

Monitoring Adverse Drug Reactions in the Public Health Programs: the case of the Nigeria TB program

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Abstract

The public health programs provide unique opportunities for improving pharmacovigilance activities in resource-limited settings. Such programs use limited number of medicines in large population of people and data is more readily available. The medicines may be new with limited experiences from their real life use. As access to medicine improves, there is a need to continually monitor the safety of these medicines throughout use. Medicine safety data will ultimately provide vital information on the rate of known side effects, the occurrence of rare ADR, and the monitoring of the risks and benefits of the medication to inform regulatory and treatment guidelines decision making. The National Tuberculosis and Leprosy Control Program (NTBLCP) of Nigeria currently implements a successful TB directly observed treatment short-course program and intends to improve on the monitoring of the safety of the medicines used in this program. An assessment was therefore conducted to identify opportunities and challenges and recommend options towards improving ADR monitoring. The assessment involved data collection through document review, structured interviews, and questionnaires administered to key stakeholders, opinion leaders and informants, site visits, and presentations to stakeholders.

Findings include weak ADR reporting culture attributed to a demanding guideline and cumbersome ADR form, limited collaboration between the public health programs and the national pharmacovigilance center, lack of awareness and training on the need for ADR monitoring, and lack of institutional capacity for improving safety monitoring. It is recommended that the NTBLCP work closely with stakeholders in the immediate to simplify and institutionalize ADR reporting using the TB treatment card.

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ACRONYMS

ACT	Artemisinin based combination therapy
ADR	Adverse Drug Reaction
AE	Adverse events
AIDS	Acquired Immune Deficiency Syndrome
ARV	Antiretrovirals
CPT	Cotrimoxazole prophylaxis therapy
DOTS	Directly Observed Treatment Short-course
EMR	Electronic medical record
ESR	Enhanced Spontaneous reporting
FCT	Federal Capital Territory
F&D	Food and Drug
HIS	Hospital information system
HIV	Human Immunodeficiency Virus
GHCW	General Healthcare Workers
IPT	Isoniazid prophylaxis treatment
M&E	Monitoring and Evaluation
MOH	Ministry of Health
NAFDAC	National Agency for Food and Drug Administration and Control
NDSAC	National Drug Safety Advisory Committee
NTBLCP	National Tuberculosis and Leprosy Control Program
PEM	Prescription event monitoring
PEPFAR	President's Emergency Plan for AIDS Relief
PHP	Public Health Programs
PhV	Pharmacovigilance
PVG/FDIC	Pharmacovigilance/Food and Drug Information Center
RLS	Resource-limited settings
TB	Tuberculosis
TBCAP	Tuberculosis Coalition for Technical Assistance
WHO	World Health Organization

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EXECUTIVE SUMMARY

The use of limited number of medicines in the public health programs that treat large number of patients provide an opportunity to quickly generate real life data on the efficacy, safety and tolerability of the medicines. The public health programs provide a unique opportunity for improving pharmacovigilance activities in resource-limited settings. The National Tuberculosis and Leprosy Control Program (NTBLCP) of Nigeria currently implements a successful TB directly observed treatment short-course program and intends to improve on the monitoring of the safety of the medicines used in this program. Since 2002 more than 300,000 patients have enrolled on the TB program, however not much data is available to either reinforce the safety and tolerability of the medicines or to characterize patients risk profile. The need for improving medicine safety monitoring becomes increasingly important as programs use new medicines that received fast-track approval from regulatory authority and as treatment is decentralized and non-professional healthcare providers are expected to deliver treatment to patients.

The NTBLCP requested the tuberculosis coalition for technical assistance (TBCAP) to provide technical assistance towards the development of systems for improving adverse drug reaction (ADR) reporting. Any effort to improve ADR monitoring in a realistic and sustainable manner should involve all stakeholders and be led by the local pharmacovigilance authority. Therefore during the provision of the technical assistance TBCAP worked closely with the National Agency for Food and Drug Administration and Control (NAFDAC), the National Drug Safety Advisory Committee (NDSAC), and other key stakeholders to assess current challenges militating against ADR monitoring. The findings are reflective of what could be done to build systems that will sustain improved medicine safety monitoring irrespective of which public health program is concerned.

Some activities that need to be carried out in the immediate to improve ADR monitoring in the TB program and within other public health programs include:

- Improve collaboration between NAFDAC (at the national and State levels) with the NTBLCP and other public health programs
- Simplify and integrate reporting into existing monitoring and evaluation system
- Develop appropriate reporting system for every level of healthcare delivery
- Develop standardized training materials and provide trainings on pharmacovigilance
- Provide technical assistance and support to the department of Food & Drugs towards the development of national pharmacovigilance policy

In the long term, efforts need to be made to establish systems that will guarantee sustained efforts at safety monitoring including the use of new technologies like the mobile phone technology and internet to improve reporting; strengthening systems and capacity at the NAFDAC Pharmacovigilance/Food and Drug information center and the National drug safety advisory committee; and setting up national ADR data warehouse to provide national picture about the safety of medicinal products being used in Nigeria.

INTRODUCTION

Need for Pharmacovigilance

At the point new medicines are registered for use in humans not much is known about those medicines beyond data obtained from clinical trials in controlled settings. Clinical trials for the evaluation of safety, efficacy and quality of new medicines are conducted in patients that may not necessarily represent all type of patients that will use the medicines when they are approved. Limited numbers of patients are exposed to the medicine during clinical trials and research settings differ from the conditions of use when the drug is marketed.¹ Lack of complete understanding of the effects of long-term exposure, comorbid conditions, and use in elderly, racial groups, children and pregnant women are other limitations of preapproval clinical trials.² Currently, there has been a spate of increasing fast-track approval so as to make life-saving drugs available to patients that need them. An example is the fast-track approvals of antiretroviral (ARV) medicines. Post-marketing surveillance and pharmacovigilance activities can help in obtaining real-life information of safety and effectiveness of medicines when they are being used in the population. These activities can be through spontaneous reporting systems and pharmacoepidemiology studies for the validation of safety signals. Post-marketing surveillance activities have resulted in the reappraisal of indications (extension or restrictions), identification of risk factors and characterization of users, identification of long-term toxicities, quality problems, etc. Safety monitoring is critical for public health programs (PHP). This is because significant harm to a few patients can destroy the credibility, adherence to and success of a program. Rumors and myths about the adverse effects of medicines can spread rapidly and are difficult to refute in the absence of good data. Pharmacovigilance can provide these data.³

Pharmacovigilance and PHP

The public health programs have different strengths and challenges that should be considered while discussing safety monitoring in these programs. With regards to adverse event monitoring, one of the key strengths of PHP is the use of limited number of medicines as 1st & 2nd lines; this may not be same with other health conditions where choice of medicines may be less restricted. For instance most tuberculosis control programs use combinations of frontline TB medicines like Ethambutol (E), Rifampicin (R), Isoniazid (H), and Pyrazinamide (Z) for the intensive and continuation phase of treatment for new adult TB patients. It is potentially possible to monitor the safety and quality of these limited numbers of medicines. Ensuring the quality of those limited products is an issue of public health importance. The prequalification program which is a United Nations program managed by WHO prequalifies priority medicines by applying unified standards of acceptable quality, safety, and efficacy. The program key output: a list of prequalified medicinal products used for HIV/AIDS, malaria, tuberculosis and for reproductive health produced by the Program is used principally by United Nations agencies — including UNAIDS and UNICEF — to guide their procurement decisions.⁴ The PHPs also have the

¹ CDER, FDA, DHHS. 1998. The CDER Handbook. Available from: <http://www.fda.gov/cder/handbook/handbook.pdf> [Accessed August 28, 2008]

² Committee on the Assessment of the US Drug Safety System, Baciú A, Stratton K, Burke SP, eds. The future of drug safety: promoting and protecting the health of the public. Washington, DC: National Academies Press, 2006.

³ WHO (2006) The safety of medicines in public health programmes: pharmacovigilance an essential tool. WHO Library Cataloguing-in-Publication Data.

⁴ PREQUALIFICATION PROGRAMME: A United Nations Programme managed by WHO. Available from: <http://healthtech.who.int/pq/> [Accessed August 28, 2008]

advantages of large, defined populations and data is more readily available. There are extensive resources available to the PHP through government support and international donors. Conversely, the PHP has several challenges with regards to monitoring of adverse events to the use of medicines including: mass exposure to treatment; use of fast-track approved medicines (for example Zidovudine and other antiretroviral medicines); disease may not be well-diagnosed and presumptive treatment is practiced (example in the treatment of Malaria); patient migration and loss to follow-up. Other factors may include the impact of task-shifting or the decentralization of prescription rights; co-morbid conditions; nutrition status; drug interactions; and inadequate safety monitoring and patient information.

Burden of ADRs

In the US alone, according to the Institute of Medicine report *To Err Is Human: Building A Safer Health System*⁵ it is estimated that 7000 deaths occur annually due to ADRs. Lazarou et al⁶ in their meta-analysis of incidence of ADR in hospitalized patients reported 2.2 million serious ADRs and 106,000 deaths in 1994, making ADR the 4th-6th leading cause of death. This study excluded errors in drug administration, noncompliance, overdose, drug abuse, therapeutic failures, and possible ADRs. It also used a very narrow definition for serious ADRs: Serious ADRs were defined as those that required hospitalization, were permanently disabling, or resulted in death. Nursing homes have high incidence of ADRs due to comorbidities and concurrent use of many medicines in the elderly.⁷ Data is not readily available on the burden of ADRs in resource-limited settings. It is however anticipated that the burden may even be more due to several factors including;

- High prevalence of HIV/AIDS, TB, Malaria and other comorbid conditions
- Risk-benefit profile may differ
- Widespread generics use, poor labeling, off-label use
- Traditional medicines and associated adverse events and interactions
- Genetic make up, nutrition status
- Regular monitoring for early signs of toxicity not feasible

Data is beginning to accumulate on the burden of adverse events to ARVs in the resource-limited settings. In the overview of current knowledge of ARV-related adverse events that reviewed 40 publications on ARV-related adverse events (AEs) from 1999-2007⁸, anemia, rash, neuropathy, lipodystrophy, and hepatitis were identified as the top 5 AEs. In Africa, neuropathy, neutropenia, and lipodystrophy were the predominant AEs that limited treatment or resulted in treatment modification. The MSF ART program in Khayelitsha, a poor township with about 500 000 residents in Cape Town, was the first primary health care ART program in Africa started in 1999. After 4 years, this MSF site has established that 14% of patients changed ARV due to AE

⁵ Committee on Quality of Health Care in America: Institute of Medicine, *To Err Is Human: Building A Safer Health System* (Washington, DC: National Academy Press, 2000)

⁶ J. Lazarou, B. Pomeranz, and P. Corey, "Incidence of Adverse Reactions in Hospitalized Patients: A Meta-analysis of Prospective Studies," *Journal of the American Medical Association* 279, No. 15 (1998): 1200-1205.

⁷ J.H. Gurwitz et al., "Incidence and Preventability of Adverse Drug Events in Nursing Homes," *American Journal of Medicine* 109, No. 2 (2000): 87-94.

⁸ WHO/Forum for Collaborative HIV Research Joint Meeting ARV Drugs Adverse Events, Case Definition, Grading, Laboratory Diagnosis and Treatment Monitoring Available from: www.hivforum.org

or contraindication. In Botswana, the Tshepo adult ART and resistance study which aims to assess the emergence of drug resistance to and the tolerability of different protease inhibitors (PI) sparing ART regimens, in a preliminary result showed that about 18% of patients experienced AE that required treatment modification. Kim et al. in their study on adverse events in HIV-Infected persons receiving ARVs in large urban slum in Nairobi from 2003-2005, established that 65% of 283 patients experienced AEs, out of which 6% had severe toxicity. As at 18 months, only about 17% of patients had a probability of not experiencing any adverse event. This study highlights the importance of monitoring AE on patients on ART in Kenya.

In tuberculosis treatment, new medicines are being introduced for multi-drug resistant (MDR) and extremely drug-resistant tuberculosis (XDR) TB. Old medicines are being withdrawn, example thiacetazone and there are continuous challenges of resistance and treatment failure. TB drugs may be administered by health care workers other than doctors and nurses and at times there is strong community participation particularly in the directly observed treatment short-course (DOTS) programs. Data is not readily available from most resource-limited settings (RLS) on the prevalence of adverse events to antiTB medicines. However cases of both known and unknown side effects and adverse events are seen in practice which includes optic neuritis, ototoxicity, jaundice, seizures, neuralgias, arthralgia, renal toxicity, and psychotic problems.

Pharmacovigilance in resource-limited settings

Both developed and developing countries recognize the vital importance of Pharmacovigilance and specifically the need for adverse event reporting. All countries face the challenges of ensuring the quality and safety of medicines. Recent global mishaps are a testament of how challenging it is to address this. Some of those recent events include the contaminated heparin with over-sulfated chondroitin sulfate, the diethylene glycol (DEG) poisoning, rofecoxib and cardiovascular events, rosiglitazone and myocardial infarction, and many others. The need for pharmacovigilance and ADR monitoring may be more needed in the resource-limited settings for a variety of reasons. These may include the significant recent increases in the availability and use of relatively new essential medicines; the systems to implement PhV are often weak or non-existent; there is lack of systematic approach to addressing medicines safety, and patients from those settings may present different susceptibility profile for adverse events due to genetic, nutritional, and other differences. In recognition of the challenges of post-registration safety monitoring, the WHO program for international drug monitoring⁹ works closely with national pharmacovigilance centers including those of resource-limited countries to monitor medicine safety. This support and the recent interest from governments and donor organizations on the issue of medicine safety have bolstered efforts at ADR monitoring in the resource-limited settings.

Pharmacovigilance in Nigeria

The Nigeria National Drug Policy¹⁰ recognizes that no active drug is entirely free from adverse reactions. The policy states that government will encourage the establishment of adequately equipped pharmacovigilance units nationwide to collect, evaluate and disseminate relevant information on adverse drug reactions and poisoning. The policy requires that all drugs shall be monitored with respect to efficacy, safety and quality so as to inform regulatory decision. The National pharmacovigilance center, that is the pharmacovigilance/Food and Drug Information

⁹ The Uppsala Monitoring Centre. Available from: <http://www.who-umc.org/> [Accessed August 28, 2008]

¹⁰ Federal Ministry of Health, Nigeria. National Drug Policy (2005). ISBN 978-067-237-0

Center (PVG/FDIC) was started in 2004 and is affiliated to the WHO Collaborating center for international drug monitoring. The PVG/FDIC is an integral part of the national drug regulatory authority; the National Agency for Food and Drug Administration and Control (NAFDAC). The regulatory authority also constituted the National Drug Safety Advisory Committee on 26th July, 2006.¹¹ The committee tasks include making recommendations to NAFDAC on safety, quality, and efficacy issues of registered drugs and assessing safety issues related to drug use. The PVG/FDIC developed a guideline for the monitoring of safety of medicines in Nigeria which set out clear objectives including¹²:

- Raise awareness on the magnitude of drug safety problems
- Convince health professionals that reporting of Adverse Drug Reactions (ADRs) is their professional and moral obligation.
- Aid health professionals in becoming vigilant in the detection and reporting of ADRs and other drug induced problems.

With respect to the ADR reporting, the Nigeria guideline is very ambitious, requiring all health care workers including traditional medicine practitioners to report all suspected adverse reactions to drugs including orthodox medicines, vaccines, medical devices and traditional and herbal remedies. Apart from the traditional pharmacovigilance activities, the Nigeria guideline hopes to use pharmacovigilance as a tool to aid the fight against counterfeiting. The National Pharmacovigilance centre (PVG/FDIC) routinely engages the public health programs (PHP) to ensure that ADR monitoring is taken seriously and acted on. It is evident that both the PVG/FDIC and the PHP need to collaborate more closely for mutual benefits. Both need data on safety of medicines. They both also need:

- Data that is reliable and verifiable
- Data that can be used to Improve public trust in the safety of PHP medicines
- Data that can be used to promote government and donor stewardship in safeguarding public health

¹¹ The PVG/FDIC Newsletter. National Agency for Food and Drug Administration and Control (NAFDAC). Vol 1 No 1 May, 2007

¹² National Pharmacovigilance centre (PVG/FDIC), NAFDAC, Nigeria. Safety of medicines in Nigeria: A guide for detecting and reporting adverse drug reactions – why health professionals must act.

BACKGROUND

The National Tuberculosis and Leprosy Control Program (NTBLCP) of Nigeria adopted the WHO recommended DOTS strategy in 1994. Since then the DOTS strategy has been successfully scaled up and as of the end of the second quarter 2006, DOTS services were available in all 36 states. About 550 out of a total of 774 local government areas currently have at least one facility providing DOTS services. Part of the components of the STOP TB¹³ strategy and implementation approaches is to pursue high quality DOTS expansion and enhancement including amongst other activities to standardize treatment with supervision and patient support, to ensure effective drug supply and management system, and establish monitoring and evaluation system and impact measurement. TB/HIV co-infection and the noxious synergy it presents is well recognized by the TB program in Nigeria. The program in the draft guideline states that TB and HIV are among the 10 leading causes of death in Nigeria. While HIV fuels the TB epidemic in immuno-compromised individuals, TB is the most common cause of death among People Living With HIV/AIDS (PLWHA). TB is responsible for around 30% of deaths among PLWHAs. Therefore interventions aimed at controlling TB and HIV will be of benefit to the Control Programs of both diseases. The program has elaborate plans to ensure that health care workers are mindful of adverse events while implementing components of the TB/HIV activities including the treatment of HIV patient that develops TB disease, Isoniazid prophylaxis treatment (IPT), Cotrimoxazole Preventive Therapy (CPT) and managing other opportunistic infections. However not such had been done on medicine safety monitoring in the TB program. Since 2002, more than 300,000 patients have enrolled on the TB program and there are no adverse event reports or data on the tolerability of the TB medicines available. This has really been a lost opportunity to either reinforce the safety of the medicines or to identify and characterize risks for toxicity.

As access to TB medicine is increased, there is a need to continually monitor the safety of these medicines throughout use. The Nigeria Pharmacovigilance center (PVG/FDIC) as a unit of the National Agency for Food and Drug Administration and Control (NAFDAC) coordinates pharmacovigilance activities in Nigeria. The NAFDAC pharmacovigilance program is responsible for monitoring safety of all medicines in Nigeria. Current efforts on safety monitoring are concentrated on spontaneous reporting of adverse drug reactions from professional health care workers. There are no experiences in building systems to facilitate patient-initiated reporting of ADR through the lowest level of health care workers. Also there is a need to strengthen ADR reporting from the public health programs like the NTBLCP DOTS strategy and link them with the activities of NAFDAC pharmacovigilance program. Every interface of patient and healthcare worker is an opportunity not just for dispensing TB medicines but for data collection on patient experience with the use of those medicines. Such data will ultimately provide vital information on the rate of known side effects, the occurrence of rare ADR, and the monitoring of the risks and benefits of the medication to inform regulatory and treatment guidelines decision making.

¹³ Draft Guideline. Part B Implementation of the TB control components.

TBCAP technical assistance to the NTBLCP

In an effort to improve the monitoring of adverse drug reactions due to TB medicines, the NTBLCP requested TBCAP to provide technical assistance towards the development of systems for patient-initiated reporting of adverse drug reactions due to TB medicines. The NTBLCP had earlier initiated efforts to work closely with PVG/FDIC of NAFDAC, the TB program and NAFDAC considered this technical assistance as critical towards addressing the issue of improving ADR reporting not just by the TB program but also all the PHP.

Objectives

To develop and implement systems for patient-initiated reporting of adverse drug reactions due to TB medicines over a five month period.

Scope of Work

The consultancy will provide an opportunity for the review of the current pharmacovigilance system in Nigeria particularly as regards ADR data collection. It will allow for the development of a first draft of a model for patient-initiated reporting with systems for delivery of data to both the national pharmacovigilance program and the NTBLCP for regulatory and treatment guidelines decisions respectively. The key activities of the consultancy will include:

- Review ADR data collection strategies of the national pharmacovigilance program
- Review current NTBLCP efforts at ADR data collection and review dispensing channels of DOTS to identify opportunities for ADR reporting
- Assess knowledge, attitude, and practice of health workers involved with DOTS and TB medicines on ADR reporting
- Make presentation on preliminary findings
- Develop an implementation plan with local stakeholders
- In collaboration with NAFDAC and NTBLCP, develop and pilot ADR forms that can be used at the lowest level where TB medicine dispensing occurs, develop draft pharmacovigilance registers, and explore opportunities for pilot active sentinel surveillance of safety of TB medicines
- Develop systems for delivery of ADR data related to TB medicines to both the national pharmacovigilance program and the NTBLCP and other relevant stakeholders

Expected deliverables

1st Consultancy

1. Presentation to the NTBLCP and NAFDAC of preliminary findings
2. Implementation plan
3. Draft SOW for follow up visit

2nd Consultancy

1. ADR data collection system for TB medicines
2. Consultancy report

ASSESSMENT OF CURRENT PRACTICES ON ADR MONITORING

An assessment was conducted to provide local information, identify opportunities and challenges and recommend options towards improving ADR monitoring. From the onset of the consultancy, the NTBLCP indicated interest to review the scope of work to address the development and implementation of systems for improving ADR monitoring in PHP. This decision was taken due to already existing relationship between the national TB program and other PHP notably the ART program.¹⁴

Assessment method

It is imperative that an assessment of this nature should obtain a clear, correct, and current understanding of situation on ground so as to inform situation analysis and the development of options and recommendations. The assessment therefore involved data collection through document review, structured interviews, questionnaires administered to key stakeholders, opinion leaders and informants, site visits, and presentations to stakeholders.

Document review and interviews

Numerous documents including policies, guidelines, forms, patient cards and others were reviewed. Data collection instruments used included an interview guide. This interview guide (ANNEX 1) was used to elicit and collect information from NAFDAC, PHP, MOH Program managers, National Drug Safety Advisory Committee, and other key informants. Below is a list of stakeholders interviewed and documents that were reviewed:

- Interviews: NAFDAC; Director General, Deputy Director/Head Pharmacovigilance/Food & Drug Information Center (PVG/FDIC), other staffs (3) of FDIC, Chairman National Drug Safety Advisory Committee (NDSAC) and other members. NTBLCP; National coordinator, staffs (4) of the logistics unit, FCT TB control program. Public health programs; National HIV/AIDS /STI Control Program. Federal Ministry of Health; Director, Food & Drug, deputy director, Clinical Pharmacy.
- Reviewed documents: National Drug Policy, guideline on safety of medicines in Nigeria, draft Pharmacovigilance policy, draft TB (Zaria) manuals, NTBLCP TB treatment card, NTBLCP suspected ADR report form, NAFDAC PhV newsletters, Pharmacy & Drug Laws in Nigeria, etc

Sites visits

A simple questionnaire (ANNEX 2) was developed for the collection of information from healthcare workers on their knowledge, attitude, and practice towards ADR reporting. Another survey instrument (ANNEX 3) was used for obtaining similar information from patients. These questionnaires were presented to the national TB coordinator and approved for use in data collection. The site visit was engaged by two staffs of the NTBLCP and a staff of NAFDAC with the consultant. A letter was obtained from the NTBLCP and the FCT TB coordinator to introduce the team to the relevant TB focal persons in the facilities they were to visit. The

¹⁴ It was however not possible to fully involve the ART and the Malaria programs in the activities. However, during the in-brief presentation many PEPFAR implementing partners were present including CDC, IHVN, FHI/GHAIN, HUCE-PACE, ENHANSE, ICAP, and WHO.

facilities visited include TB clinics in Kwali and Abaji. The Training Centre for TB and Leprosy in Zaria was also visited. During the site visits, the questionnaires were administered to healthcare workers and patients.

Presentations to stakeholders

To ensure common understanding of the issues related to PhV and ADR monitoring in the PHP, a presentation was made to key stakeholders at the beginning of the assessment. The presentation was attended by representatives from NTBLCP, NAFDAC, WHO, and several PEPFAR implementing partners. After the presentation there was a session of questions and answers and comments. Most of the comments are included in this report. Another presentation was made to the National Drug Safety Advisory Committee (NDSAC). This presentation elicited numerous comments related to the monitoring of ADR within the PHP. Those comments are also captured within the report. The third and last presentation was made to share assessment findings with stakeholders. After the presentation, discussions were held in plenary and thereafter a small group came together to address next steps and formulate an implementation plan.

RESULTS AND DISCUSSIONS

The NAFDAC has made tremendous efforts to set up a national coordinating center for drug safety monitoring through the establishment of the Pharmacovigilance/Food & Drug Information Center. The need for drug safety monitoring is well articulated in the National Drug Policy. The need for a national PhV policy was identified as a priority by both NAFDAC and the department of Food and Drug (F&D). There is currently a working document that is serving as draft and F&D indicated that they are currently soliciting for technical assistance and support towards the finalization and publication of a national PhV policy. A national PhV policy will clearly set out, from a policy perspective, the roles and responsibilities of all involved in product safety monitoring including the role of the product sponsors. The PVG/FDIC guideline on *Safety of Medicines in Nigeria – A guide to detecting and Reporting Adverse Drug Reactions* provides overview on PhV and clearly provides guide to health professionals on the need for ADR reporting. The guideline also informs potential reporters on what, when, and how to report suspected adverse events. It was not possible during the study to assess if the guideline is widely distributed. However, the availability of a national guideline on medicines safety is an important step that may soon encourage greater awareness on the need for safety monitoring. National guideline for ADR monitoring exists in other countries including Kenya¹⁵ and Ethiopia¹⁶. The Nigeria guideline recommends that all suspected reactions including minor ones for new medicines should be reported. Also all health professionals including traditional medicines practitioners are expected to report. This is a very rigorous reporting requirement. The ADR reporting form meets international standards in having necessary fields for key information on identifiable patient, event, suspect drug, and reporter. However, the complexities of the form makes it highly unlikely that busy healthcare workers will routinely complete ADR forms for all suspected adverse reactions to new medicines. Also, it can be a challenge for the busy health providers and de-motivate ADR reporting if all the fields of the ADR forms must be completed for every event including the well known ones in the case of new medicines. At the lowest health delivery level like the TB DOTS center the chances that the ADR forms in its current format will be completed is highly remote. There were also anecdotal reports that the TB program view the NAFDAC ADR form as a foreign document. To address this, the NTBLCP and NAFDAC developed a customized version of the NAFDAC ADR form specifically for the NTBLCP program (ANNEX 4). The thinking behind this initiative is very commendable and highlights the fact that efforts are being made by NAFDAC and NTBLCP to find avenues for improving safety monitoring within the TB program. The proposed ADR form for the TB program was reviewed and its main difference was in branding the form for the NTBLCP. The form however still remained complex. The reporting requirements is still very rigorous and the chances of such a complex form being completed at the lowest health delivery point like the TB DOTS centers is highly unlikely.

¹⁵ Ministry of Health Kenya, Pharmacy and Poison Board. Guideline for the National Pharmacovigilance system in Kenya. December 2007. Available from:

<http://www.pharmacyboardkenya.org/assets/files/Pharmacovigilance%20Guideline.pdf> Accessed 12th June, 2008

¹⁶ Drug Administration and Control Authority (DACA) Addis Ababa. Guideline for adverse drug reaction reporting Available from: <http://www.daca.gov.et/Documents/ADR%20Guideline.pdf> Accessed 31st July, 2008

The NTBLCP have shown interest in improving the safety monitoring of its medicines. The program works closely with a staff of NAFDAC to address ADR reporting issues. It was through this collaboration that the NTBLCP ADR form was developed. Developing such a routine relationship with the national PhV center is an exemplary initiative that can be emulated by all the PHPs. Through that collaboration the NTBLCP has indicated interest in integrating the ADR monitoring form into its M&E system. During the consultancy the draft TB guidelines were reviewed. Also the TB treatment card was reviewed. The draft manual discusses side effects that are noted with the TB medicines, it also discusses their management. The draft manual however did not clearly mention the need for ADR reporting and a standard approach for safety monitoring. The TB treatment card does not have any field for the reporting of side effects or adverse events. The TB treatment card is the most important form used in the program and is routinely completed by healthcare workers including the General Health Care Workers (GHCW) during the TB DOTS clinics. This TB treatment card therefore provides a great opportunity for ADR reporting. It appeared that opportunities for ADR reporting at the lowest healthcare delivery levels are lost because of poor data management and other system issues including the rigor of the reports that are required. It also appears that there is a lack of a strategy for the application of different reporting plans depending on the healthcare delivery level. Mehta et al¹⁷ developed 5 surveillance methods to monitor the safety of antimalaria in Mpumalanga province of South Africa. Those methods reflected the diagnostic capability and population exposed to treatment at each level of healthcare provision. Such a strategy may be applicable to the NTBLCP. Some clinicians interviewed reported their interest in ADR reporting and how they have advocated for some form of patient-initiated reporting or patient direct reporting through the use of mobile phones. The idea of reducing the complexity of the reporting requirement based on the sophistication of the level of care was discussed and will be further explored in this report.

Some PHP, particularly the ART programs, collect ADR reports. However there are no standardization with respect to the data they collect, there are no indicators, and no directives with regards to upward transmission of the reports to NAFDAC. The PHP are disconnected from NAFDAC in their PhV related activities. For instance the ADR data collected from the programs are not made available to NAFDAC and are not used to inform regulatory decisions. NAFDAC reported that some of the PHP conduct PhV trainings without NAFDAC involvement. According to the PVG/FDIC the major challenge of NAFDAC as regards improving ADR monitoring within the PHP is the need to ensure that data captured from the PHP are sent to NAFDAC and also made use of to improve safety and treatment outcome. They also want PHP to provide support and resources towards the strengthening of NAFDAC capacity to improve safety monitoring. During a presentation made to the NDSAC, the committee emphasized the need for the PHP to partner with PVG/FDIC to improve ADR monitoring. The committee hopes that such partnership will lead to the establishment of systems for data collection, causality assessment, and conduct of further (pharmacoepidemiology) studies with the ADR reports obtained from the PHP. The committee is of the view that some of the resources available to the PHP can be used to support NAFDAC PhV activities to ensure that the benefits and risks of medicines used in PHP in Nigeria are clearly understood. Collecting ADR data is of mutual benefit to the PHP and the regulatory authority. The data generate can be used to improve public trust in the safety of

¹⁷ Mehta U, Durrheim D, Mabuza A, Blumberg L, Allen E, Barnes K. Malaria Pharmacovigilance in Africa: lessons from a pilot project in Mpumalanga Province, South Africa. *Drug Safety* 2007; 30 (10): 899-910

PHP medicines. Also ADR data can be used to promote government and donor stewardship in safeguarding public health. Funding and support for ADR monitoring activities can be included in Global Fund grant budget according to the guide to the Global Fund's policies on procurement and supply management.¹⁸ Many ART and Malaria programs also consider safety monitoring of the medicines they use in their programs as important activities. There is therefore a potential for leveraging resources to improve the capacity of NAFDAC towards ADR monitoring.

Below is a summary of the key findings from the review of the documents and the structured interview:

- Lack of policy and governance seem to be stalling PVG/FDIC efforts at institutionalizing ADR reporting and safety monitoring. The F&D, PVG/FDIC, and the NAFDAC's expert committee (NDSAC) all clearly identified the development of a national PhV policy as the first priority towards improving safety monitoring in Nigeria. It is hoped that the national policy will clearly delineate roles and responsibilities of all stakeholders and establish accountability, transparency, and good governance in safety monitoring in Nigeria. The existing laws related to medicines regulations did not clearly spell out PhV and related activities. An amendment to that law is currently with the national assembly.
- Lack of capacity, infrastructure, and resources at PVG/FDIC. There is a need to improve the institutional capacity of the PVG/FDIC with the provision of basic tools like online subscription of current literature, toll-free lines and other communication technologies that can improve services at the center. The PVG/FDIC currently lacks some critical SOPs. Also their staffs lack training in major aspects of their work including the areas of data management. Both staffs and members of NDSAC can benefit from additional training in signal detection, causality analysis, active surveillance and pharmacoepidemiology methods.
- Transmission of ADR reports from the PHP to PVG/FDIC is not practiced. The NTBLCP does not routinely communicate with NAFDAC on safety of products used in the program. ADR reporting during the administration or dispensing of TB medicines in the TB DOTS program is not practiced. The PhV center and the Malaria program are currently collaborating in a joint active surveillance activity (cohort event monitoring of the Artemisinin based combination therapy, ACT)
- Data management and logistics of reporting is very weak. NAFDAC has huge challenges in entering the reports they receive into the international database. This is due to the poor internet connectivity at the center. To send out reports, an intern goes out to an outside internet café and spends about 5 hours daily in an effort to send reports to the online international database. There is a need for a high speed internet facility to support this activity.

¹⁸ The Global Fund To Fight AIDS, Tuberculosis and Malaria. Guide to the Global Fund's policies on procurement and supply management. November 2006. http://www.theglobalfund.org/pdf/guidelines/pp_guidelines_procurement_supplymanagement_en.pdf

- PhV training is discrete, uncoordinated, and insufficient. PhV training has been concentrated at the tertiary health institutions. It is estimated that about 85% of healthcare workers from tertiary institutions have been trained in PhV. There has not been training at below this level. There is no standard national curriculum for PhV trainings. The NTBLCP has not had any form of PhV training for TB DOTs staffs or for any healthcare provider involved in the TB program. ADR monitoring curriculum is not included during health providers training on treatment guidelines. The need for ADR reporting is not reinforced by the PHP.
- No medicine safety indicators for routine reporting by the PHP exists. There are no clear reporting requirements from the national PhV center to the PHP.
- Reporting rate is low, awareness on responsibility for reporting is low, and reporting guideline is very demanding to achieve. For example the ADR reporting forms and the safety monitoring guideline were distributed during a TB activity in 2006, there has not been a single ADR report received since to reward that effort.
- Interest in participating in reporting is weakened by the current ADR form. Some of the respondents clearly stated that the current ADR form is cumbersome and not user-friendly. It is obstructive to normal clinical duties and is seen as foreign (since it is not from the TB program). Some of the PEPFAR implementing partners are currently collecting ADR reports and are willing to share them. They are also willing to participate in the development of standardized and acceptable ADR data collection system. The Department of Food & Drugs does not want each PHP to set up vertical PhV system but will prefer that ADR monitoring is institutionalized.
- Limited collaboration between NAFDAC and the PHP. NAFDAC's PVG/FDIC has taken the initiative to appoint its staff to work closely with the PHP to improve their collaboration. This is a very commendable initiative and can be developed further to address all issues related to improving medicine safety monitoring in the PHP. NAFDAC planned to have PhV officers in every state of Nigeria and these PhV officers will have access to NAFDAC PhV documents and materials. These officers are strategically located to participate in the TB program's State quarterly review meetings. During these meetings the ART program also attends because of the TB/HIV/AIDS mainstreaming strategy. These meetings are therefore common ground for discussions at the state level on ADR monitoring issue and for data collection and feedback. NAFDAC needs support to implement this strategy.
- Routine ADR reporting using the existing form is an untenable challenge for TB DOTs. The ADR reporting requirement is very rigorous and the chances that the current ADR forms can be completed at every point and by all cadre of HCW is very slim. There is a need to structure complexity of ADR reporting form to suite the healthcare delivery level.

Survey feedback: Health worker ADR reporting

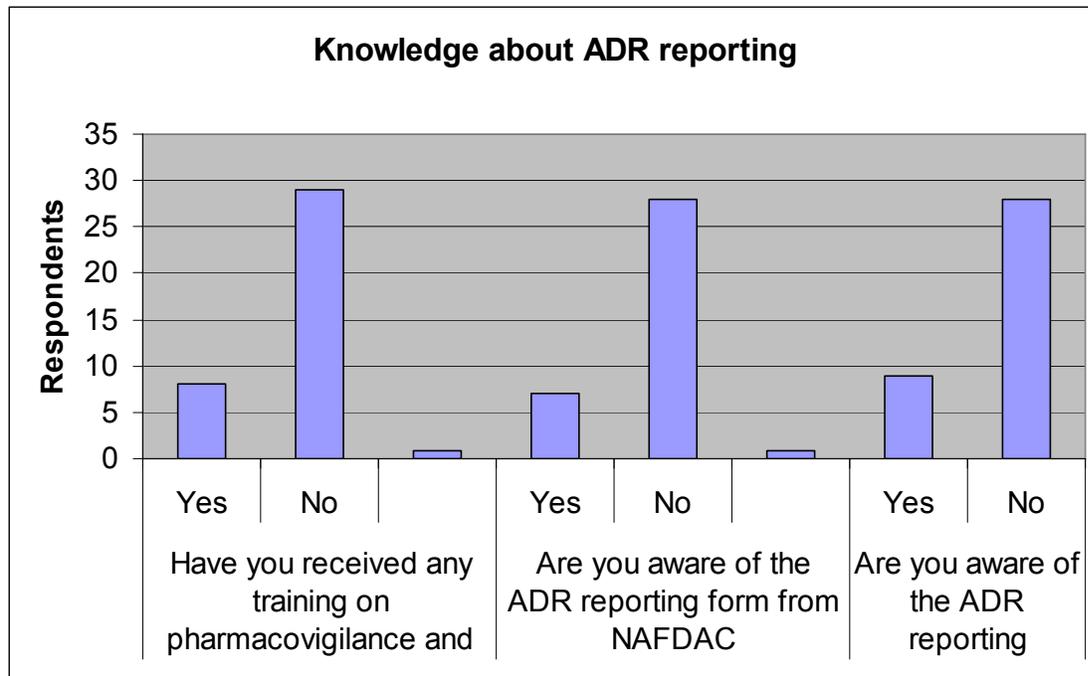
Understanding of knowledge, attitude, and practice related to ADR reporting provides useful information that guide interventions to improve reporting. Literature is scarce on attitudes

towards ADR reporting in Nigeria. However, Enwere and Fawole¹⁹ studied ADR reporting by physicians in Ibadan, Nigeria; nearly 90% of physicians surveyed had observed at least one ADR but only 32% had ever reported it. The commonest factors that militate against ADR reporting were lack of knowledge that reporting forms were available (70.9%) and ignorance of reporting procedure. The values from this study can not be extrapolated to the entire country or to the PHP because of some differences. The PHP are mass treatment programs that utilize other healthcare providers besides physicians in the management of patients. Some of these providers may be non-professional healthcare workers. Example the general healthcare workers are used in the TB DOTS program. Since the providers in the TB DOTS program are different, we conducted a survey of healthcare providers who administer or dispense TB medicines so as to understand their knowledge, attitude and practice related to ADR reporting. A convenient sample of 36 TB program healthcare workers from Abaji and Kwali within the FCT, and Zaria were administered questionnaires. Also a total of 32 patients were also surveyed in an exit interview to obtain their knowledge, attitude and practice towards ADR reporting.

From the healthcare workers surveyed; 21 (57%) were general healthcare workers who attend to patients in the TB DOTS clinics (ANNEX 5). About 60% of the surveyed health providers work at ART clinics that also offer IPT & TB/HIV services. Some of the feedbacks from the survey include:

- About 78% has not received any training on pharmacovigilance and /or ADR spontaneous reporting
- A total of 80% are not aware of the ADR reporting form from NAFDAC and 76% are not conversant with the reporting procedure
- While all surveyed healthcare workers (100%) think ADR reporting is useful to their practice, only 58% know that all ADRs should be reported; nearly 40% do not report because ADR reporting forms are not available
- When asked about their satisfaction with the data collection process, only 21% were very satisfied with the process
- Only 1 respondent has ever submitted an ADR form
- A total of 54% said they have documented patient reported side effects on the case note. It therefore appears that healthcare workers are interested in documenting ADRs but find the current forms obstructive to practice and complex to use.

¹⁹ Okezie E, and Olufunmilayo F. Adverse drug reactions reporting by physicians in Ibadan, Nigeria. *Pharmacoepidemiology and Drug Safety* 2008; 17: 517-522

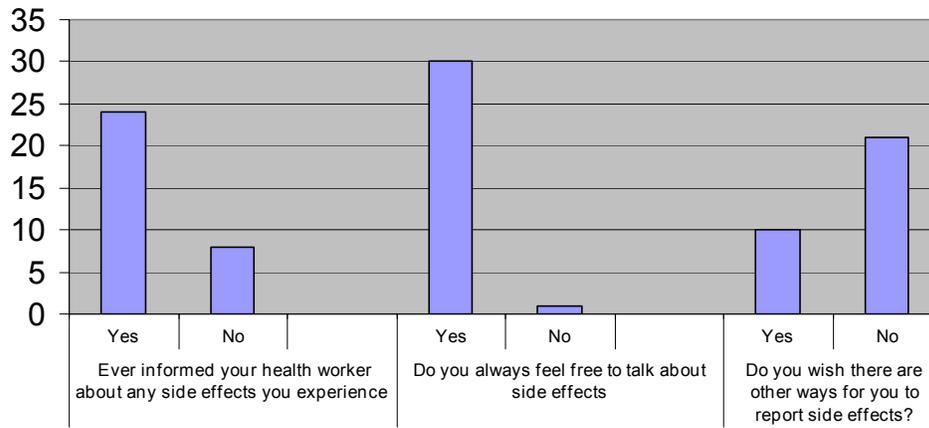


Survey feedback: Patient ADR reporting

There is currently no published study on patient’s attitude to ADR reporting in Nigeria. However there are traditional health orientations and ethnographic statements that patients in Nigeria consider side effects to medication as a proof that the medicine is powerful and likely to relieve illness. How much these believe effects the attitude towards ADR reporting is not well studied. Patients attending clinic on the days of site visits to Abaji, Kwali and Zaria were enrolled for an exit interview with the questionnaires developed. A total of 32 patients responded to the interviewer-administered questionnaire (ANNEX 6). Some of the key findings from the survey include:

- With the exception of 1 patient, nearly all patients (97%) responded that they were told the side effects to expect from their medicines and 76% were able to correctly mention these side effects
- When asked what they should do when they experience side effects they were not warned about, 79% answered correctly that they should report it to their doctor or nurse
- Three out of every four patients have informed health worker about side effects they experience. This is a very high reporting rate and suggests that poor reporting from health workers can not be attributed to lack of reporting from patients
- When asked “Apart from talking to your healthcare provider, do you wish there are other ways for you to report side effects?” 32% of patients answered yes. This may seemingly suggest that one third of all patients seek for alternative avenues for reporting.

Patients ADR reporting behaviour



RECOMMENDATIONS FOR IMPROVING ADR MONITORING IN PHP

Improve collaboration

The challenges with ADR monitoring in the NTBLCP can be addressed by exploring the broader issues of limited collaboration between the PHP and the State and National PhV centers. The challenges are usually manifest when the PhV programs are not able to provide data or information on the tolerability of medicines used in PHP in their country. Some PHP are mindful of the need to monitor tolerability and safety profile of the medicines they use in their programs. This is the case with the NTBLCP. However, that understanding can only be translated into meaningful effort if the guidelines and standards for reporting and transmission of ADR data are clearly developed by the PhV center and discussed with the PHP. Effort to improve ADR monitoring in the TB programs should start with utilizing opportunities for collaboration between the NTBLCP and NAFDAC. This collaboration will potentially result in improved ADR data tracking and transmission to the regulatory authority. One avenue for improving this collaboration is for NAFDAC to catch-in on the TB program's State quarterly review meetings. Participation in these review meetings by NAFDAC State PhV officers will provide a platform for discussions on challenges with ADR reporting from the TB DOTS clinics and within the local government areas in the State. The State quarterly review meetings are attended by all involved in the TB/HIV activities, the National Professional Officers of WHO and other stakeholders in the PHP. This platform should be maximized to encourage greater emphasis on the need for ADR monitoring and reporting.

Simplify reporting and integrate into existing system

ADR reporting can be improved through several strategies including the simplification of the reporting form, sensitization of healthcare workers to participate in the process, and engagement of patient in the reporting process. The use of checklist in ADR reporting has been criticized due to several drawbacks²⁰ including that it allows for poor description of events and ticking only the available options. It has also been argued that while reporting, ADR events recorded should not be restricted or predefined since doing this may cause confusion. It is also argued that unrestricted entries offers the best chance for detecting the unexpected and provides more event data for analysis. However, innovative approaches to simplifying the reporting process needs to be explored. One approach may involve to allow the submission of an abridged report which will serve as a first step towards subsequent completion of a detailed ADR form. The WHO guide on pharmacovigilance for antiretrovirals in resource-poor countries²¹ states that any clinical event that is recorded in the patient record should also be recorded as an adverse event. A brief description of the event is usually all that is necessary since these will be subsequently reviewed by the PhV staff and standard adverse event terminology applied.

What is known about engaging patients in ADR reporting has centered more on empowering patients towards directly reporting ADR. This is currently a standard practice in some developed countries including the US, UK, and Netherlands. A lot has also been written in the literature about patient ADR reporting.^{22,23,24} The feasibility for implementing direct patient reporting in

²⁰ Finney J. The design and logic of a monitor of drug use. *J. chron. Dis.* 1965, Vol. 18, pp. 77-98

²¹ WHO (2007) Pharmacovigilance for antiretrovirals in resource-poor countries. WHO/PSM/QSM/2007.3

²² Jarernsiripornkul, N., Krska, J., Capps, P., Richards, R., Lee, A. (2002) Patient reporting of potential drug reactions: a methodological study. *J Clin Pharmacol*, 53. 318-325

resource-limited setting is very remote because of the literacy level and lack of access to the internet. However patient in RLS can participate in the ADR reporting activity through initiating the report. This simply means that the patient spontaneously sends a simplified abridged report to either the health worker or directly to a PhV center which ever they are more comfortable with. The reports are spontaneously sent in a timely manner and do not have to wait until next clinic day. Patient-initiated report can not be considered as a complete ADR report until a healthcare worker or PhV staff gets back to the patient and completes all the required fields in a standard ADR form. The advantage is that patients can report any adverse event they experience almost immediately. Another advantage is that unlike the direct patient reporting, this method will ensure that un-useful and poorly completed ADR forms do not reach the PhV center and overburden the center. When patients send a report, the callback to obtain more information provides a great opportunity for an intervention that in some instances may be life saving. Imagine a situation where a patient sends a text that they have experienced rash and fever, upon interview, the nurse identifies a severe reaction with ulceration of the mucous membrane, the nurse will then be in a position to advise the patient to immediately stop treatment and request that patient come to the hospital to see a doctor. A callback to patient can also be an opportunity to reinforce that a side effect being experienced by the patient is well known, mild and transient, and that the patient should continue taking their medication as advised. This advice will go a long way towards improving adherence and treatment outcome.

Patient-initiated report can be in the form of a text message, patient-reported side effects questionnaires, a pictogram, a checklist, or indeed any form of an abridged report that is sent in real time. This simplified report or alert is subsequently followed up by a healthcare provider or a PhV staff. Patient-initiated report will involve a structure where initial reports are received in the following forms:

- Ticks in the embedded form in the TB patient treatment card
- Alerts on toxicity or tolerability problems: these alerts can be sent by the patient through text message in mobile phone technology
- Ticks in checklist developed through a patient focus group discussion
- Pictograms
- Patient-reported side effect questionnaire

As PHP take treatment closer to the patients and recruit non-professional healthcare workers to oversee dispensing and administration of medicines (as in the TB DOTS program), a system should be developed to ensure regular communication between the health worker and the patient. The key thing is to ensure that the complexity of the ADR reporting form does not preclude who can participate in the medicine safety monitoring process. Feedback from the survey indicates that patient wants to have other avenues for reporting safety concerns; a simple and cost-effective patient-initiated reporting model can address that.

On their part the healthcare providers are convinced about the importance of ADR reporting as can be seen from the survey. They also showed a preference for documenting adverse events in

²³ Fisher, S., Bryant, S., Solovitz, B., Kluge, R. (1987) Patient-initiated postmarketing surveillance: a validation study. *J Clin pharmacol.* 27. 11 pgs 843-54

²⁴ Blenkinsopp, A. Wilkie, P Wang, M & Routledge, P. (2007) Patient reporting of suspected adverse drug reactions: a review of published literature and international experience. *B Journ Clin Pharmacol* 63 (2), 148–156.

the patient card. This can be achieved through embedding a simplified abridged version of the ADR form into the NTBLCP TB treatment card. Some key ADR report information is already contained in the TB treatment card, example patient demographics. The remaining data needed include the drug and the event. A form in a checklist format with few text fields can be developed and embedded in the NTBLCP TB treatment card. An example of what the abridged form can look like is shown below.

Abridged ADR form proposed to be embedded in the TB treatment card

Adverse event (code)		Severity (1,2,3,4)	Outcome (code)	
Known Adverse reaction	Drug			
Peripheral neuropathy			Recovered fully	<input type="checkbox"/>
Hepatitis			Recovered with disability	<input type="checkbox"/>
GIT side effects			Congenital malformity	<input type="checkbox"/>
Joint pains			Hospitalization	<input type="checkbox"/>
Auditory and vestibular damage			Life threatening	<input type="checkbox"/>
Optic neuropathy			Death	<input type="checkbox"/>
Other known AEs			Modified treatment	<input type="checkbox"/>
Counterfeit/med error			Others (specify)	<input type="text"/>

New unknown adverse event		
	Describe	Suspect drug
New unknown AE (Please describe)	<input type="text"/>	<input type="text"/>

List all other drugs patient took (*within the past 3 months*)

The above is merely an example to show the key data elements that can be captured with this sort of abridged form. The features, advantages and benefits of such an abridged form include:

1. Part of the 'normal' consultation process since the provider routinely completes the TB treatment card
2. Checklist format make for quick and easy completion. The form fits into the 'normal' and routine duties of a busy clinician
3. Captures both the known and the unknown reactions as required by the national guideline
4. The known adverse reaction checklist can be populated based on clinical experience, based on product literature, or based on patient-reported side effects
5. Provides denominator and prevalence of both known and new adverse events
6. Improves reporting rate since complete ADR form must be filled during every treatment modification
7. Can be completed by non-professional healthcare workers at the lowest level of healthcare delivery, like the GHCW who participate in the TB DOTS activities
8. Reduces reporting burden since complete ADR forms are only filled for the suspected new cases
9. PhV focal person can follow up on the new adverse events to complete the standards ADR form specifically for those adverse events thereby improving focus on identification of new unknown events
10. Treatment facility and PHP can compile aggregate number of reports for each known reaction, they can compile the proposed indicators (all the indicators proposed below are captured in the above form), and they can send reports to NAFDAC
11. PHP are now informed about the tolerability of products used in their program (by monitoring the frequency of adverse events) and they are complying with NAFDAC's reporting requirements

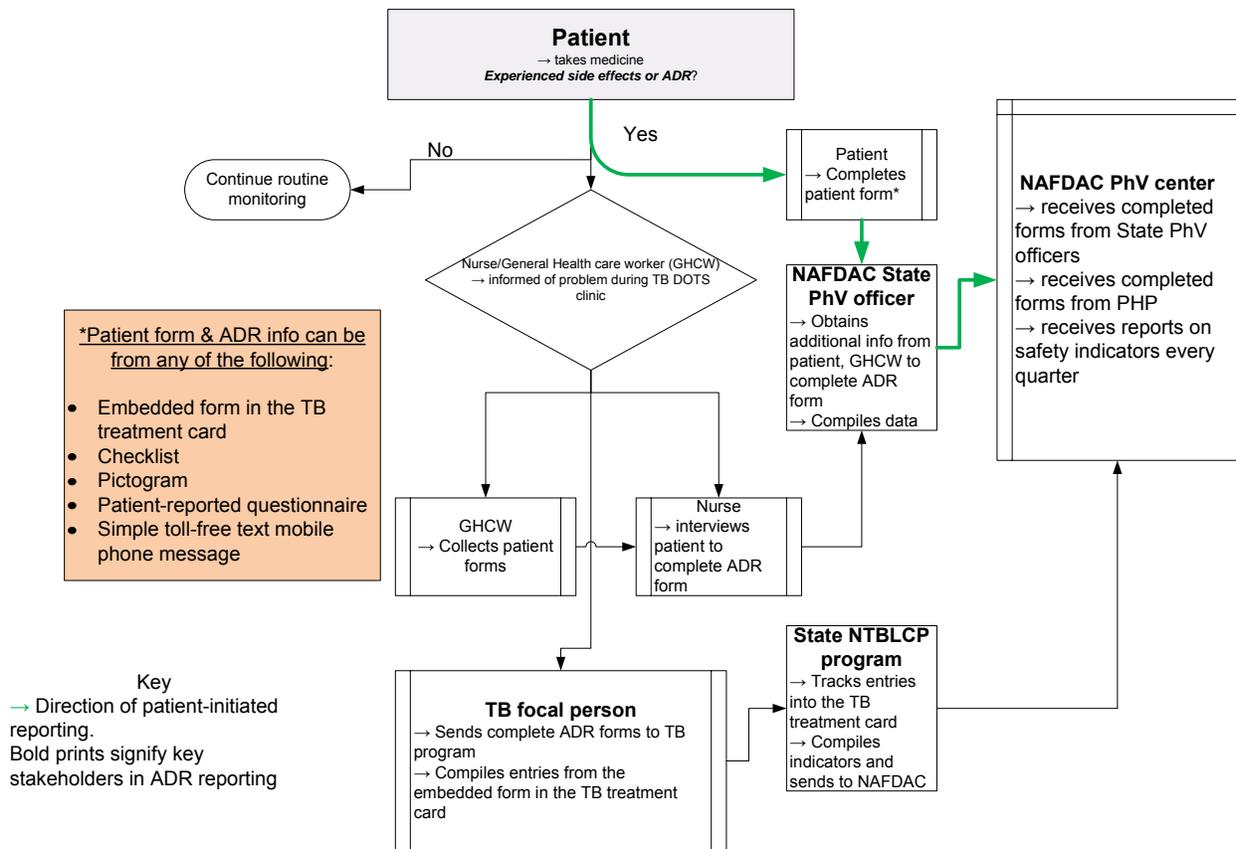
An example of the above abridged ADR form that is embedded into the back portion of the current NTBLCP TB treatment card is shown in ANNEX 7.

ADR reporting can be integrated into existing M&E system of the PHP. This will ensure sustainability and guarantee that data collected at the lowest level of healthcare delivery is tracked up to the national program and to NAFDAC. Collecting ADR data can surely piggy-back on the collection of other routine reports. ADR reporting can be integrated into the existing system through the following sequential steps:

1. Routine healthcare worker reporting using the an abridged ADR form embedded into the patient card
2. Entries on the ADR portion of the patient card (TB treatment card) is collected into a PhV register or included in the central register
3. Facility data is collated as part of the local government area TB DOTS M&E activities
4. Local government area data is collated together during the State quarterly review meetings
5. Data is consolidated by the program at the national level through the M&E unit
6. Report is stored for use by the program
7. Quarterly report is sent to NAFDAC

Simplifying reporting by healthcare providers and developing a simple reporting format for patients can greatly improve ADR monitoring within the PHP. A proposed model for ADR reporting involving patients and non-professional healthcare workers like the GHCW is shown by the schema below.

A proposed model for improving ADR reporting



Use new technologies

The use of new technologies provides a great opportunity for improving medicine safety monitoring and patient outcome in general. These new technologies particularly the mobile phone technology and internet can be of great assistance to NAFDAC in improving safety monitoring in Nigeria. NAFDAC requires high speed internet to enhance data collection and transmission. Toll-free lines can be set up at the regional, state, or national level to enhance the ability of patients and consumers to report adverse events. Such toll-free lines can also support the provision of drug information. Some PHP are already using electronic tools for prescriptions and dispensing medicines. The ADR form can be uploaded into these electronic medical records

(EMR) and hospital information systems (HIS) so that during the normal consultation and prescription of medicines patient reported adverse events can be captured by calling up the ADR form. The form can be pre-populated with patient demographics and other existing relevant data at the point of call-up. The physician will then only need to enter the reported adverse event and complete other remaining critical fields to generate a complete ADR form. This form can be printed out and sent to the PHP and NAFDAC. With improved technology such forms can also be e-transmitted directly to NAFDAC. A protocol can be set up in such EMR or HIS that requires mandatory completion of the ADR form upon every treatment modification attributed to drug toxicity. ADR data entry can also be done at the dispensing end in situations where there is drug dispensing software in use.

Establish medicines safety indicators for the PHP

Routine reporting from the program level on medicine safety related issue of the program can be improved through making a requirement that some safety indicators should be reported on periodically. The South Africa monitoring and evaluation framework²⁵ for the comprehensive HIV and AIDS Care, Management and Treatment Program proposed some indicators to help it achieve plans for comprehensive monitoring of the efficacy and adverse events of drugs being used in the program. NAFDAC and the NDSAC can work closely with the PHP to identify a few critical indicators that PHP can be requested to report on every quarter. It must be ensured that indicators to be reported to NAFDAC are collected at the lowest level of healthcare delivery. A review of the abridged embedded form described above informs key indicators that can be routinely collected. Some proposed NAFDAC indicators for the PHP may include the following:

- % of patients experiencing adverse events of WHO severity grades 2-4
- # of patients modifying treatment due to toxicity
- % of patients experiencing “New unknown AE”
- # of mortality attributed to specific drugs
- # of morbidity attributed to specific drugs

These indicators can easily be collated by tracking relevant checked boxes in the abridged ADR form embedded in the TB card. It can also be easily collated from electronic prescription tools (EMR/HIS) used in the hospital and reports can be generated and transmitted to the relevant authorities.

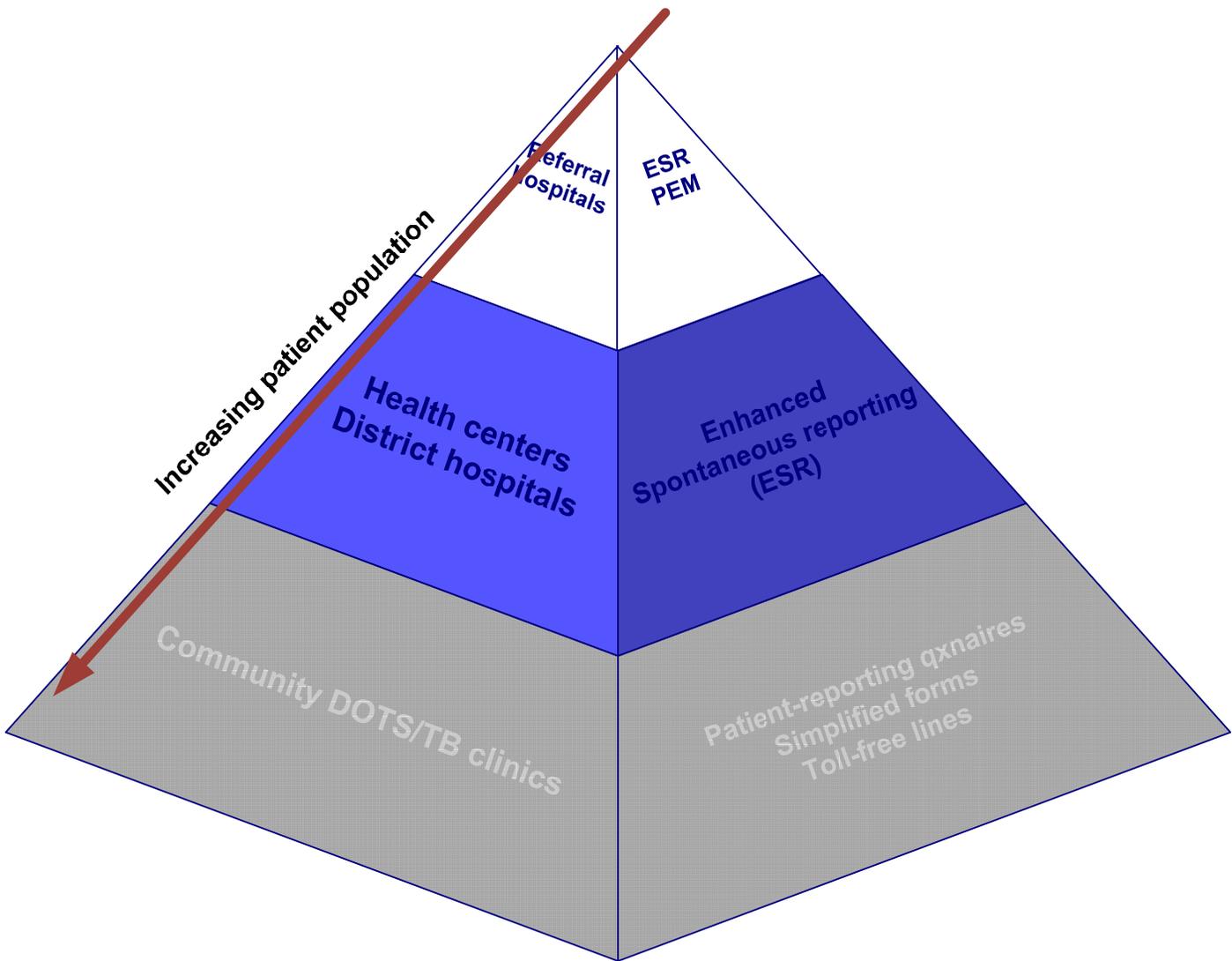
Develop appropriate reporting system for every level of healthcare delivery

The National reporting requirement is very demanding and requires that all healthcare workers including traditional medicine practitioners submit reports, all types of events should be reported including known and minor ones for new medicines, and all responses which is noxious and unintended including lack of efficacy should also be reported. It may not be feasible for the NTBLCP and other PHP to fully meet this reporting requirement. However, efforts can be made towards meeting this national guideline by ensuring that the capacity to file reports informs the sophistication of the reporting forms and methods. The PHP and NAFDAC can develop

²⁵ Department of Health. Cluster: Health information, evaluation and research. Monitoring and Evaluation framework for the Comprehensive HIV and AIDS Care, Management and Treatment Programme for South Africa. Available from: <http://www.doh.gov.za/docs/reports/2004/hivaids-care/monitorevaluation.pdf> Accessed January 22, 2008

appropriate reporting system for every healthcare delivery level and implement tools that will aid the process. At the district and referral hospital level the current spontaneous report system should be enhanced (enhanced spontaneous reporting, ESR) through easy availability of the reporting forms, training of all healthcare workers on how to report, identification of a PhV focal person for each institution, establishment of a PhV register, adding ADR form into the electronic prescription tool, and other strategies that can improve spontaneous reporting. The more costly and sophisticated active surveillance methods like the prescription event monitoring (PEM) can be used at the referral hospital level or in sentinel surveillance sites for the monitoring of newer medicines like MDR TB medicines, 2nd line ARVs, and the new Malaria medicine (ACT). The figure below shows pyramid with more sophisticated surveillance methods (ESR and PEM) recommended at the tertiary healthcare level.

Appropriate ADR reporting methods for every level of the health system



Provide trainings

From the survey administered to healthcare workers, nearly 80% responded that they have never received training on PhV. The assessment also indicated that training on ADR monitoring is not part of the training provided by the PHP to clinicians. PhV topics are not captured during trainings on treatment guidelines. In an instance there was a PhV training that was carried out without input from the national PhV center. There is a need for the development of a national standardized PhV training curriculum. This effort can be initiated through support from NTBLCP to NAFDAC and the Zaria training center with technical assistance from TBCAP. The other stakeholders including the ART and Malaria programs can be invited to support and participate in the process. The training materials developed through this effort can be used for a training of trainers that will precede a cascade of trainings. The Zaria training center will also use the curriculum in the pre-service and in-service trainings thereby ensuring sustainability. Technical assistance should also be provided to NAFDAC staffs and members of the NDSAC by providing trainings on causality assessment, active surveillance and other pharmacoepidemiology studies.

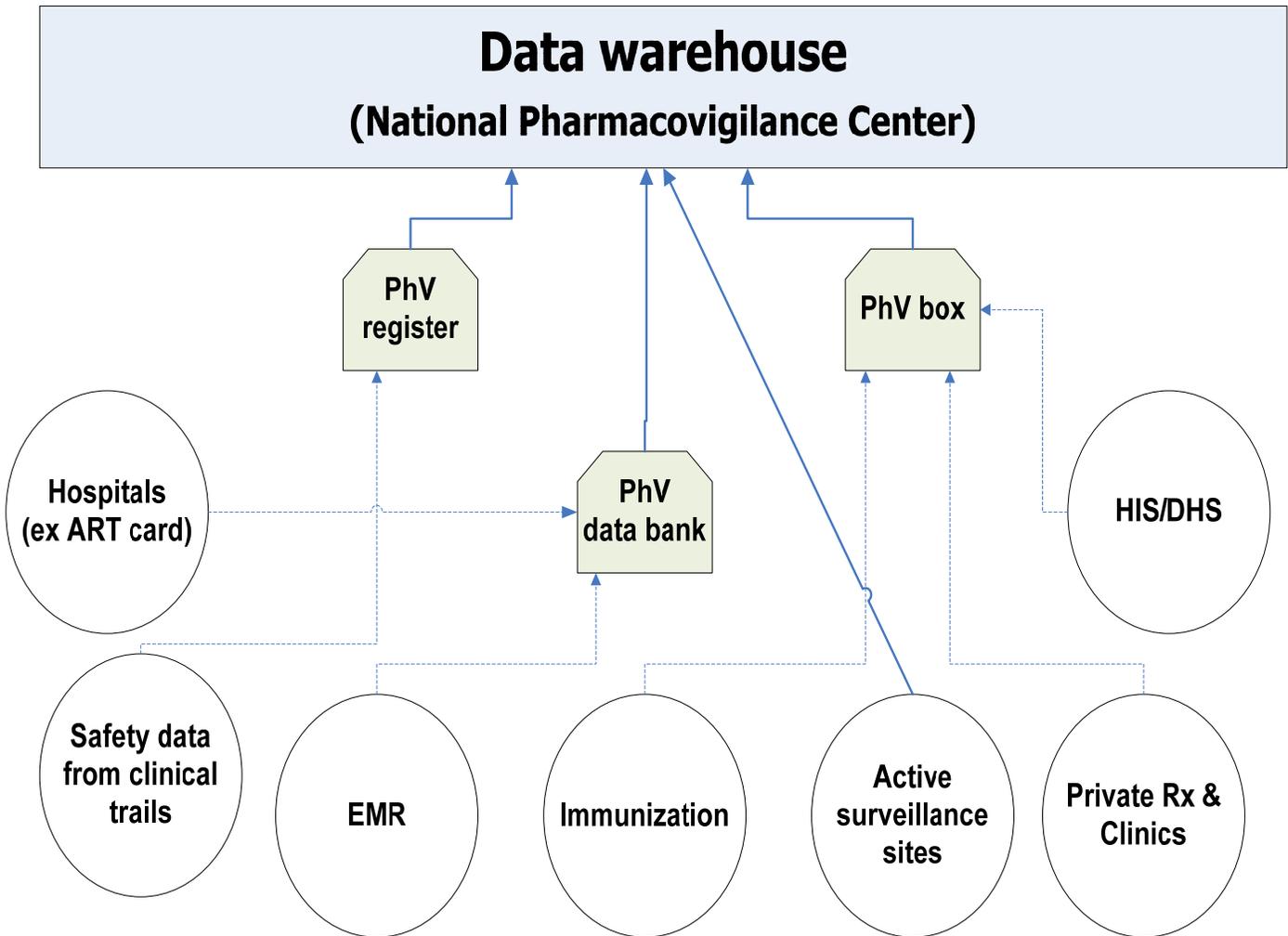
Include importance of ADR reporting in the clinical manual

In an effort to institutionalize ADR reporting, the need to report adverse events and the tools for reporting can be highlighted in all standard treatment guidelines, clinical manuals, formulary, etc. The Kenya national leprosy and tuberculosis program's²⁶ clinical guideline under the section on treatment monitoring clearly states that "all adverse events irrespective of the severity must be recorded in the patient record card." The TB treatment manual should include such statements on the need to report all adverse events using the abridged embedded form. A copy of the form can also be annexed to the clinical manual.

Set up national data warehouse

All data related to safety of medicines used in Nigeria should be available to NAFDAC. There can be several sources of medicine safety related data; it may be from hospital patient cards, registers, EMR or HIS. Efficacy and safety data can also be generated during preregistration clinical trails or during post-registration phase IV studies and other sources. These data should be consolidated at one source in a national data warehouse. The advantage of this is an opportunity to have a national picture about the safety of medicinal products in use. The adverse events data at the national data warehouse should be de-identified so as to address confidentiality concerns. Such database will serve as a resource for NAFDAC and the NDSAC for regulatory decisions. It can also support further research on drug safety in Nigeria. Safety data from whatever source should therefore be tracked up to this central data warehouse. Below is a representation of sources of data for such a national data warehouse.

²⁶ Ministry of Health. National NLTP Guideline: what the Healthcare worker needs to know. August 2005



Improve systems and capacity

Support should be provided to NAFDAC to improve systems and capacity of the PVG/FDIC. Also the NDSAC should be supported to improve their advisory role to NAFDAC. With additional support the PVG/FDIC will be able to meet their safety monitoring function and provide useful services to all stakeholders including the PHP. These supports include the provision of necessary infrastructure and the development of systems including SOPs. A key priority of the department of Food & Drugs is the development of a national PhV policy. Technical assistance and support should be provided to enable the department accomplish this objective.

CONCLUSIONS

Monitoring adverse drug reactions in mass treatment initiatives is an important aspect of the public health programs. In many developing countries this has not been possible because of weak or non-existence medicine safety monitoring system. Often the pharmacovigilance unit through the drug regulatory authority is not working closely with the PHP. However the opportunity created by the PHP can serve to reinvigorate or even establish PhV systems in resource-limited settings.

An approach towards making the best of this opportunity is for PHP like the NTBLCP to improve its own ADR monitoring strategies and work with other programs to provide support to the regulatory authority towards building capacity and systems that will yield a sustainable medicine safety monitoring system. When such a system is built, the outcomes include ability to prevent avoidable adverse events, strengthen medicines regulation and enforcement capacities, promote government and donor stewardship in safeguarding public health, and improve public trust in the safety of public health program medicines.

ANNEX 1. NIGERIA TBCAP ADR ASSESSMENT CONSULTANCY

Interview guide for eliciting information from NAFDAC, Public health programs (TB/ART/Malaria), MOH Program managers, National Expert Advisory Committee

Introductions

1. Consultant introduced by local counterpart or introduces self
2. Interviewee introduces self(ves)
3. Interviewee introduces their organization, their position, roles and responsibilities, describes PhV system in place

Briefly describe the SOW

1. Consultant introduces the SOW of the consultancy and itinerary
2. Consultant discuss the deliverables from the SOW
3. Consultant enquires how the deliverables are relevant to the interviewee and their organization

Solicit for information

1. Are there policies, laws & regulations, guidelines, etc related to PhV. Are they available to HCWs, Is the information contained in all policy and regulatory documents consistent
2. Consultant request interviewee to provide information & documents to ensure complete understanding of current efforts in medicine safety and ADR monitoring (ex. Guidelines, side effects & ADR section of patient ART card/case notes)
3. Discuss capacity and resources of the PhV center (# of staffs, SOPs, indicators, softwares, database, tollfree lines, literature, IEC materials, etc.
4. What are the gaps and challenges being faced in improving ADR reporting
5. Is need for ADR reporting highlighted in the treatment guidelines, is the ADR forms included in the CPGs
6. Is there a system for the collection of ADR information at every point where PH medicines are dispensed or administered
7. What are the PHPs currently doing to address ADR reporting
8. What are the key challenges in linking the PHP to the PhV activities
9. Describe methods to enhance ADR reporting in PHP and ask interviewee to react to them
10. Do you agree that any of these methods or used in combination is applicable to your setting and can improve ADR reporting locally
11. Has there been trainings on PhV, is there any PhV module in the training materials of the PHPs
12. Mention Okezie & Olufunmilayo –ADR reporting by physicians in Ibadan – are there other local studies available. Are the identified factors in the article being addressed
13. Present current thinking and some best practice ideas and ask for reactions
14. Ask interviewee to list top 3 things that must be done immediately to improve current situation

Next steps

1. Request if there are other stakeholders that needs to be interviewed
2. Inform about the stakeholders workshop and invite
3. Thanks interviewee for the time and information provided

ANNEX 2. ADR SURVEY FOR HCW

Adverse drug reaction Survey

Print Form

Submit by Email

Dear Health care worker,

Thank you for taking your time to respond to this Adverse drug reaction Survey. This survey is meant to collect information from Health care workers on their knowledge, attitude, and practice towards ADR reporting. Information you provide will assist in improving ADR reporting, patient safety and treatment outcome. Please be very frank in your answers. Notice that there are no personal identifiers in this form. The survey should take less than ten minutes of your time to complete.

This questionnaire should *only* be completed by health workers who prescribe, dispense, or administer medicines to TB/HIV patients. You can return completed form by clicking the "Submit by Email" button to submit the survey.

Demographics

1. What is your role in TB/HIV patient management?

Physician Nurse Pharmacist Community Health worker Others

2. What is your health facility setting?

TB clinic ART clinic offering IPT & TB/HIV services TB DOTS MDR TB clinic Others

3. Approximately how many TB/HIV patients do you attend to per week?

1-50 51-100 111-150 151-200 >200

4. How many years of experience as a health care worker do you have?

<5yrs 5-10 yrs 11-15 yrs >15 yrs

Knowledge

5. Have you received any training on pharmacovigilance and /or ADR spontaneous reporting?

Yes No

6. Are you aware of the ADR reporting form from NAFDAC?

Yes No

7. Are you aware of the ADR reporting procedure?

Yes No

8. The following statements are true about ADR reporting? (tick all that apply)

- All serious ADRs are documented by the time a drug is marketed when not certain drug caused ADR it should not be reported All ADRs should be reported
- ADRs should only be reported if absolute certainty exists that the ADR is related to a particular drug 1 case reported by individual HCW can not contribute to knowledge about the drug None of these statement is true

9. How ***certain*** are you about the following? (tick all that apply)

- % of my patients that experience side effects %Pts in my health facility that experience side effects %Pts in the TB program that experience side effects

Attitude

10. Reason for not completing ADR forms ? (tick all that apply)

- The ADR is known No time Unaware of what should be reported Reporting process is obstructive to normal routine Form not available

11. Rate your overall satisfaction with the ADR data collection process

- Very satisfied Somewhat satisfied Neutral Somewhat dissatisfied Very dissatisfied

12. Do you think ADR reporting is useful to your practice

- Yes No

Practice

13. Have you ever submitted an ADR form?

- Yes No

14. Do you routinely tell patients about side effects to expect from their medicines?

- Not necessary, it will scare them from taking the meds No Yes, always

15. Do you routinely ask patients to report unexpected side effects to you or other HCWs?

- Yes No

16. Have you ever documented patient reported side effects on the case note?

- Yes No

17. What do you think should be done to improve ADR reporting?

End. Thanks for your participation!

ANNEX 3. ADR SURVEY FOR PATIENTS

Survey on side effects of medicines on Patients

Dear Patient,

Thank you for taking your time to respond to this survey on side effects of medicines on patients. This survey is meant to collect information from patients on their experiences with the medicines prescribed for them. Information you provide us will assist to improve treatment you receive from health facilities. We therefore rely on you to provide us truthful information on your experiences. It is not mandatory to participate in this survey. Your choice to participate or not and the responses you provide will in no way effect your relationship with your health care providers. This survey will take less than ten minutes of your time.

1. Did you receive medicine today? Yes No
2. Were you told how to take your medicines Yes No
3. Were you told the side effects you may experience with these medicines?
 Yes No
4. Please kindly tell us those side effects
 Patient was able to mention key side effects Patient was not able
5. What do you do when you experience side effects you were not warned about?
 Nothing, continue taking my medicines Stop taking the medicines
 Report to my Doctor/Nurse
6. Have you ever informed your health worker about any side effects you experience with medicines?
 Yes No
7. Do you always feel free to talk about side effects with your health care provider?
 Yes No
8. Apart from talking to your health care provider, do you wish there are other ways for you to report side effects?
 Yes No

ANNEX 4. NTBLCP ADR FORM
National TB & Leprosy Control Programme
SUSPECTED ADVERSE DRUG REACTION REPORT FORM
NTBLCP/NAFDAC TBL12

Treatment Centre:		Town:	
Local Government Area:		State:	

1. PATIENT'S DETAILS

Full name or initials:		Hospital clinic No:	
Age (yrs):	Sex (M or F):	LGA No:	
Weight (kg):			

2. ADVERSE REACTION

A. Description of adverse reaction		C. Outcome of reaction (tick as appropriate)	
		<input type="checkbox"/>	Recovered fully
		<input type="checkbox"/>	Recovered with disability
		<input type="checkbox"/>	Congenital malformity
		<input type="checkbox"/>	Hospitalization
		<input type="checkbox"/>	Life threatening
		<input type="checkbox"/>	Death
Date Started:	Date stopped:	<input type="checkbox"/> Other (specify)	
B. Treatment of the reaction		D. Response to Re-Challenge	
Was patient admitted?	Yes: <input type="checkbox"/> No: <input type="checkbox"/> tick	Was re-challenge done?	
If yes, duration of Admission (days):		Yes: <input type="text"/>	No: <input type="text"/>
Treatment given:		Did adverse reaction re-appeared on re-challenge?	
		Yes: <input type="checkbox"/>	No: <input type="checkbox"/>

3. RELEVANT TESTS OR LABORATORY DATA

--

4. SUSPECTED DRUG

A. Drug Details

Brand Name: _____	Generic Name: _____
Batch Number: _____	NAFDAC No: _____
Expiry Date: _____	Name and address of manufacturer _____

B. Drug administration

Indications for use	Dosage given	Route of administration	Date started	Date stopped

C. Source of Drug (please tick as appropriate)

Hospital Pharmacy	Community Pharmacy	Patent medicine Store	Traditional Herbal practitioner	or	Street vendor	Other (specify)

Was it Prescribed? (tick)		Was it obtained over the counter? (tick)	
Yes: _____	No: _____	Yes: _____	No: _____

5. DRUGS TAKEN WITHIN THE LAST 3 MONTHS

(All concomitant medicines including herbal medicines and self medication)

Name (Brand or Generic)	Dosage	Route	Date started	Date Stopped	Reasons for use

6. OTHER RELEVANT MEDICAL HISTORY

(e.g. allergies, Pregnancy, previous exposure to drug, alcohol, tobacco, etc)

SOURCE OF THIS REPORT:

Name of Reporter: _____

Signature: _____

Address: _____

Profession: _____

Tel no. _____
/Email: _____

NOTES:

1. Reporting of suspected adverse reactions is very critical for promoting drug safety and rational use of drugs. Please actively participate and support this monitoring exercise.
2. Report adverse experiences with all medications (drugs, biologicals, medical devices and traditional herbal medicines). Please use extra paper where space is inadequate and indicate the number accordingly.
3. Please note that the submission of a report does not necessarily mean that the drug caused the adverse reaction
4. Identities of the patient and the reporter will remain strictly confidential.

ANNEX 5. RESULTS OF HCW ADR SURVEY

HCW survey of ADR KAP			
<u>Qxn. #</u>	<u>Variable</u>	<u>Result</u>	
-	-	<u>Category</u>	<u>Responses</u>
	Demographics		
1	What is your role in TB/HIV patient management?	Physician	2
		Nurse	12
		Pharmacist	2
		Community Health worker	21
		Others	
2	What is your health facility setting?	ART clinic	
		ART clinic offering IPT & TB/HIV services	21
		TB DOTS	6
		MDR TB clinic	
		Others	7
3	Approximately how many TB/HIV patients do you attend to per week	1 to 50	13
		51 to 100	10
		111 to 150	3
		151 to 200	1
		>200	
4	How many years of experience as a health care worker do you have	<5yrs	5
		5 to 10	17
		11 to 15	3
		>15	12
	Knowledge		
5	Have you received any training on pharmacovigilance and /or ADR spontaneous reporting	Yes	8
		No	29
6	Are you aware of the ADR reporting form from NAFDAC	Yes	7

		No	28
7	Are you aware of the ADR reporting procedure	Yes	9
		No	28
8	The following statements are true about ADR reporting? (tick all that apply)	All serious ADRs are documented by the time a drug is marketed	5
		When not certain drug caused ADR it should not be reported	5
		All ADRs should be reported	21
		ADRs should only be reported if absolute certainty exists that the ADR is related to a particular drug	5
		1 case reported by individual HCW can not contribute to knowledge about the drug	
		None of these statement is true	
9	How certain are you about the following? (tick all that apply)	% of my patients that experience side effects	2
		%Pts in my health facility that experience side effects	10
		%Pts in the TB program that experience side effects	10
	Attitude		
10	Reason for not completing ADR forms? (tick all that apply)	Form not available	14
		The ADR is known	2
		No time	2
		Unaware of what should be reported	14
		Reporting process is obstructive to normal routine	5
11	Rate your overall satisfaction with the ADR data collection process	Very satisfied	6
		Somewhat satisfied	8
		Neutral	5
		Somewhat dissatisfied	6
		Very dissatisfied	4
12	Do you think ADR reporting is useful to your practice	Yes	36

		No	
	Practice		
13	Have you ever submitted an ADR form	Yes	1
		No	35
14	Do you routinely tell patients about side effects to expect from their medicines	Not necessary, it will scare them from taking the meds	
		No	3
		Yes, always	30
15	Do you routinely ask patients to report unexpected side effects to you or other HCWs	Yes	36
		No	6
16	Have you ever documented patient reported side effects on the case note	Yes	20
		No	17
17	What do you think should be done to improve ADR reporting	Training, capacity, sensitization, others	31

ANNEX 6. RESULTS OF PATIENTS ADR SURVEY

Patient ADR KAP survey			
<u>Nos.</u>	<u>Question</u>	<u>Category</u>	<u>Results</u>
1	Did you receive medicine today	Yes	30
		No	
2	Were you told how to take your medicines	Yes	30
		No	
3	Were you told the side effects you may experience with these medicines	Yes	30
		No	1
4	Please kindly tell us those side effects	Patient was able to mention key side effects	13
		Patient was not able	4
5	What do you do when you experience side effects you were not warned about	Nothing, continue taking my medicines	4
		Stop taking the medicines	3
		Report to my Doctor/Nurse	26
6	Have you ever informed your health worker about any side effects you experience with medicines	Yes	24
		No	8
7	Do you always feel free to talk about side effects with your health care provider	Yes	30
		No	1
8	Apart from talking to your health care provider, do you wish there are other ways for you to report side effects?	Yes	10
		No	21

ANNEX 7. NTBLCP TB TREATMENT CARD WITH ABRIDGED ADR FORM EMBEDDED

Prescribed regimens and dosages

Tick: CAT 1 CAT 2

4FDC: 4FDC S

Loose drugs: RH Z E Loose drugs: S RH Z E

Indicate daily number of tablets and dosage in (grams) in each box

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	
Month/Year																																

Enter x on day when medications were swallowed under direct observations and "A" if patient is absent.
 Enter S (in pencil) for estimated date (1 week to end of intensive phase) for collection of sputum for follow-up examination.
 Draw a horizontal line through the number of days supply given (note this does not apply during intensive phase).

II. CONTINUATION PHASE (see Guidelines)

CAT 1: Regimen and number of tablets: RH daily for 4 months

CAT 2: Regimen and number of tablets: RH Z E 3 times in a week for 2 months

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	
Month/Year																																

Enter x on day of supervised administration or when medications are collected. Draw a horizontal line through the days to indicate number of days supply given.
 Write A in the appropriate box if patient is absent.

REMARKS

Adverse event (code)	Severity (LLI6)	Outcome (code)
Adverse reaction	Drug	
Recurrent neuroglycopenia		Recovered fully
Recurrent neuroglycopenia		Recovered with disability
ACT site effects		Congenital malformation
Drug para		Hospitalization
Asthma and ventilator usage		Life threatening
Optic neuroglycopenia		Death
Other cause AIDS		Modified treatment
Concurrent malnutrition		Others (specify)

New unknown adverse event

Describe	Specify drug

AE phase code

List of other drugs patient took within the past 2 months:

Date treatment completed _____

Treatment outcome _____

Sign _____