pharmacoVIGILANCE newsletter

This publication is meant to provide updates on medication safety issues to health care professionals, and not as a substitute for clinical judgement.

ISSUE 1 05/2023

EDITOR'S NOTE

Botswana Medicines Regulatory Authority (BoMRA) is mandated to conduct pharmacovigilance and post marketing surveillance for safety, efficacy, and quality of medical products among other regulatory functions as per the Medicines and Related substances Act of 2013.

Safety Monitoring activities for medicinal products is done through a coordinated mechanism that involve different stakeholders such as healthcare professionals, patients, health facilities, public health programs and, marketing authorization holders. The Authority carry out routine analysis and evaluation of individual safety case reports received through spontaneous and active surveillance systems for trends identification, early signal detection safety and effective communication of safety concerns to all stakeholders.

This newsletter is aimed at providing medicine safety information to healthcare professionals. In this first issue, we introduced the concept of Pharmacovigilance and Pharmacovigilance program in Botswana. Further, adverse drug reactions received at BoMRA are discussed and safety concerns of some medicines are highlighted.

Editorial Team

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Medicine Safety

Globally, medicines are among the most important health interventions. Healthcare practitioners & patients seek safe and effective drugs. Unfortunately, NO drug is 100% safe. Safety of a medicine is always defined in a given context. Hence "Safety" means benefits exceed risks for defined population and use. When a medicine is registered for use, we will not have the full understanding of the safety of this medicine. Safety information will be gathered through clinical trials and often there is missing information. Post Authorization Surveillance for both safety and quality are essential. This is done though detection, assessment, understanding and prevention of adverse effects or any other drug-related problem", this is known as Pharmacovigilance.

Mandate for BoMRA is to ensure that all medicines and related substances used in Botswana are in conformity with established criteria of quality, safety, and efficacy. To establish the safety of a medicine in our population in Botswana, Post Authorization Surveillance for both safety and quality are essential. In building a National Medicines Safety Monitoring Program, BoMRA is actively engaging all stakeholders. Healthcare Professionals and healthcare facilities are one of the most important in this endeavour of BoMRA.

WHAT TO REPORT

Please report any Known, Unknown, Trivial, Serious, Mild, Moderate and Severe Adverse reactions or any discomfort presented by a patient suspected to be due to the medicine/vaccines taken by him/her.

WHAT HAPPENS TO YOUR REPORTS WHEN THEY REACH BOMRA

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ADVERSE DRUG REACTION MONITORING CENTRES

BoMRA has established the need to monitor the safety of the medicines countrywide, thus came up with a program called Adverse drug reaction monitoring program in 2020. The program is established to carryout awareness and sensitization of healthcare professionals and the public on the importance of adverse drug reaction reporting and medicine safety. To date, BoMRA has launched 11 AMCs at Sbrana Psychiatric Hospital, Bamalete Luthren Hospital, Princess Marina Referral Hospital, Scottish Livingston Hospital, Sekgoma Memorial Hospital, Nyangabwe Referral Hospital, Tati River Private Hospital, Kasane Primary Hosptal, Letsholathebe 11 Memorial Hospital, Ghanzi Primary Hospital and Orapa Mine Hospital.

Further, there are Pharmacovigilance Associates at the following hospitals who carry out Pharmacovigilance activities in those areas.

SBRANA PSYCHIATRIC HOSPITAL

Kemo Kalasi
Email: kkalasi@bomra.co.bw
Tel: +267 73 385 543

SEKGOMA MEMORIAL HOSPITAL

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ANALYSIS OF ADRs RECEIVED AT BoMRA

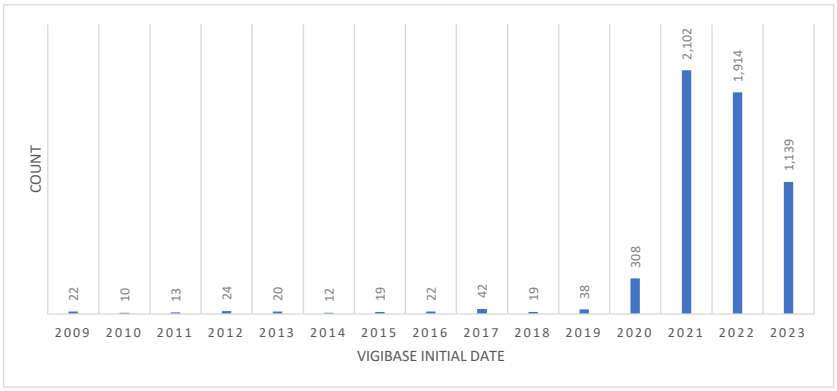


Figure 2: Number of reports in Botswana National Database

As of 26th April 2023, BoMRA has received a total of 5704 reports since its establishment (figure 2). The received reports are for vaccines and drugs. Of all the reports, 60.3% were for females, 37.6% males and 2.1% are unknown. There was sharp increase in reports from 2019 i.e., after BoMRA took over the Pharmacovigilance program. The reports came from nurses (70.9%), followed by doctors (14.5%) and pharmacists (13.6%) (figure 3).

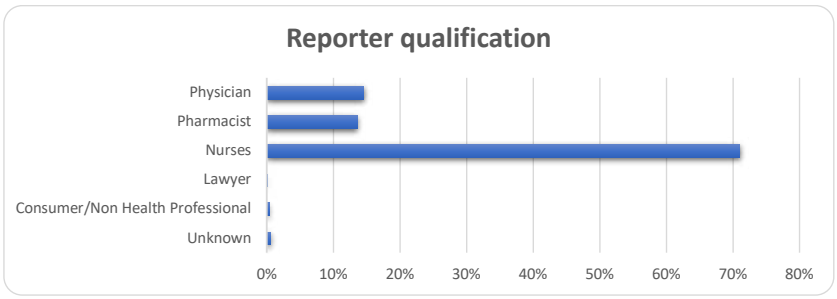
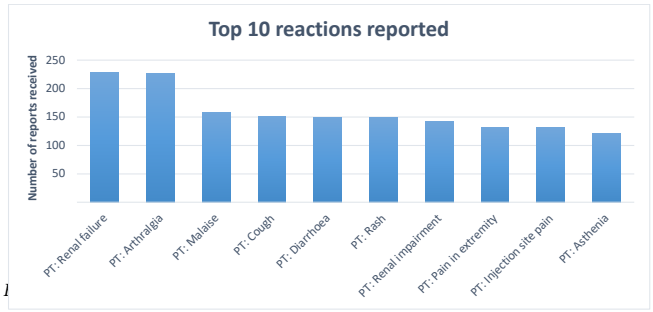


Figure 3: Reporter qualification

42.9% of all reports are for people aged 18 - 44 years, followed by people aged 45 – 64 years at 31.6% and least reports are for individuals aged 0 - 27 days at 0.2%. Of all the reports, 15.6 % were reported to be serious, 82.7 % non-serious and 1.7% classified as unknown. Reports are considered serious if they fall within one of the following criteria: Life threatening, Caused/ prolonged hospitalization, Disabling/incapacitating, Congenital anomaly/birth defect, Death, and Other medically important condition.

The top 10 reported ADRs are shown below in figure 4. The most reported ADR is renal failure followed by Arthralgia, general malaise, diarrhea, and rash. The authority has received 389 suspected ADRs associated with tenofovir disoproxil, lamivudine and dolutegravir combination (TLD), followed by 300 ADRs associated with efavirenz, emtricitabine, and tenofovir combination and 156 ADRs associated with Isoniazid use. Further, there are other reports for non-communicable diseases (NCDs) e.g., there are 118 and 97 reports for Enalapril and metformin respectively.



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Renal adverse events associated with Tenofovir (TDF)

BoMRA has received reports on renal adverse effects associated with tenofovir disoproxil, lamivudine and dolutegravir combination (TLD). TLD is considered as first line treatment of human immunodeficiency virus (HIV) infection in adults and adolescents weighing at least 30kg. The risk of renal adverse effects on patients taking TDF is well documented in literature and in Summary of Product Characteristics (SmPCs). Risk factors of TDF induced renal impairment are well characterized. These include comorbid conditions like hypertension, diabetes, hepatitis B or C co-infection, HIV associated kidney disease, and TDF in combination with a ritonavir-boosted protease inhibitor. Examples of ritonavir-boosted protease inhibitors are lopinavir, atazanavir, fosamprenavir, darunavir, tipranavir, and saquinavir. It must be noted that renal and urinary disorders; increased creatinine, proximal renal tubulopathy (including Fanconi syndrome) are listed as uncommon reactions in product information of TDF. All the above listed medications have an influence on the normal functioning of multidrug resistance protein systems therefore, possible interactions are predictable and preventable.

PRACTICE POINTS FOR HEALTHCARE PROFESSIONALS

Healthcare professionals are advised to assess renal function of patients before initiating tenofovir therapies, and to monitor renal function during treatment as per the Botswana National HIV & AIDS Treatment Guidelines. Further, HCPs should educate patients on how to notice and report signs and symptoms of renal adverse events and to be cautious when co-prescribing any nephrotoxic medicinal products. HCPs should consider discontinuation of TDF if there is decline in renal function or Fanconi syndrome is suspected. All ADRs should be reported to BoMRA.

POSSIBLE SIGNS AND SYMPTOMS OF RENAL ADVERSE EVENTS

- **Decreased urine output, although occasionally urine output remains normal.**
- **Fluid retention, causing swelling in your legs, ankles, or feet**
- **Shortness of breath**
- **Fatigue**
- **Confusion**
- **Nausea**
- **Weakness**
- **Irregular heartbeat**

Sodium Valproate contraindicated in girls and women of childbearing potential

Use of Sodium Valproate in women of childbearing potential is associated with congenital malformations in the newborn. Hence it is recommended to follow pregnancy prevention program. Current published data confirms the risks of congenital malformations and developmental disorders in children exposed to valproate during pregnancy. 1 in 10 babies (10%) exposed to valproate in pregnancy are born with a congenital malformation while this risk in general population is about 2–3%. Around 3 to 4 in 10 children (30–40%) exposed to valproate in pregnancy have delays in their development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding), and memory problems. The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal, and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems.

Further, a comparative study has shown that all doses of valproate increased the risk of major congenital malformations i.e., there is no safe dose of valproate that can be used in pregnancy. It must be noted that the therapeutic benefits of sodium valproate remain greater than the risk posed in this population given the risk minimization measures are taken into consideration.

ADVICE TO HEALTHCARE PROFESSIONALS

Healthcare professionals (HCPs) should;

- **Provide counselling on effective contraception and pregnancy prevention during use of valproate containing products**
- **Provide full information about the risks of using valproate during pregnancy and ensure patient understanding**
- **Advice patients to urgently contact an HCP when planning or in the case of suspected pregnancy**
- **Assess the potential for pregnancy for all female patients and conduct pregnancy testing prior to initiation of treatment and during treatment, as needed.**

Bedaquiline-containing regimens cardiac adverse events

Bedaquiline is an antimycobacterial drug used for the treatment of pulmonary multidrug resistant tuberculosis. Bedaquiline inhibits adenosine 5'-triphosphate (ATP) synthesis, a process that is crucial to the growth of mycobacterium and to its survival in its non-growing dormant state. Bedaquiline is recommended for the treatment of pulmonary Multidrug Resistant Tuberculosis (MDR-TB) and Rifampicin Resistant-Tuberculosis medicines (RR-TB) by world health organization. Bedaquiline is used in Botswana for management of MDR-TB and RR-TB.

WHO International Program on Drug Monitoring has published a potential safety signal of Bedaquiline associated with cardiac arrhythmia. 401 reported cases were identified and reviewed from the global data base of Bedaquiline associated with an adverse drug reaction (ADR) term 'cardiac arrythmia' including 28 with fatal outcome. In Botswana, as of 9th March 2023 there are 4 reported cases of Bedaquiline associated ADRs reported in the National Database. None of the reports are cardiac adverse events. Eventhough there are no such reports locally, there is an important need for close monitoring of patients on Bedaquiline-containing regimens for MDR-TB. The review of the global data base of ADR reports identified a potential safety issue concerning weight-based dosing of Bedaquiline. Patients with very low body weight may be at greater risk of cardiac arrhythmia if appropriate weight-dosing is not followed. Therefore, it is necessary to collect data and analyze safety of use of Bedaquiline in patients with lower body weight and body mass index (BMI).

INFORMATION FOR HEALTHCARE PROFESSIONALS

Bedaquiline prolongs the QTc interval. Therefore, electrocardiogram before initiation of treatment is recommended and should be repeated monthly after starting treatment with Bedaquiline. Baseline serum potassium, calcium and magnesium should be obtained and if abnormal must be corrected before initiating treatment. Electrolytes must be closely monitored when QT prolongation is detected.

There is a possibility of additive or synergistic effect on QT prolongation when Bedaquiline is co-administered with other medicines that prolong QT interval such as ciprofloxacin, levofloxacin, erythromycin, ketoconazole, itraconazole. quetiapine, risperidone, and olanzapine. Healthcare professionals should be cautious when prescribing medicines with established risk of QT prolongation.

Bedaquiline should not be prescribed to patients with the following conditions unless the potential benefits outweigh the potential risk:

- **Heart failure**
- **QT interval as corrected by the Fridericia method (QTcF) > 450 ms (confirmed by repeat electrocardiogram)**
- **A personal or family history of congenital QT prolongation**
- **A history of or ongoing hypothyroidism**
- **A history of or ongoing bradyarrhythmia**
- **A history of Torsade de Pointes**
- **Concomitant administration of fluoroquinolone antibiotics that have a potential for significant QT prolongation (i.e., moxifloxacin and sparfloxacin).**
- **Hypokalemia**

Where a patient develops clinically significant ventricular arrhythmia or a QTcF interval of > 500 ms (confirmed by repeat electrocardiogram) treatment should be discontinued.

Pholcodine consumption increases the risk of perioperative anaphylaxis to neuromuscular blocking agents

Benefit-risk balance of medical products changes over time as the product is used and real-world evidence is gathered. BoMRA proactively review scientific literature, safety communications from other regulatory Authorities and other relevant sources. Safety concern that Pholcodine consumption increases the risk of perioperative anaphylaxis to neuromuscular blocking agents has been previously suggested. Medicines containing pholcodine are used in adults and children to treat non-productive (dry) cough and, in combination with other active substances, for the treatment of symptoms of cold and flu. Pholcodine, an opiate that contains an ammonium group, is identified as an important risk factor for Neuromuscular blocking agents (NMBA) sensitization. Evidence from ALPHO study have demonstrated a clear association between Pholcodine consumption and increased risk of POA to NMBAs (Sadleir et. al 2021).

In 2011, European Medicines Agency (EMA) launched a referral procedure for the re-evaluation of the benefit/risk ratio of pholcodine. A multicenter study (ALPHO) which was a case-control study, comparing pholcodine exposure within a year before an anesthesia between patients with NMBA-related POA (cases) and control patients with uneventful an aesthesia was initiated. The ALPHO has confirmed a significant association between pholcodine consumption in the year preceding NMBA exposure and NMBA-related POA (OR adjusted=4.2 CI 95% [2.5; 6.9]). Other environmental factors, including occupational exposure to quaternary ammonium, should be considered in the risk of NMBA-related anaphylaxis, but they currently remain poorly defined. The findings have been reviewed by EMA and has since recommended the revocation of the European Union, Malaysian, Australian, South African and United Kingdom Authorities.

BoMRA assessed the available data and has concluded that the available evidence shows that the risk of using Pholcodine containing medicines outweighs the therapeutic benefits. In addition, there are other alternatives available to treat non-productive (dry) cough in adults and children. Hence, BoMRA has withdrawn all pholcodine containing products out of Botswana market and instructed all Marketing Authorization accordingly.

Advice to healthcare professionals *

- **Current evidence from ALPHO study has demonstrated a clear association between Pholcodine consumption and increased risk of POA to NMBAs. Therefore, for patients scheduled to undergo general anesthesia with NMBAs, healthcare practitioners should check whether patients have used pholcodine-containing medicines in the last 12 months and maintain awareness about potential peri-anesthetic anaphylactic reaction related to NMBAs.**
- **Healthcare professionals are advised to re-evaluate their patients, consider other treatment alternatives.**
- **Inform patients that these products will no longer be available for use as a precautionary measure due to safety concerns and consider recommending appropriate alternative treatments to manage non-productive coughs.**
- **Report all suspected adverse events associated with NMBA- or pholcodine-containing products to BoMRA.**

* Reference
Sadleir PHM, Clarke RC, Goddard CE, Day C, Weightman W, Middleditch A, Platt PR. Relationship of perioperative anaphylaxis to neuromuscular blocking agents, obesity, and pholcodine consumption: a case-control study. Br J Anaesth. 2021 May;126(5):940-948.

Adverse Drug reactions associated with Angiotensin converting enzyme inhibitors (ACEs)

As of 28th March 2023, BoMRA has received 122 individual case safety report (ICSRs). Majority of the reports received were observed in females (66.4%).

Patients aged between 45-64 years experienced more ADRs (39.3%) followed by age group 65-74 years (22.1%). The most affected system is respiratory, thoracic, and mediastinal disorders at 59.0%, followed by gastrointestinal system and least affected is the musculoskeletal and connective tissue disorders at 0.8%. Four topmost common co-reported medicines are metformin, hydrochlorothiazide, nifedipine and atorvastatin at 22.1%, 15.6%, 13.9% and 10.7% respectively.

Figure 5: Top 10 reported ADRs associated with ACEs

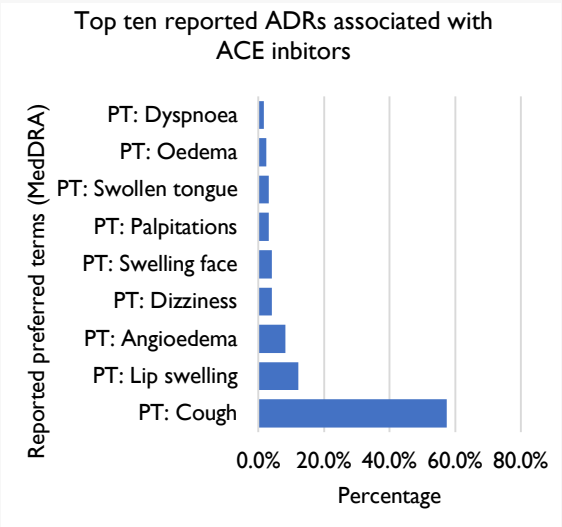


Figure 6: Reporters by qualifications

Reporter qualification	Percentage
Physician	7.4%
Pharmacist	45.9%
Nurses	45.9%
Consumer/Non-Health Professional	0.8%

These ADRs were reported by nurses (45.9%), pharmacists (45.9%) and doctors (7.4%) (figure 6). The most common reported ADRs are cough (57.4%), lip swelling (12.3%), angioedema (8.2%), dizziness and swelling of face both at (4.1%) (see figure 1). These are all known ADRs associated with ACEIs, and they are well characterized and included in both the patient information leaflet and summary of product characteristics. Of all the cases only 23.8% were classified as serious and 75.4% are non-serious. The reports received at BoMRA and findings of subsequent analysis of these reports is consistent with the global data.

ANGIOEDEMA AND LIP SWELLING

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx have been reported in patients taking ACE inhibitors, including enalapril. Angioedema may occur at any time during treatment; reported to occur more frequently in Black African origin patients than in non-black patients. Enalapril should be promptly discontinued, and appropriate therapy and monitoring provided until complete and sustained resolution of signs and symptoms occur. Laryngeal oedema may be fatal, in cases with involvement of the tongue, glottis or larynx, appropriate therapy should be initiated immediately. Angioedema has been reported in clinical trials at 0.5% to 1% in patients taking enalapril compared to those taking placebo or compactor drugs. The incidence rate in clinical trials is similar to incidence rate reported in post-marketing surveillance.

Post Authorization Studies have reported dry cough in 1.3% hypertensive patients and 2.2% of congestive heart failure patients treated with enalapril compared to 0.9% and 0.6% of patients who received placebo for the hypertensive and heart failure patients. Mechanism of action for both angioedema and dry cough is currently unknown; however, it has been suggested that bradykinin might be responsible for angioedema and dry cough in patients. Angiotensin converting enzyme (ACE) is identical to kininase. As a result, ACE inhibition may block bradykinin metabolism resulting in more severe angioedema and dry cough.

Figure 7: Angioedema and Lip Swelling

Predisposing factors

Angioedema and dry cough are not dose and duration dependent. Clinical trials and post marking experience have shown that people of Chinese, Japanese, Indian, and African origin appear to be more susceptible. Further, females are 2 to 3 times more susceptible than males and elderly patients are at higher risk.

PRACTICE POINTS TO HEALTHCARE PROFESSIONALS

Angioedema and dry cough resolve few days after discontinuation of the ACEIs. Further rechallenge with another ACE inhibitor usually results in recurrence in most patients therefore, itis a class effect. Crossross-sensitivity when patients take other AECIs is well documented. Health care professionals are advised to monitor any adverse drug reactions or discomfort reported by patients after treatment with ACEIs. Healthcare professionals should report suspected ADRs to BoMRA.

Pharmacovigilance Trainings

The main objectives of pharmacovigilance trainings are to capacitate healthcare workers on reporting adverse drug reactions and adverse events following immunization of all medicines and vaccines used in Botswana. These trainings help in strengthening of the national pharmacovigilance system by improving reporting of adverse events and promoting patient safety to prevent drug-related adverse effects. To date BoMRA has trained over 3000 healthcare professionals which includes doctors, nurses, pharmacists and pharmacy technicians, dieticians, dentists and dental therapists, and health care assistants.

BoMRA is in a quest of building a robust National Pharmacovigilance System, as a result BoMRA has established 12 Adverse drug reaction monitoring Centre (AMCs) in Botswana. The AMCs serve to support and encourage Adverse Drug Reactions (ADRs) Monitoring and Reporting.

Modules taught

- **Introduction to BoMRA**
- **Pharmacovigilance – The Basics**
- **Pharmacovigilance global scenario and national perspective**
- **ADR Reporting tools**
- **Basics of vaccines**
- **Vaccine Pharmacovigilance**
- **AEFI Surveillance in Botswana**
- **AEFI Reporting (System) & AEFI Reporting Form**
- **Introduction to National Medicines information Centre**

Figure 8: Healthcare professionals from Ghanzi DHMT attending Pharmacovigilance training.

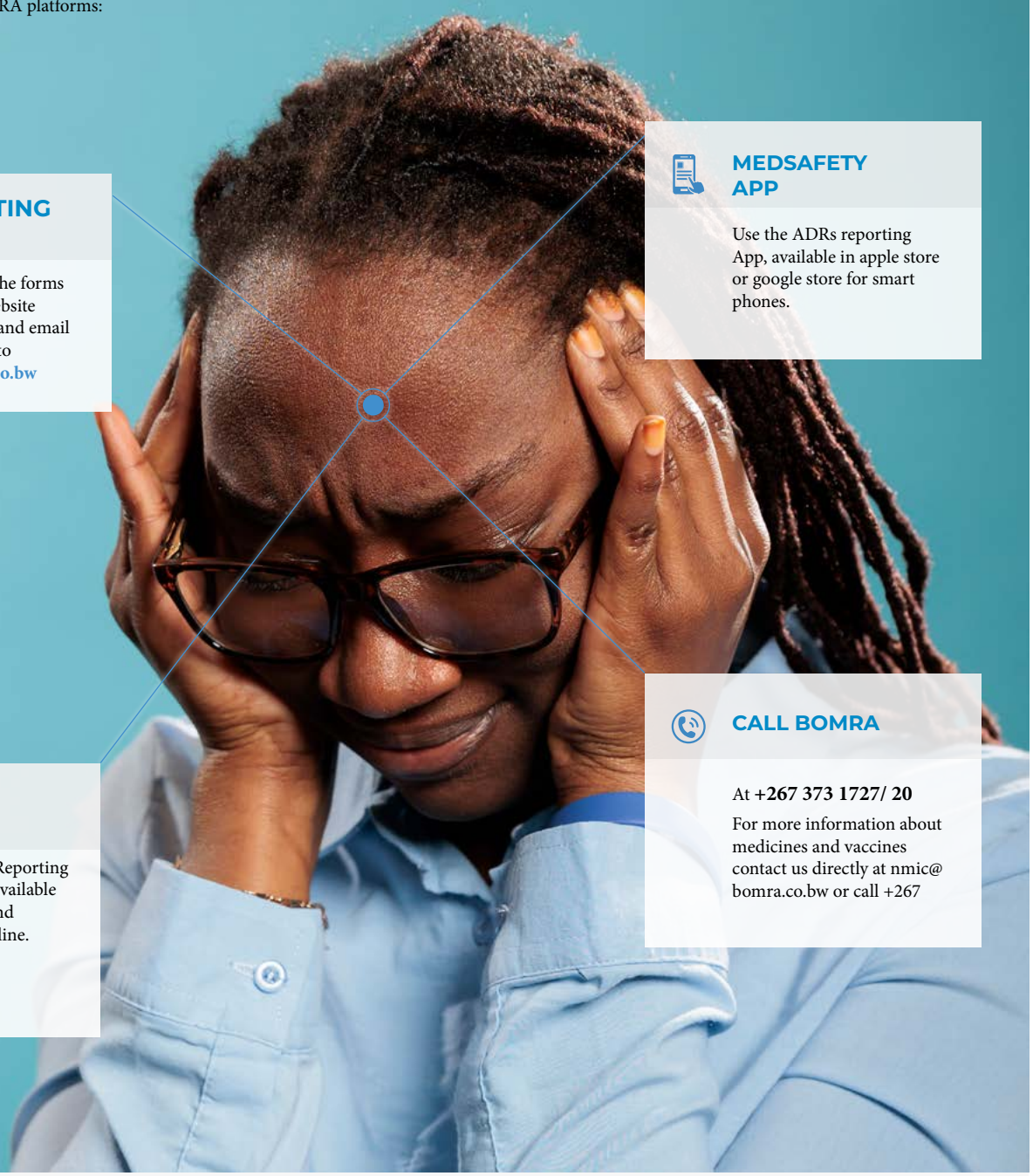
Figure 9: Pharmacovigilance Associate, Boago Mmusi conducting PV training at Broadhurst 3 clinic

Cohort Event Monitoring of 3HP Tuberculosis (TB) preventative therapy (TPT)

Ministry of Health (MOH) in collaboration with Botswana-University of Maryland School of Medicine Health Initiative (BUMMHI) initiated TPT early 2022 with 3HP. 3HP is a medication prescribed to prevent Tuberculosis (TB) for people at high risk of contracting TB. 3HP contains two anti-TB drugs: Isoniazid (H) and rifapentine (P). BoMRA through PVCT initiated Cohort Event Monitoring of all patients given TPT and this is carried out as a routine patient care activity NOT a study. BoMRA has since trained HCPs in most of DHMTs on safety monitoring of 3HP treatment.

How to Report

Healthcare professionals can report suspected ADRs to BoMRA using any of the following BoMRA platforms:



ADR REPORTING FORMS

You may download the forms from the BoMRA website www.bomra.co.bw and email the completed form to reportadr@bomra.co.bw

MEDSAFETY APP

Use the ADRs reporting App, available in apple store or google store for smart phones.

E-REPORTING.

Follow the Primary eReporting (who-umc.org) link available on BoMRA website and complete the form online.

CALL BOMRA

At **+267 373 1727/ 20**

For more information about medicines and vaccines contact us directly at nmic@bomra.co.bw or call +267

BOMRA
MEDICINES REGULATORY AUTHORITY

bsi. ISO 9001:2015 Quality Management

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