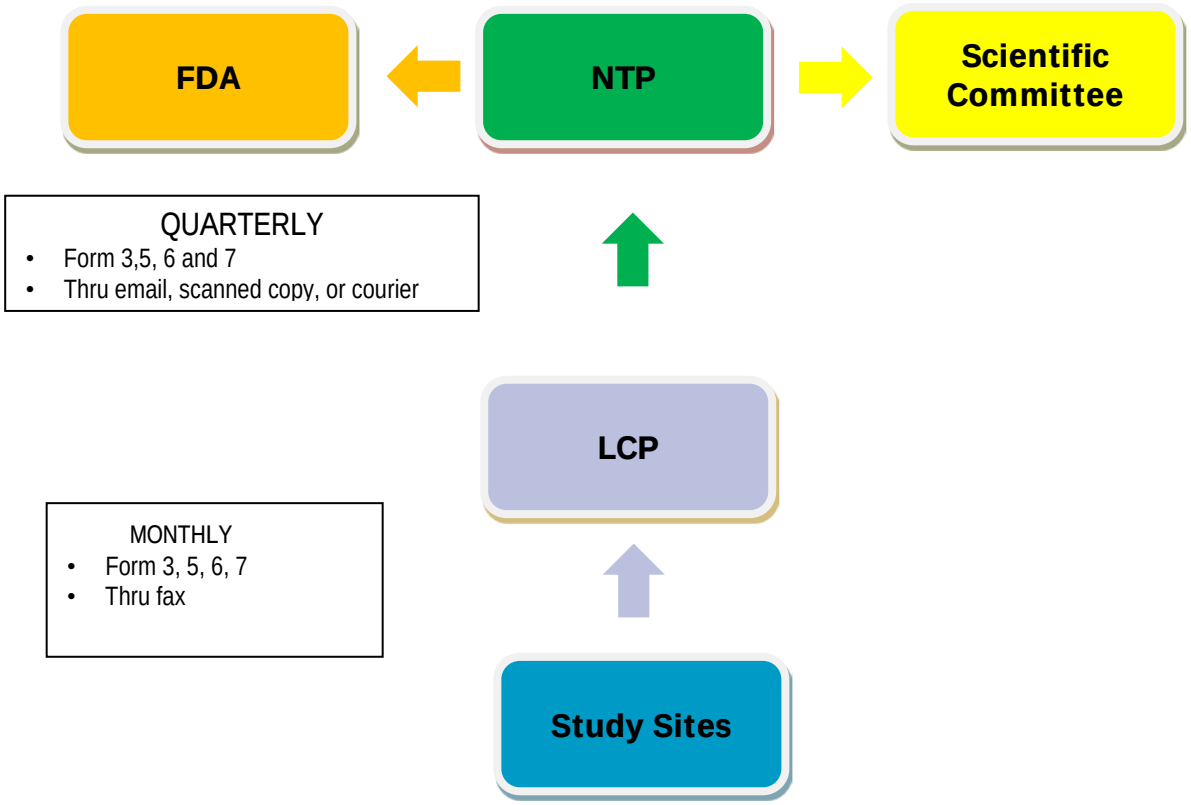

Figure 3 – Reporting Flow For All AEs

6.10 Feedback

6.10.1 Feedback should be given to health professionals and health workers in order to encourage compliance.

6.10.2 Regular information to be sent to them by the Pharmacovigilance Centre.

6.10.3 This information needs to be relevant and helpful to their work. Occasional meetings to discuss the results are valuable**.**

6.11 Next Steps

6.11.1 Consider implementing the Sentinel Site-based Active Surveillance for the Safety of Anti-TB (SSASSA) Tool, an electronic tool for the longitudinal collection of data on exposure to and outcomes of use of anti-TB medicines at health facilities.

- To facilitate the quantification and characterization of adverse events
- To improve the understanding of the safety and tolerability of ATBMs
- To minimize medicines-related morbidity and mortality

6.11.2 Consider implementing the Data Collation and Analysis Tool (DCAT) Tool. DCAT makes implementation of active surveillance activities feasible by addressing the entire data collection, data analysis process; data cleaning and integration, preliminary analysis, and exploratory analysis.

7 Definitions

7.1 Pharmacovigilance

Pharmacovigilance has been defined as: *The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem* (WHO).

7.2 Pharmacovigilance Centre

The Pharmacovigilance Centre (PvC) of an individual country is responsible for meeting the requirements for pharmacovigilance of all medicines and is a centre of expertise for the art and science of monitoring and analysis, and use of the analysed information for the benefit of patients. National and any regional Pharmacovigilance Centers should be set up with the approval of the authority responsible for the regulation of medicines ("regulatory authority"). The centre may function within the regulatory authority, a hospital, an academic institution or as an independent facility such as a trust or foundation.

7.3 Signal

Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information. (WHO)

7.4 Adverse Drug Reaction

A response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function. (WHO)

7.5 Serious adverse reaction

Any *untoward medical occurrence that at any dose results in death, is life threatening, requires or prolongs patient hospitalization, results in persistent disability/incapacity, or is a congenital anomaly/birth defect* (International Conference on Harmonization (ICH)). The term Life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it was more severe.

7.6 Adverse Event

Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a casual relationship with this treatment. (WHO)

7.7 Healthcare Provider

For the purposes of suspecting adverse reactions, healthcare proffessionals are defined as medically qualified persons such as physicians, dentists, pharmacists and nurses.

7.8 References

List resources that may be useful when performing the procedure; for example, Admin policies, Municipal Code, government standards and other SOPs.

WHO Website

http://www.who.int

The Uppsala Monitoring Centre (UMC)

This site provides very useful information about practical pharmacovigilance including definitions and advice on pharmacovigilance policy.

http://www.who-umc.org/

International Society of Pharmacovigilance (ISOP)

www.isoponline.org

Systems for Improved Access to Pharmaceuticals and Services (SIAPS)

This site provides tools and guidance for strengthening pharmacovigilance systems.

http://siapsprogram.org

ANNEX H. ACTION PLANS

FDA Action Plan

What needs to be done?	Who should take action to complete this step?	When should this step be completed?	What do you need in order to complete this step?	Are there any potential challenges that may impede completion? How will you overcome them?	Was this step successfully completed? Were any new steps identified in the process?
Pharmacovigilance AO Revision	FDA	Q3 2015	Stakeholder consultation / collaboration	Workload of focal person	For comments from stakeholders
Revision & additional SOPs on AE/ADR	FDA	Q3 2015	QMS approval	Workload of focal person	With draft revisions
Electronic Transmission of PV Data from LCP to FDA in E2B format (VigiFlow Compatible)	LCP, NTP, SIAPS	-	IT System & collaboration	Compliance with the system	
Creation of National Drug Advisory Committee with subcommittee on PV	SIAPS, WHO	Q3 2015	Experts, Funding	Availability of Experts, COI	
In-house Consultant to Review Existing System and Strengthen PV with focus on Active Surveillance (CEM)	SIAPS	Q3 2015	Consultant	Availability of Experts, Funding of SIAPS	
Additional Staff for CEM	NTP	Q2 2015	Staff, Funding	Transfer of Funds	
Data Management and Analysis Training (including statistical analysis)	SIAPS	-	Funding	Availability of In-country Training	
Feedback form	FDA, SIAPS	Q2 2015			
Decentralization of PV System	FDA	(after AO approval)	Stakeholder Collaboration, Funding	Coordination and cooperation of target monitoring centers	
Training for Decentralization	FDA	-	Funding	Approval of AO	
Implementation and Sustainability of Decentralization	NTP	-	Funding		
Incorporation of Suspected ADR form in NTP Training Module	NTP	-	Stakeholder Collaboration		
Advocacy	NCPAM	Q4 2015	Funding		

NTP, LCP, IMPACT, and TASC Action Plan

Goal: To implement Cohort Event Monitoring for the 9-month treatment regimen and introduction of BDQ in the Philippines.					
Action Step	**Person Responsible**	**Deadline**	**Necessary Resources**	**Potential Challenges**	**Result**
What needs to be done?	Who should take action to complete this step?	When should this step be completed?	What do you need in order to complete this step?	Are there any potential challenges that may impede completion? How will you overcome them?	Was this step successfully completed? Were any new steps identified in the process?
Finalize the PV Procedure for the study	LCP, NTP, FDA, TASC, IMPACT, SIAPS and WHO	ASAP	Technical Assistance from experts	Alignment of PV system with FDA. Close coordination with FDA thru regular meetings and consultation.	
Develop data base	LCP, NTP, PBSP and TASC	End of May 2015	Review proposal of contracting agency; signing of the contracting agency.	Compatibility of system to be use with FDA. Close coordination with FDA thru regular meetings and consultation.	
Ethics review for BDQ	LCP, NTP, IMPACT, PBSP, WHO and TASC	Q3	Protocol development; technical review approval	Approval process; contracting a consultant to draft the protocol.	

NCPAM/Pharmaceutical Division Action Plan

ACTION STEP	**RESPONSIBLE PERSON**	**DEADLINE**	**NECESSARY RESOURCES**	**POTENTIAL CHALLENGES**	**RESULT**
What needs to be done	Who should take action to complete this step?	When should this step completed?	What do you need in order to complete this step?	Are there any potential challenges that may impede completion? How will you overcome them?	Was this step successfully completed? Were any new steps identified in the process?
1. Support FDA in strengthening their PV activities	Pharmaceutical Division – Department of Health	Immediately (2015) until 2016	Budgetary requirements	Changes in the administration (Secretary of Health) prioritization	Capacitated FDA in PV activities
2. Strengthening the supply chain management of medicines including TB medicines both procured & donated	Pharmaceutical Division – Department of Health	Immediately (2015) until 2016	Budgetary requirements for training	Policy realignment	Good SCM for DOH facilities and LGUs as well