Standard Operating Procedure on Targeted Spontaneous Reporting for Dolutegravir-based and Pre-exposure Prophylaxis Regimens

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About the Philippines Food and Drug Administration (FDA)

As a regulatory agency under the Department of Health, the Food and Drug Administration, created under Republic Act No. 3720, series of 1963, as amended by Executive Order 175, series of 1987, otherwise known as the "Food, Drugs and Devices, and Cosmetics Act", and subsequently Republic Act No. 9711 otherwise known as "The Food and Drug Administration Act of 2009", is mandated to ensure the safety, efficacy or quality of health products which include food, drugs, cosmetics, devices, biologicals, vaccines, in-vitro diagnostic reagents, radiation-emitting devices or equipment, and household/urban hazardous substances, including pesticides and toys, or consumer products that may have an effect on health which require regulations as determined by the FDA.

About the USAID MTaPS Program

The goal of the USAID Medicines, Technologies, and Pharmaceutical Services (MTaPS) Program is to enable low- and middle-income countries to strengthen their pharmaceutical systems – to ensure sustainable access to and appropriate use of safe, effective, quality-assured, and affordable essential medicines and medicine-related pharmaceutical services. Toward this end, the MTaPS result areas include strengthening pharmaceutical sector governance; increasing institutional and human resource capacity for pharmaceutical management and services, including the regulation of medical products; increasing the availability and use of pharmaceutical information for decision making and advancing the global learning agenda; optimizing pharmaceutical-sector financing, including resource allocation and use; and improving pharmaceutical services, including product availability and patient-centered care, to achieve desired health outcomes.

Recommended Citation

FDA and MTaPS. 2023. Standard Operating Procedures for Targeted Spontaneous Reporting of adverse events for dolutegravir-based regimen and PrEP.

ACRONYMS AND ABBREVIATIONS

AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
DOH	Department of Health
DPCB	Disease Prevention and Control Bureau
DTG	Dolutegravir
FDA	Food and Drug Administration
HIV	Human immunodeficiency virus
PLHIV	People living with human immunodeficiency virus
PrEP	Pre-exposure prophylaxis
PV	Pharmacovigilance
SAE	Serious adverse event
TLD	Tenofovir disoproxil fumarate/lamivudine/dolutegravir
TSR	Targeted spontaneous reporting
WHO	World Health Organization
UMC	Uppsala Monitoring Centre
MTaPS	Medicines, Technologies, and Pharmaceutical Services
USAID	United States Agency for International Development

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1. INTRODUCTION

Human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) continues to be a major global public health concern. It was estimated, at the end of 2020, that 37.7 million people were living with HIV. Unfortunately, the disease has no cure – one reason as to why the morbidity rate is still increasing.[1] However, with increasing access to effective HIV/AIDS care and management, including prevention, diagnosis, and treatment, covering all opportunistic infections, the disease has become a manageable chronic health condition, enabling people living with HIV (PLHIV) to lead long and healthy lives. The World Health Organization (WHO), through the Global HIV Program, leads the development and implementation of the global health sector strategy on the elimination of HIV as a public health threat.[2]

According to the Philippine Department of Health (DOH), in April 2022, 1,198 new HIV cases were confirmed, bringing the cumulative total number of cases ever confirmed and reported to 98,990 since January 1984. Out of the cases confirmed in April 2022 (1,198), 94% were male, and 6% were female.[3] There were a total of 59,955 PLHIV on anti-retroviral therapy at the end of April 2022: 96% on the first line regimen, 3% on the second line, and 1% on other regimens.[3]

In the past two years, the Philippines has introduced dolutegravir (DTG)-based regimens, including the tenofovir disoproxil fumarate/lamivudine/dolutegravir (TLD) regimen as the preferred first-line anti-retroviral treatment regimen for PLHIV and pre-exposure prophylaxis (PrEP) for clients at risk of exposure to HIV.[4]

Introducing PrEP, DTG-based regimens require monitoring of adverse events (AEs) to understand the safety profile of these newly introduced regimens and to inform the decisions of the national programs for improving client safety and treatment adherence. Also, monitoring the adverse events of the DTG-based regimen is important because of a possible risk of neural tube defects and spinal bifida among newborn babies to women using the drug at the time of conception.[5]

With ongoing evolution in the health care system and continued advancement of the HIV/AIDS regimen, patients have more choice of treatment that have lesser side effects. But despite DOH-established clinical management to enhance follow-up and monitoring of PLHIV, underreporting of adverse events remains an issue. Building capacity in treatment facilities for targeted spontaneous reporting and safety reporting of DTG-based regimens including TLD will encourage health care workers to document, manage, and report the complaints of their clients. In addition, conducting targeted spontaneous reporting (TSR) on selected HIV/AIDS facilities can provide safety data for DTG, including TLD and PrEP, which can be used to assess the benefit, harm, effectiveness, and risk of medicines, leading to the prevention of harm and maximization of benefits to PLHIV.

[1] https://www.who.int/news-room/fact-sheets/detail/hiv-aids
[2] https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/hiv/overview
[3] https://www.aidsdatahub.org/resource/hiv-aids-and-art-registry-philippines-april-2022
[4] https://www.who.int/publications/i/item/WHO-CDS-HIV-18.51
[5] https://www.natap.org/2019/IAS/IAS_65.htm

TSR is a stimulated form of spontaneous reporting that focuses on capturing AEs in a well-defined group of patients on a medical intervention/treatment. It is intended to ensure that patients are monitored, and that AEs are reported as a normal component of routine patient monitoring, to achieve the requisite standard of care. Health professionals in charge of patients are sensitized to report-specific or patient-related safety concerns.

TSR is a focused approach has the same objectives and flow of information as for spontaneous reporting. It requires no active measures to look for events.

2. PURPOSE

The purpose of this standard operating procedure is to outline a step-by-step approach for TSR for monitoring the safety of DTG-based and PrEP regimens.

3. SCOPE

The procedure applies to all health care providers involved in the TSR of DTG-based and PrEP regimens for HIV/AIDS. The scope includes the selection of treatment facilities, enrollment of clients, monitoring, reporting of serious adverse events (SAEs), data analysis, investigation, and feedback and data management.

4. REPORTING PROCESS

A schematic diagram (figure 1) illustrates the structures and stakeholders involved in the TSR pharmacovigilance (PV) surveillance for DTG-based and PrEP regimens for HIV/AIDS treatment in the Philippines.

When a client reports AEs and SAEs to a treatment facility, the health care provider needs to document the reported SAE in the client's chart, complete the FDA Suspected Side Effects Reporting Form, and submit this form to FDA online. They should then inform the DOH Disease Prevention and Control Bureau (DPCB) that they have submitted a report to FDA. The hard copy of the submitted FDA Suspected Side Effects Reporting Form should be in the client's chart. The health care provider also needs to track the submitted report to FDA and ensure that FDA acknowledges its receipt.

FDA should promptly acknowledge the report upon receipt, conduct causality assessment and analysis, and give feedback, as necessary. Also, the FDA should all send the report to WHO's Uppsala Monitoring Centre (UMC), and update DPCB on any developments relating to the submitted report and whether these require additional investigation. The Global HIV Program should also be made aware of the results of FDA's and UMC's analysis.

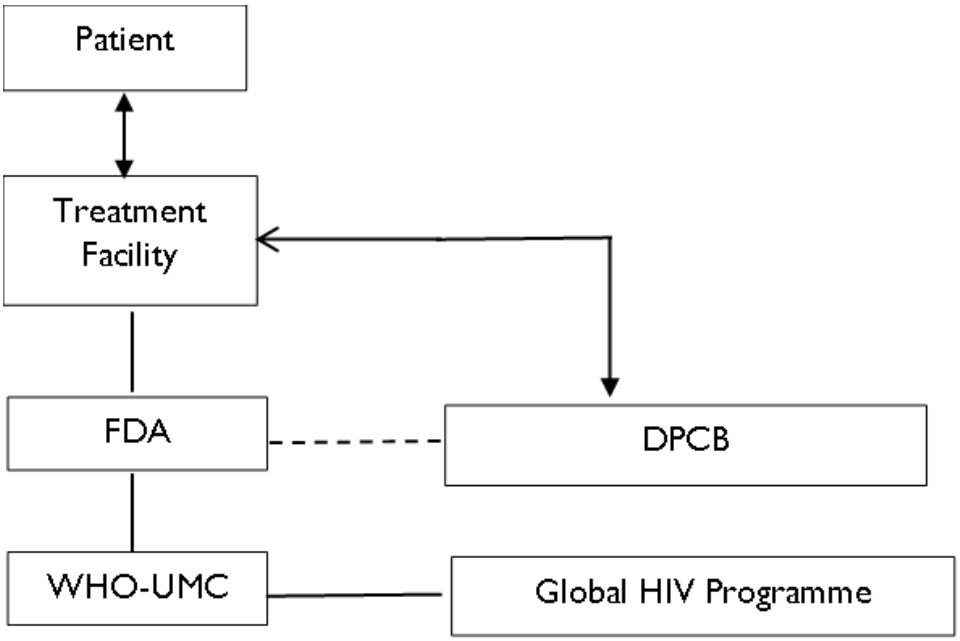

Figure 1: Targeted Spontaneous Reporting Structure

The following sections outline the management and coordination required among DPCB, FDA, and treatment facilities for TSR of DTG-based and PrEP regimens. The responsibilities of different agencies at the national level are outlined in table 1.

4.1. TREATMENT FACILITY PERSONNEL

Treatment facility personnel such as clinicians, nurses, case managers, and pharmacists are responsible for:

a) Detecting, managing, and reporting AEs and SAEs.
b) Educating clients through counseling and explanation about AEs/SAEs to promote clients' confidence and adherence.
c) Documenting reported AEs/SAEs in a client's chart and the report submitted to FDA.
d) Tracking the report submitted to FDA.
e) Collaborating with the FDA Pharmacovigilance Unit and DPCB for case follow-ups and causality assessment.

4.2. NATIONAL LEVEL PERSONNEL

The DPCB and FDA are the main agencies involved in pharmacovigilance for HIV/AIDS medicines at the national level. To ensure information sharing between these institutions, clear and consistent collaboration and coordination mechanisms should be established.

As the overall technical authority of health in the country, the DOH strives to ensure that national health policies and regulatory responsibilities for pharmacovigilance are properly implemented by its

agencies and public health programs. FDA and DPCB should ensure constant coordination with each other for the safety, efficacy, and quality of health products.

Food and Drugs Administration

All AE reports submitted by the staff of treatment facilities are verified by the PV unit of the FDA under the Center for Drug Regulation and Research. FDA has the following responsibilities:

a) Plan all PV activities
b) Budget PV activities
c) Develop a training plan ensuring that all staff involved in TSR monitoring receive appropriate training
d) Develop standard operating procedures to be adopted from the national level to the facility level
e) Develop plans for data analysis, signal identification, and communication
f) Accurately process and manage all PV data collected, which includes data checks and validation and storage
g) Conduct causality assessment and signal detection as necessary
h) Provide feedback on the SAEs received from the treatment facilities
i) Process and enter all reports received from the facilities to VigiFlow
j) Analyze the SAEs reported from treatment facilities
k) Provide feedback on SAE reports to the reporting treatment facility and the DPCB
l) Conduct signal detection
m) Promote mechanisms to facilitate the reporting of SAEs
n) Take and implement regulatory action, if necessary
o) 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 medicines under targeted spontaneous reporting

Disease Prevention and Control Bureau

The DPCB should support the pharmacovigilance activities to be implemented in the treatment facilities, through the following responsibilities:

a) Plan all PV activities
b) Budget PV activities
c) Develop a training plan ensuring that all staff involved in TSR receive appropriate training
d) Train staff
e) Manage and supervise all aspects of PV data collection, including monitoring of data collection and supportive supervision of the selected sites by follow-up through email, telephone, and site visits
f) Assist the FDA to accurately process and manage all PV data collected, which includes data checks and validation and storage
g) Advocate for treatment facilities to report the AEs/SAEs relating to DTG-based regimens and PrEP to the FDA
h) Ensure the monitoring of the selected facilities
i) Implement the recommendations of the FDA

j) Assist the FDA to 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 medicines under targeted spontaneous reporting

Table 1. Summary of Responsibilities of Different Agencies at the National Level

PV Component	Lead Responsibility
Establish a National Pharmacovigilance Advisory Committee	FDA
Plan all PV activities	Collaboration between DPCB and FDA and in coordination with partners
Budget PV activities	Collaboration between DPCB and FDA and in coordination with Partners
Develop a training plan ensuring that all staff involved in targeted spontaneous reporting receive appropriate training	Collaboration between DPCB and FDA and in coordination with Partners
Train staff	Collaboration between DPCB and FDA and in coordination with Partners
Promote mechanisms to facilitate reporting	FDA
Develop standard operating procedures to be adopted from the national level to the facility level	FDA in coordination with Partners
Develop plans for data analysis, signal identification, and communication	FDA
Collect data	Treatment facilities (health professionals)
Report adverse events from client interviews and counseling	Treatment facilities (health professionals)
Manage and supervise all aspects of PV data collection, including monitoring of data collection and supportive supervision of selected sites by follow-up through email, telephone, and site visits	Collaboration between FDA and DPCB and in coordination with partners
Accurately process and manage all PV data collected, which includes data checks and validation and storage	Treatment facility, DPCB, and FDA
Conduct causality assessment and feedback	FDA
Transfer cleaned and validated data to the WHO Uppsala Monitoring Centre	FDA
Analyze the SAEs reported by treatment facilities	FDA
Provide feedback on the SAEs reported by treatment facilities	Collaboration between DPCB and FDA
Detect signals	FDA
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 medicines under targeted spontaneous reporting	Collaboration between FDA and DPCB

5. PROCEDURE

There are essential procedures in targeted spontaneous reporting that need to be followed by stakeholders for the effective implementation of the system. These include enrollment of clients; detecting, managing, and recording adverse events experienced by the clients; reporting AEs; conducting causality assessment and other statistical analyses; and developing and implementing communication strategies.

5.1. TREATMENT FACILITIES

All facilities implementing the use of PrEP and DTG based regimens in the country should be included in the TSR analysis.

5.2. ENROLLMENT OF PATIENTS/CLIENTS

Inclusion Criteria

These criteria are:

a) All clients taking a DTG-based and PrEP regimen from the initiation of treatment will be enrolled in the TSR.
b) All clients transitioned to TLD will be included.
c) The baseline data of the clients will be documented in each client's chart.
d) All clients included will be followed up for four months through phone calls, Messenger, and other means of communication.
e) If necessary, the client should contact the facilities to further evaluate the status of the reportable adverse events.

Exclusion criteria

Clients will be excluded from the analysis if:

a) He/she is not taking DTG-based and PrEP regimen.
b) He/she is more than four months from the time that TLD was initiated.
c) He/she is not willing to report the adverse events he/she experiences.
d) He/she does not want to be followed up.

5.3. MONITORING

1. All health care providers should observe and monitor for any adverse events that the clients might experience.
2. All identified adverse events should be managed and treated accordingly and should also be documented in the client's chart.
3. All health care providers should ensure that all adverse events are reported using the FDA Suspected Side Effects Reporting Form.

5.4. REPORTING OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

1. Reportable adverse events are hepatitis, depression, neural tube defect, insomnia, abnormal creatinine clearance, elevation on transaminase, discoloration of skin, abnormal blood sugar, abnormal liver enzymes, lactic acidosis, and any SAEs.
2. Health care providers should report all the AEs listed above, experienced by the clients, to FDA within 30 calendar days for non-serious AE and within 48 hours for serious AEs using the FDA

Suspected Side Effects Reporting Form upon knowledge of the event. A hard copy of the report should be filed in the patient/client's chart.

3. Health care providers should follow up the status of the reported SAEs.
4. Any improvement or worsening condition of the event should be submitted to FDA using the FDA Suspected Side Effects Reporting Form within 15 calendar days or upon resolution of the AE/SAEs. This should be indicated as a follow-up report.
5. All suspected adverse events related to DTG-based regimen and PrEP should be recorded and reported regardless of the judgment of the clinician or case manager about its causality in the patients' charts.

The following essential data elements should be included in the FDA Suspected Side Effects Reporting Form, for it to be valid:

a) Client details

- Client's name/client's initials – the first letter of client's/client's first name, middle name, and last name. This is to maintain their confidentiality
- Age – the client's/client's age at the onset of adverse effects
- Sex – male or female.
- Medical record number – patient's treatment registration number
- Address – name of the facility

b) Details of medicine

- Suspected medicine – indicate the suspected medicine that the client took or the vaccine that was administered that may have caused the adverse event. Name (generic or brand) must be indicated
- Batch/lot no. – this is the batch/lot no. of the suspected medicine/vaccine that may have caused the event.
- Dosage and frequency
- Route
- Date medicine started and date stopped
- Reason for using the medicine
- All concomitant medicines and/or vaccination taken over the past four weeks

c) Details of adverse events

- Date started – the date when the client first experienced the adverse event
- Description of adverse events
- Outcome
- Serious or non-serious
- Seriousness criteria, if serious
- License number of the health care professional (optional)

d) Reporter's information

- Name

- Address
- Contact phone number and email address
- Signature
- Reporter qualification – physician, pharmacist, nurse, dentist, other health professional, patient/consumer

5.5. INVESTIGATION

1. The FDA PV unit should regularly review the reported AEs/SAEs to check for any discrepancies/deviations and completeness of the report.
2. If there is a need for further investigation, the FDA must inform the health care provider or reporter and DPCB through email not later than seven days upon receipt of the report.
3. The health care provider or reporter should respond to the request within two days upon receipt of the email.
4. The investigation team should prepare a case investigation report and present it to the causality assessment committee.

6. DATA MANAGEMENT

Data management is crucial in all aspects of analysis. This section will describe the processes and procedures at the facility and national levels, covering the overall data flow within and between these levels and including data security and client confidentiality.

The whole duration of data collection and follow-up lasts for five months. Once the clinicians or case managers are notified of an adverse event by a client, it should be assessed and managed accordingly and must be documented in the client's chart. After that, the data flow procedure must be followed.

6.1. DATA FLOW

The process of data flow is outlined in figure 2.

1. Once the treatment facility (reporter) receives a report from the client, the FDA Suspected Side Effects Reporting Form should be completed.
2. The completed FDA Suspected Side Effects Reporting Form should be submitted to FDA online or through pharmacovigilance@fda.gov.ph. The treatment facility should inform the DOH DPCB that they have submitted a report to FDA.
3. Treatment facilities need to track the submitted report to FDA and should ensure that FDA acknowledges receipt of their report.
4. Upon receipt of the reports, FDA's PV Unit should acknowledge and assess the completeness of the report.

    - If the report is complete, FDA's PV Unit should proceed to conduct the causality assessment.
    - If the report is incomplete, FDA's PV Unit should send back the report via email to the treatment facility (reporter) and identify the lacking data.

5. The treatment facility should address the concern/s of FDA's PV Unit and revised the report accordingly. The revised FDA Suspected Side Effects Form must then be sent to FDA's PV Unit within two working days. The FDA PV Unit should check if the lacking data has been compiled by the treatment facility (reporter). If yes, FDA's PV Unit can proceed with the causality assessment.
6. After conducting the causality assessment, FDA's PV Unit should give feedback to the treatment facility (reporter) and DPCB. The treatment facility (reporter) must take appropriate action/s based on the recommendation/s of FDA. At the same time, DPCB must ensure that the recommendation/s is/are being implemented.
7. FDA's PV Unit must submit recommendations to DPCB. Also, FDA's PV Unit should release its final decision to DPCB and report to WHO's Uppsala Monitoring Centre.
8. FDA should organize quarterly, or ad hoc, meetings as needed with the National Pharmacovigilance Advisory Committee, depending on the degree of urgency on conducting causality assessments.

6.2. DATA SECURITY AND DATA CONFIDENTIALITY

1. Paper documents should be retained safely in a secured area inside a locked filing cabinet or drawer in a room, accessible only to health care providers.
2. Identifiable data of the clients included in the analysis must be confidential.
3. A client's initial, first letter of first name, middle name and last name should be utilized instead of their complete name.
4. Health care providers should ensure that a client's confidentiality is always maintained.
5. If any supporting documents such as laboratory results are sent to the FDA, the name of the client should be blacked out and only initials written.

6.3. DATA ANALYSIS

1. FDA in collaboration with DPCB and other partners should conduct regular descriptive analysis of data to determine the frequency, timing, seriousness, outcomes of AEs, and factors contributing to their occurrence.
2. Baseline demographics such as age, sex, presence of comorbidities, and the safety of DTG-based regimens and PrEP should be analyzed.
3. FDA should organize quarterly, or ad hoc, meetings as needed with the National Pharmacovigilance Advisory Committee, depending on the degree of urgency on conducting causality assessments.

6.4. FEEDBACK

1. FDA should acknowledge receipt of all reports submitted to them within 48 hours of receipt of the email.
2. FDA should give feedback to the reports submitted to them through email.
3. FDA should inform the treatment facilities of any management interventions such as stopping a client's treatment or reducing the dose, after the causality assessment.

RESPONSIBLE	NOTES
Patient/Client	
Treatment Facility	Treatment facility completes the FDA Suspected Side Effects Reporting Form and reports within 48 hours upon gaining knowledge of the event. Treatment facilities ensure there is a copy of the report in the patient's/client's chart.
PV Unit	
PV Unit	Evaluator gives feedback to the reporter if the data is complete by acknowledging the report.
Evaluator	If the data is complete, the evaluator needs to acknowledge receipt of the report. If the data is incomplete, the evaluator sends back the report to the treatment facility through email and identifies which data is lacking.
Treatment Facility	After addressing the concern, the treatment facility sends back the report to FDA.
PV Unit	
PV Unit	FDA gives feedback to treatment facility and DPCB via email.
Treatment Facility DPCB	Treatment facility takes appropriate action/s based on the feedback of FDA. It also informs the client/patient about the result of causality assessment. Treatment facility ensures the recommendation is being implemented.
PV Unit	

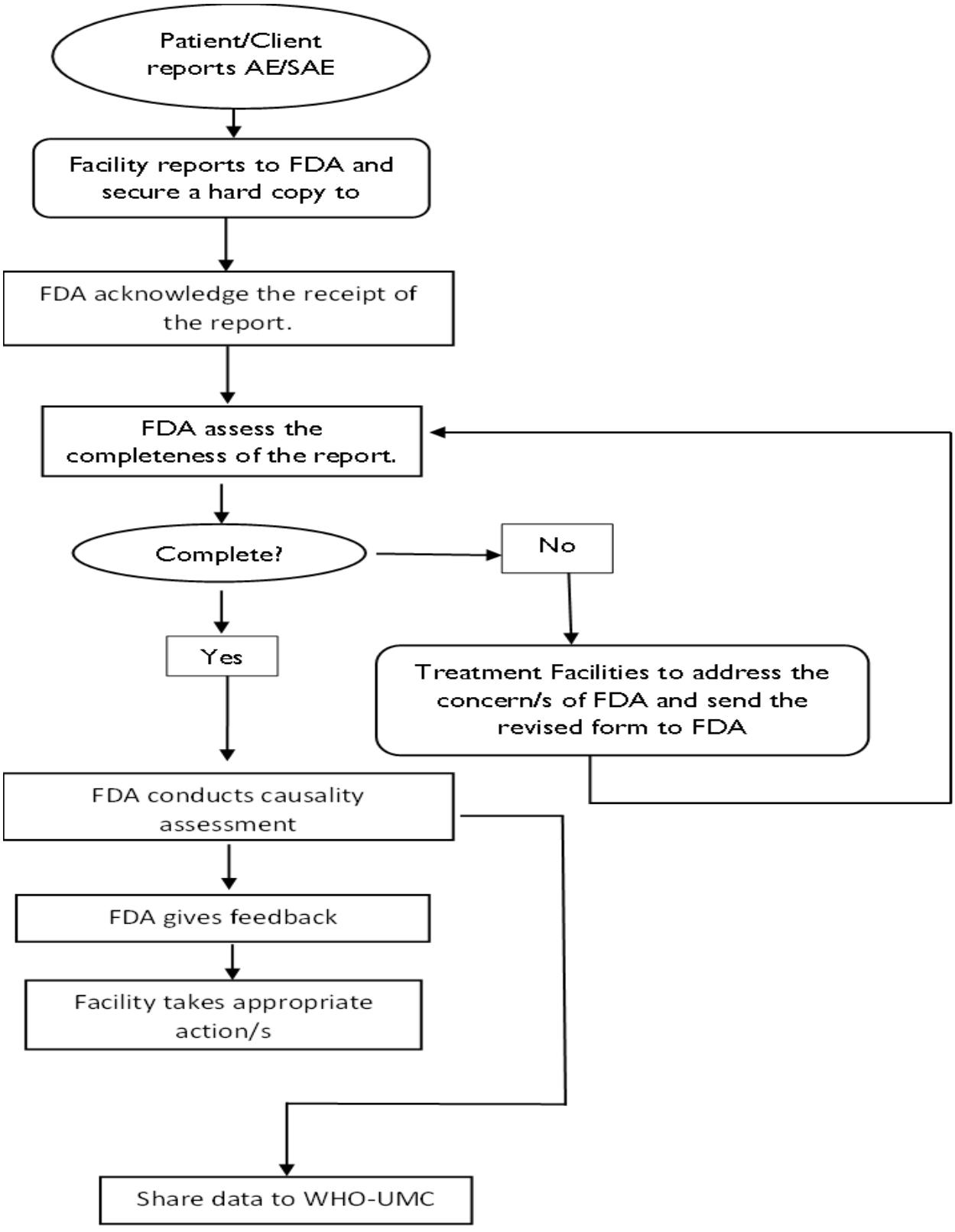

Figure 2. Process Flow of Targeted Spontaneous Reporting

7. DEFINITION OF TERMS

7.1. PHARMACOVIGILANCE

Pharmacovigilance has been defined by WHO as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problem."

Source: http://www.who.int

7.2. PHARMACOVIGILANCE UNIT

The national PV unit of an individual country is responsible for meeting the requirements for PV of all medicines. It is a unit of expertise for the art and science of monitoring and analysis, and use of the analyzed information for the benefit of clients. National and regional PV units should be set up with the approval of the authority responsible for the regulation of medicines ("regulatory authority"). The unit may function within the regulatory authority, a hospital, or an academic institution, or as an independent facility such as a trust or foundation.

Source: WHO. Safety Monitoring of Medicinal Products: Guidelines for Setting Up and Running a Pharmacovigilance Centre. Uppsala, Sweden; 2000. Source: https://www.who.int/publications/i/item/9789241503198

7.3. SIGNAL DETECTION

Signal detection involves reporting 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.

Source: WHO. Safety Monitoring of Medicinal Products: Guidelines for Setting Up and Running a Pharmacovigilance Centre. Uppsala, Sweden; 2000.

Available at: https://www.who.int/publications/i/item/9789241503198

7.4. ADVERSE DRUG REACTION

An adverse drug reaction is a response to a medicinal product which is noxious and unintended, and which occurs at doses normally used for the prophylaxis, diagnosis, or therapy of disease or for the restoration, correction, or modification of physiological function.

Source: WHO. Safety Monitoring of Medicinal Products: Guidelines for Setting Up and Running a Pharmacovigilance Centre. Uppsala, Sweden; 2000.

Source: https://www.who.int/publications/i/item/9789241503198

7.5. SERIOUS ADVERSE REACTION

A serious adverse reaction is any untoward medical occurrence that at any dose results in death, is life threatening, requires or prolongs client hospitalization, results in persistent disability/incapacity, or is a congenital anomaly/birth defect[6]. Life threatening refers to an event in which the client was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

7.6. ADVERSE EVENT

An adverse event is any untoward medical occurrence that may be present during treatment with a pharmaceutical product, but which does not necessarily have a causal relationship with the treatment.

Source: WHO. Safety Monitoring of Medicinal Products: Guidelines for Setting Up and Running a Pharmacovigilance Centre. Uppsala, Sweden; 2000.

7.7. HEALTH CARE PROVIDER

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

7.8. VIGIFLOW

VigiFlow is a web-based pharmacovigilance management system with streamlined easy-to-follow workflows that uses integrated standardized medical terminologies such as WHO Drug Global and MedDRA.

[6] Source: https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use_en-15.pdf

8. REFERENCES

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5. https://www.natap.org/2019/IAS/IAS_65.htm
6. World Health Organization http://www.who.int
7. Uppsala Monitoring Centre http://www.who-umc.org/
8. International Society of Pharmacovigilance www.isoponline.org
9. Systems for Improved Access to Pharmaceuticals and Services http://siapsprogram.org
10. https://who-umc.org/pv-products/vigiflow/