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Adverse event reporting in drug resistant tuberculosis facilities in South Africa

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Background

Although the incidence of adverse events surrounding medication used in the treatment of tuberculosis (TB), including the treatment of various forms of drug-resistant (DR)-TB, have been well documented, the reporting of these adverse events to clinical and governmental bodies is lacking. The World Health Organisation (WHO) has defined pharmacovigilance as 'the science and activities relating to the detection, assessment, understanding and prevention of adverse effects and all other problems related to medicines' (WHO, 2002a: 7). The definition has since expanded from simply adverse reactions or events to include various aspects of medication safety. These include medication errors, counterfeit or substandard medication, lack of efficacy of medication, the misuse or abuse of medication and the interaction between medications and include the surveillance of herbal products, other traditional and complimentary medication, biologicals, vaccines, blood products and medical devices (WHO, 2015).

An adverse reaction of a medication is defined by the WHO as 'a response to a drug that is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function' (WHO, 2002b: 5). An adverse drug event is defined as 'an untoward medical occurrence that may appear during treatment with a pharmaceutical product, but which does not necessarily have a causal relationship with the treatment' (WHO, 2002b: 5). Part of the pharmacovigilance process occurs after the product has been approved by the necessary regulatory authorities and is available for public consumption. This is referred to as the post-marketing surveillance (WHO, 2002b). This part of the pharmacovigilance chain is crucial as certain vulnerable populations such as elderly people, pregnant women and children are not generally included in clinical trials and safety information regarding medication use in these groups are gathered largely through post-marketing surveillance (WHO, 2002). Rare adverse reactions and the implications of chronic use of medications are also detected during post-marketing surveillance (WHO, 2002b).

The treatment of DR-TB is often influenced by adverse effects of the medication used and can impact treatment outcomes (Shean, Streicher, Pieterson, et al., 2013; Zhang, Wu, Xia, et al, 2017). A study in China (Zhang, Wu, Xia, et al, 2017) showed that of 751 patients with multidrug-resistant (MDR) TB enrolled, 90.7% (n=681) experienced an adverse event and 55.2% of these patients required a change in regimen and 6.8% required permanent discontinuation of certain drugs due to adverse events. In a South African study (Shean, Streicher, Pieterson, et al., 2013), 115 records of patients with extensively drug-resistant (XDR)-TB were retrospectively reviewed to find that 58% (n=68) of patients experienced adverse events. Of these patients, 34.0% (n=23) required a change in medication, 28% (n=19) of patients necessitated discontinuation of the offending drug, 3.0% (n=2) experienced life-threatening adverse events and 9.0% (n=6) died. Gastrointestinal related adverse events are

the most commonly detected (Shean, Streicher, Pieterson, et al., 2013; Rathod, Borkar, Lamb, et al., 2015; Tag El Din, El Maraghy and Abdel Hay, 2015; Zhang, Wu, Xia, et al, 2017). The treatment regimens of DR-TB are fluid and constantly changing to accommodate new information. Most recently, the South African National Department of Health decided to replace the injectable agent amikacin, which is strongly associated with hearing loss and nephrotoxicity in a large number of patients, with bedaquiline (Medical Brief, 2018). This change was a welcome one, but pharmacovigilance practices should be particularly encouraged moving forward as the initial uptake of bedaquiline was slow due to concern of potentially severe adverse effects (Medical Brief, 2018).

The spontaneous reporting system of adverse events is the adopted system worldwide (Pal, Duncombe, Falzon, et al., 2013). This system provides the highest volume of information with the lowest maintenance cost. However, the disadvantage of this system is underreporting as reporting is left to the motivation of the individual (Pal, Duncombe, Falzon, et al., 2013). The WHO has recommended the use of targeted spontaneous reporting in which a defined group of patients, such as those with MDR-TB, are monitored for adverse events (WHO, 2012). The programme may be adapted to report all adverse events or only severe adverse events which lead to a modification in medication, discontinuation of a drug or death and should be included as standard of care. In South Africa, targeted spontaneous reporting has been successfully adopted by human immunodeficiency virus (HIV) programmes (Dheda, Distefano, Sunduzwayo, et al., 2013). A similar strategy may be adopted for patients being treated for DR-TB.

There is a dearth of information regarding pharmacovigilance and reporting frequencies in healthcare facilities in South Africa. The National Pharmacovigilance Committee (NPC) have investigated the effects of training provided to healthcare staff in two districts in the Northern Cape (Dheda, Kambafwile and Oosthuizen, 2018). The training indicated an improvement in overall knowledge, but it was noted that certain aspects of the training needs to be emphasized and the long-term impact of this training needs to be evaluated. Another study conducted by the NPC in the Eastern Cape aimed to understand the existing systems surrounding pharmacovigilance practices (Dheda, Kambafwile, Oosthuizen, Bakor, Soka and Malangu, 2016). The study showed that there was limited knowledge, awareness and practices among healthcare professionals from public primary healthcare facilities, community health centres and hospitals regarding pharmacovigilance, which implied that training interventions were required. Given the ever-changing scope of DR-TB treatment, pharmacovigilance becomes a crucial part of patient care to ensure that patients are receiving safe and effective medication.

Primary aim and objectives

The primary aim of the study was to understand the current adverse event reporting practices in specialised DR-TB treatment facilities in South Africa and develop appropriate interventions if needed.

The specific objectives of the study were to:

- understand experiences of healthcare professionals in adverse event reporting;
- map out the current adverse event reporting practices and identify best practices (based on successful reporting of adverse events);
- analyse quality of adverse event reporting according to minimum requirements of National Pharmacovigilance Centre (NPC);
- understand the activities of NGOs working in pharmacovigilance and their linkages to regulatory authorities; and
- develop an intervention plan based on findings.

Methodology

The study was descriptive and cross sectional in nature, employing the use of structured interviews (Appendix A). A random sample of the most recently completed adverse event report forms at the time of the visit to the selected facilities, were audited to determine the extent and quality of adverse event reporting using a self-developed data collection tool (Appendix B). Facility managers, matrons or quality assurance managers were asked if there were any NGOs at the facility involved in pharmacovigilance activities in an attempt to understand their role and linkage to the regulatory authorities (Appendix C).

Study site and population

The study focused on the Centres of Excellence (CoEs) in each province. The CoEs admit and treat all clinically unstable patients living with MDR-TB, pre-XDR or XDR-TB. The incidence of adverse effects may have been higher in such environments, given that hospitalised patients may be more susceptible to the adverse effects of the medication due to low body weight or mineral imbalances. Healthcare professionals at CoEs set the baseline for decentralised sites and share best practices. The included facilities are listed in Table 1 below.

Table 1: Facilities visited

Province	Facilities
Eastern Cape	Jose Pearson TB Hospital Nkqubela TB Hospital
Free State	Dr JS Moroka Hospital

Gauteng	Sizwe Tropical Disease Hospital
KwaZulu-Natal	King Dinuzulu Hospital Complex
Limpopo	FH Odendaal Hospital
Mpumalanga	Witbank TB Hospital
North West Province	Tshepong Hospital (Klerksdorp Hospital)
Northern Cape	West End Specialised DR-TB Hospital
Western Cape	Brooklyn Chest TB Hospital

The targeted research population comprised of doctors, matrons/facility managers, professional nurses, pharmacists and quality assurance managers based at each facility. Structured interviews were conducted with consenting participants. Facility managers, quality assurance managers or matrons were asked about NGO-related pharmacovigilance activities in their facility and the relevant NGO were contacted and interviewed telephonically where needed.

The adverse event report forms for review were selected at random and comprised between 2% and 5% of the hospitalised population at the time of the study visit. The reports on adverse events, their management and outcomes were reviewed to determine how healthcare professionals recorded these events.

Data collection

Before visiting the facility, the manager of the various facilities was contacted requesting an appropriate date and time for visiting, to not disrupt the flow of work. Two research assistants were trained to effectively conduct interviews with staff. Following written informed consent (Appendix D), structured interviews were conducted by the researchers or research assistant in a private area in the facility. The interviews took approximately 30 to 45 minutes to complete and all attempts were made to ensure that staff were not kept from their duties for extended periods of time. Only the principal investigator and project manager conducted the review of the adverse event reports using a self-developed data collection tool.

Data analysis

The data from interviews and adverse event report reviews were coded and captured in an Excel® spreadsheet, after which a descriptive analysis was performed using Stata version 15.0.

Ethics

Ethical approval for the study was obtained from the Human Sciences Research Council Research Ethics Committee (REC) (6/22/08/18) as well as from all provincial Departments of Health through the National Health Research Ethics Council (NHREC). All of the relevant district managers were informed of the study and written permission was obtained to visit the facilities. The facility managers were then asked to provide a preferred date and time of visit (Appendix E). Informed consent was obtained before interviews commenced and personal participant information was collected only on the informed consent form. When compiling manuscripts for publication, study sites will not be named or linked to responses to ensure that no participant may be linked to specific responses. All responses will remain anonymous and all identifying information will be removed.

Results

The results are reported in accordance with the specific objectives set out in section 2 above.

Objective 1 and 2: Understand experiences of healthcare professionals in adverse event reporting and map out the current adverse event reporting practices and identify best practices (based on successful reporting of adverse events)

In total, 164 health care workers participated in the study. Nurses comprised the majority of the study population, accounting for 59.8% (n = 98) of the participants. Second were doctors at 19.5% (n = 32) and pharmacists at 10.4% (n = 17). Positions occupied by the remaining participants included matron (6.7%; n = 11), facility manager (0.6%; n= 1), quality assurance manager (2.4%; n = 4) and an occupational health nurse (0.6%; n = 1). A majority of 43.3% of participants had been working at their current place of employment between one and five years, and more than half (53.0%; n = 87) of the participants had more than 10 years of total work experience in their respective professions. While 62.2% (n = 102) of participants reported that they were introduced to the concept of pharmacovigilance during their tertiary education, only 39.0% (n = 64) indicated that they had had any training in this field since completing their qualifications. However, 44.5% (n = 73) reported that they had received training regarding adverse event reporting in the 12 months prior to the study. Just more than half of the participants (53.7%; n = 88) claimed that they had reported an adverse reaction within the last six months, but fewer than half (48.2%; n = 79) used an adverse event report form, although most (84.8%; n = 139) participants reported that they were aware of a Standard Operating Procedure (SOP) in place regarding adverse event reporting. While almost all participants (99.4%; n = 163) indicated that reporting adverse events was necessary and believed that it was their personal responsibility (98.8%; n = 162), when asked how many adverse effect forms the participant completed over the last six months at the facility, 52.4% (n = 86) of participants said none. Just under one-quarter (24.45%, n = 40) indicated one to

five reports, 9.8% (n = 16) said between six and 10 reports, and 12.8% (n = 21) claimed that they had completed more than 10 reports in the last six months. More participants felt that reporting adverse events was the responsibility of doctors (90.9%; n = 149) and professional nurses (95.1%; n = 156) rather than pharmacists (70.1%; n = 115) or other healthcare professionals (41.4%; n = 68).

About three quarters (75.6%; n = 124) of the study population felt that the medication used to treat drug resistant tuberculosis (DR-TB) posed a risk to the patient's safety while just 71.3% of participants felt they had sufficient knowledge about the medication to identify an adverse reaction. However, when asked to identify common adverse reactions associated with DR-TB medication, participants were largely successful. These included; gastrointestinal disturbances (99.4%; n = 163), peripheral neuropathy (99.4%; n = 163), hepatic abnormalities (98.8%; n = 162), skin reactions (98.2%; n = 161), ocular toxicity (90.2%; n = 148), psychosis (97.0%; n = 159), electrolyte imbalance (93.3%; n= 153), anaemia (93.3%; n = 153), musculoskeletal pain (90.9%; n = 149) and renal abnormalities (98.2%; n = 161). Adverse reactions that participants were unsure of included gynaecomastia (47.0%; n = 77), hyperuricemia (54.3%; n = 89), diabetes (31.1%; n = 51) and bronchospasm (53.0%; n = 87); the last two of which are not associated with DR-TB medication. All values reported represent participants who agreed that the adverse reaction was positively associated with DR-TB medication.

In addition to reporting adverse drug reactions, participants indicated the methods they have used to detect these reactions. Figure 1 below summarises the methods of detection of adverse reactions.

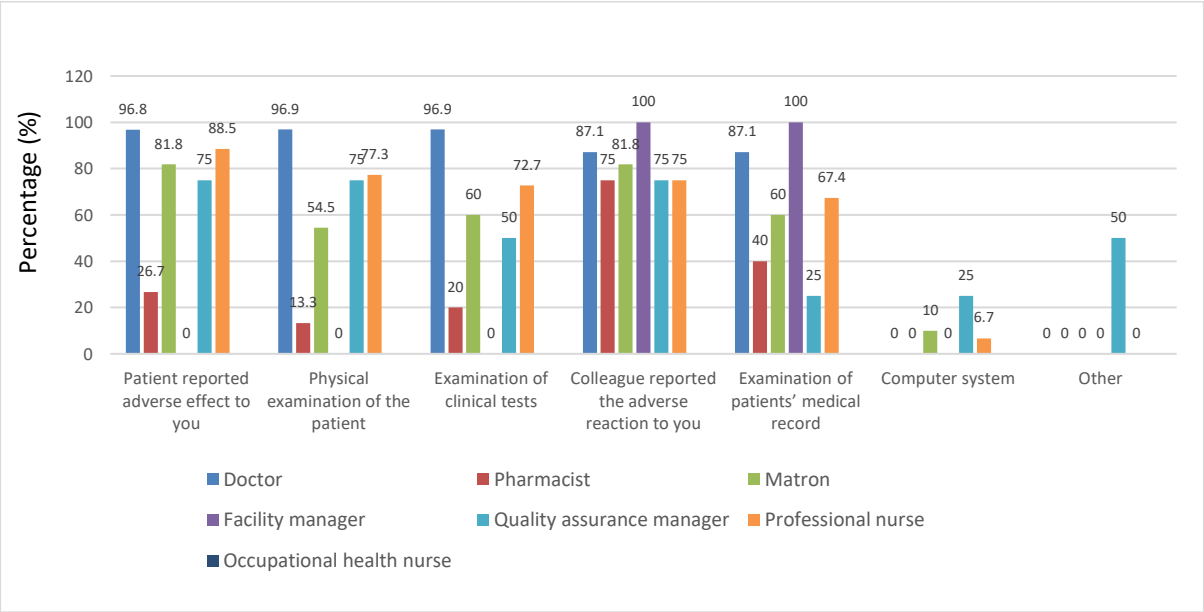

Figure 1: Methods of detection of adverse reactions associated with DR-TB medication

Participants most often indicated that their patients reported adverse effects of medication to them (79.9%), were told by a colleague (75.6%) or detect it themselves whilst physically

examining the patient (71.3%). In other cases, the examination of clinical test results (68.3%) and examination of patients' medical records (64%) revealed adverse reactions. Doctors and professional nurses detected adverse drug reactions through these methods more than pharmacists, who relied more on colleagues' reports of adverse drug reactions and an examination of the patient's medical record.

Participants were asked about the procedure they followed once an adverse reaction has been identified. The majority of participants (87.8%; n = 144) stated that they knew where to find an adverse event report form and are able to complete it without assistance (69.5%; n= 114). Some participants (39.6%; n = 65) stated that they would inform another health professional of the adverse reaction for reporting purposes. Once the form was completed, participants reported the actions as summarised in Table 2 below.

Just over half of the participants (50.6%; n = 83) reported that adverse event reports were submitted to an external regulatory body and most were unsure (63.4%; n = 104) to which body the forms were sent. The majority (98.8%; n = 162) of participants felt that it is good practice to report adverse reactions and that there was a benefit to both patients and health professionals in reporting.

Table 2: Action taken once adverse reactions are identified

Action	Frequency	Percentage (%)
Insert the form into the patient's folder	57	34.8
Hand the form to the ward manager	33	20.1
Hand the form to the doctor overseeing the patient	36	22.0
Hand the form to the medical staff supervisor/chief medical supervisor	11	6.7
Hand the form to the hospital matron	22	13.4
Hand the form to a designated person within the facility concerned with adverse effects/pharmacovigilance activities	68	41.5
Have never completed an adverse effect form in this facility	52	31.7
Copy sent to pharmacist	17	10.4
Sent to Department of Health	2	1.2
Sent to Pharmaceutical and Therapeutics Committee	2	1.2

Participants felt that the process of reporting an adverse drug reaction within their facility was a straight-forward process, but fewer than half (48.8%; n = 89) of participants felt that their reporting influenced clinical practices at the facility. The adverse event report form includes a section on the management and outcome of the patient. Participants reported that guidelines, consulting with their colleagues and using their own clinical judgement were methods they used to best determine how to manage the patient. Doctors agreed unanimously on all three, while nurses and pharmacists, the various aspects of patient management not all falling within their scopes of practice, preferred consulting guidelines for advice. Almost half of participants were unsure if their reports reached a central body but, 86.2% (n = 156) of participants stated that they had never received any feedback from an external regulatory body. Figure 2 summarises various factors that would encourage health professionals to increase the frequency of adverse event reports.

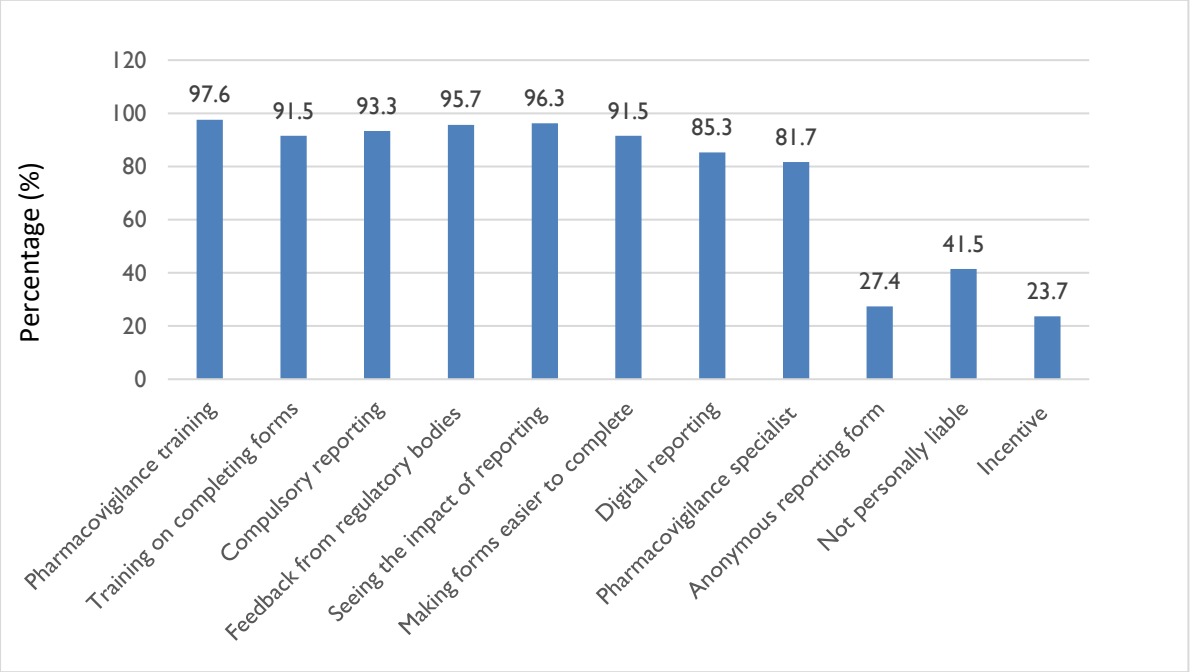

Figure 2: Factors that would encourage health professionals to report adverse events

Training on pharmacovigilance relevance (97.6%), seeing the impact of reporting on the clinical management of patients (96.3%) and receiving feedback from regulatory bodies regarding reports submitted (95.7%) were the top three factors that would encourage participants to report adverse drug reactions. In addition, making adverse effect reporting compulsory on health care professionals (93.3%), more training on completing adverse effect reporting forms (91.5%) and making said forms easier to complete (91.5%) also received a high number of responses. The introduction and availability of a digital reporting system (85.3%), as well as having a pharmacovigilance specialist available at the facility (81.7%) also elicited interest. Interestingly, not many participants indicated that not being personally held liable for the information reported (41.5%), the use of an anonymous reporting form (27.4%) or that any financial or other incentives to report (23.7%) will encourage them to report adverse events.

Just over half (56.7%; n = 93) of the participants indicated that their facility has an active Pharmaceutical and Therapeutics Committee (PTC), but less than a third (26.8%; n = 44) of all participants indicated that they were a part of this committee. However, 29.9% (n = 49) of participants indicated that pharmacovigilance matters formed a standing part of the PTC's agenda. Where PTCs were active, more doctors were members compared to nurses and pharmacists. Participants were unsure of the availability of clear procedures for follow up and reporting the outcomes of adverse reactions and only 26.2% (n = 43) felt that there was consensus between the clinicians of a facility on how best to manage particular adverse reactions. Participants claimed that the minutes or outcomes of PTC meetings were not shared with the larger staff body at their facilities.

Objective 3: Analyse quality of adverse event reporting according to minimum requirements of National Pharmacovigilance Centre (NPC)

A total of 78 reports were analysed across the 10 study sites. The aim was that between 2% and 5% of the available forms would be analysed at each site but, there was only one site where this was possible. Elsewhere, due to the small numbers of completed forms, all forms were analysed. The number of completed adverse event report forms available in each province are reported in Table 3 below.

Table 3: Number of completed adverse event report forms at each study site

Province	Number of completed adverse event report forms
Eastern Cape	24
Free State	10
Gauteng	7
KwaZulu-Natal	10
Limpopo	5
Mpumalanga	4
Northern Cape	6
North West Province	2
Western Cape	10
Total	78

Variables checked and analysed can be found on the adverse event report audit form attached (Appendix B). All variables are mandatory parameters as outlined by the South African Health Products Regulatory Authority (SAHPRA) and the National Pharmacovigilance Centre (NPC). Identifying information such as hospital number was absent on 80.7% (n=68) of forms and DR-

TB registration number was absent on 35.9% (n=28) of forms. Other pertinent information often missing was HIV status (53.8%; n=42); initiation on ART (71.8%; n=56); the ART regimen (75.6%; n=59); viral load (82.1%; n=64) and other concomitant conditions (89.7%; n= 70).

Objective 4: Understand the activities of NGOs working in pharmacovigilance and their linkages to regulatory authorities

No facilities reported the presence of NGOs which were involved in pharmacovigilance activities.

Objective 5: Develop an intervention plan based on findings

Based on the above results, the following recommendations are made to the National Pharmacovigilance Centre (NPC) of the Department of Health:

1. Standardization of the adverse event report forms across facilities
2. Evaluate various methods of incorporating the form into the daily routine or standard patient examination;
3. Train all staff working with DR-TB patients (including non-RNs, social workers, physiotherapists, pharmacists, CHWs) regarding adverse event reporting and its value as part of a national intervention;
4. Implement a pre/post assessment of the training intervention (for research purposes);
5. Implement a formal audit for operational management purposes;
6. Consolidate guidelines from SAHPRA and NPC concerning the reporting of adverse reactions associated with TB and HIV;
7. Clarify which health professionals can complete these forms;
8. Encourage feedback from the NPC on reports received;
9. Encourage the use of digital applications for reporting which will eventually replace paper-based reports and
10. Encourage PTC meetings at all study sites and provide training on basic analysis of reports in the facility and how they can be used at a facility level.

Discussion

Pharmacovigilance activities are important to understand the safety of a medication in various populations. As clinical trials can only afford to include a small number of participants, the bulk of reporting is expected to occur during the post-marketing phase which relies on healthcare professionals for the detection and reporting of adverse drug reactions. South Africa relies on a system of voluntary spontaneous reporting of adverse drug reactions. While this is the norm for most countries (Pal, Duncombe, Falzon, et al., 2013), a more targeted approach is required for diseases such as DR-TB (WHO, 2012), the treatment of which can be toxic and has undergone many changes in the past and may still in the future. South Africa has successfully implemented a targeted spontaneous reporting programme for HIV during the rollout of antiretrovirals (Dheda, Distefano, Sunduzwayo, et al., 2013), but the same success has not been achieved with DR-TB.

The current study aimed to explore the adverse event reporting practices at DR-TB facilities throughout the country, focusing on those CoEs that set baseline practices for the decentralised sites. The majority of the respondents were professional nurses, which is in line with the composition of most public-sector healthcare facilities in South Africa. It was a challenge to include managerial staff in the study. This is a limitation of the current study as their opinions on pharmacovigilance policy, adverse event reporting and related SOPs within their facilities, could not be included.

In order to report adverse drug reactions of DR-TB medication, it must first be identified and this may be challenging given the overlap with antiretrovirals used in HIV treatment. Health professionals in direct contact with the patient such as doctors and nurses detected adverse drug reactions through physical examination of the patient, interviewing the patient and analysing laboratory results. Pharmacists, who do not always have direct contact with patients, particularly in-patients, detected adverse drug reactions through analysing the medical record. Encouraging a multidisciplinary effort during ward rounds may assist in detecting the adverse reaction as soon as possible, thus mitigating any serious outcomes (Epstein, 2014).

The overall reporting frequency in this study was low, even though it is expected in environments with spontaneous voluntary reporting. The lack of feedback from regulatory bodies, the perceived lack of impact of the reports and lack of understanding of which health professionals are able to report adverse drug reactions may be reasons for low reporting rates. Terblanche (2018) noted that possible reasons for low reporting rates included health professionals desiring incentives to report and their fear of litigation should the adverse event be attributed to their practice. Another study (Bogolubova, Padayachee and Schellack, 2018) reported that a lack of training on pharmacovigilance activities and how to report adverse events deterred health professionals from reporting and, that while health professionals believed that reporting was important, translating knowledge into practice was challenging.

Similarly, the current study showed that health professionals felt that reporting of adverse drug reactions was important, and their actual knowledge of common adverse drug reactions of DR-TB medication was good, but actual levels of reporting were low. They reported that training on pharmacovigilance and completing the adverse event forms would stimulate higher reporting rates, but that they were not interested in incentives to report and they did not necessarily fear litigation from information included in the reports.

Additionally, while adverse event report forms may be completed, the forwarding of this information to regulatory bodies such as the NPC or SAHPRA was not well known or understood by most participants. Reviewing the completed adverse event reports showed that while most information was available, a gap existed in terms of co-morbidities, especially HIV and its treatment. Given that the TB/HIV co-infection rate is high in South Africa, TB medication and antiretrovirals are often prescribed together. Providing complete information about the patient would assist in the later stages of signal detection and causality assessments of the pharmacovigilance process. A thorough understanding of the need and process as well as inclusion in the feedback cycle would be beneficial to encourage reporting among health professionals.

Conclusions

While health professionals showed good knowledge of the common adverse reactions associated with DR-TB medication, translating the knowledge into action was challenging. Training and regular refresher training on the need for pharmacovigilance and instruction on the completion of adverse event report forms would assist in empowering all health professionals and encourage reporting as well as the inclusion of facilities in the feedback process. Encouraging multidisciplinary interaction with patients would serve to improve the quality of care beyond simply the detection and management of adverse drug reactions. Facilities need to be motivated to revive and engage PTCs where they can collate ad utilise their own pharmacovigilance data generated at the facility to inform clinical practice.

References

Dheda M, Distefano K, Sunduzwayo K, Williams F and Kambafwile H. 2013. Decentralized HIV/AIDS pharmacovigilance in South Africa: Mpumalanga success & moving forward. *Journal of AIDS and HIV Research*, 5(9): 370-379.

Dheda M, Kambafwile H and Oosthuizen F. 2018. Investigation on the effect of a one-day pharmacovigilance training of healthcare professionals. *Journal of Public Health and Epidemiology*, 10(6): 183-189.

Dheda M, Kambafwile H, Oosthuizen F, Bakor A, Soka A and Malangu N. 2016. A cross-sectional baseline assessment of the pharmacovigilance systems, processes and challenges faced by healthcare professionals in three South African districts prior to pharmacovigilance training and programme roll-out. *Botswana Journal of African Studies*, 30(1): 100-111.

Medical Brief. 2018. SA signs deal with Janssen to lower price of TB medicine[online]. Available at https://www.medicalbrief.co.za/archives/sa-signs-deal-janssen-lower-price-tb-medicine/] [Date accessed 01/08/2018].

Pal SN, Duncombe C, Falzon D and Olsson S. 2013. WHO strategy for collecting safety data in public health programmes: complementing spontaneous reporting systems. *Drug Safety*, 36(2): 75-81.

Rathod KB, Borkar MS, Lamb AR, Suryavanshi SL, Surwade GA and Pandey VR. 2015. Adverse events among patients of multi drug resistant tuberculosis receiving second line anti TB treatment. *International Journal of Scientific Reports*, 1(6): 253-257.

Shean K, Streicher E, Pieterson E, Symons G, van Zyl Smit R, Theron G, Lehloenya R, Padanilam X, Wilcox P, Victor TC, van Helden P, Groubusch M, Warren R, Badri M and Dheda K. 2013. Drug-associated adverse events and their relationship with outcomes in patients receiving treatment for extensively drug-resistant tuberculosis in South Africa [online]. *Plos One*, 8(3). Available at http://journals.plos.org/plosone/article/file?id=10.1371/journal.pone.0063057&type=printable [Date accessed 28/02/2018].

Tag El Din MA, El Maraghy AA and Abdel Hay AHR. 2015. Adverse reactions among patients being treated for multi-drug resistant tuberculosis at Abbassia Chest Hospital. *Egyptian Journal of Chest Diseases and Tuberculosis*, 64: 939-952.

WHO. 2002a. The importance of pharmacovigilance: safety monitoring of medicinal products. United Kingdom: WHO, pp. 52.

WHO. 2002b. Safety of medicines: a guide to detecting and adverse drug reactions, why health professionals need to take action. Geneva: WHO Press.

WHO. 2012. A practical handbook on the pharmacovigilance of medicines used in the treatment of tuberculosis: enhancing the safety of the TB patient [online]. France: WHO Printer. Available at http://www.who.int/medicines/publications/Pharmaco_TB_web_v3.pdf [Date accessed 28/02/2018].

WHO. 2015. WHO Pharmacovigilance Indicators: a practical manual for the assessment of pharmacovigilance systems. France: WHO Press.

Zhang Y, Wu S, Xia Y, Wang N, Zhou L, Wang J, Fang R, Sun F, Chen M and Zhan S. 2017. Adverse events associated with treatment of multidrug-resistant tuberculosis in China: an ambispective cohort study. *Medical Science Monitor: international medical journal of experimental and clinical research*, 18(23): 2348-2356.

Appendices

Appendix A: Structured interview schedule

Participant ID:					

A. DEMOGRAPHIC CHARACTERISTICS

1) Province ***(tick '✓' only ONE option)***

1 = Eastern Cape	
2 = Western Cape	
3 = KwaZulu-Natal	
4 = Gauteng	
5 = Mpumalanga	
6 = Northern Cape	
7 = North West Province	
8 = Limpopo	
9 = Free State	

2) Age in years: _____

3) How do you identify? ***(tick '✓' only ONE option)***

1 = Male	
2 = Female	
3 = Transgender	
4 = Intersex	

4) Urban/rural status of facility ***(tick '✓' only ONE option)***

1 = Urban	
2 = Rural	
3 = Other ***(ask participant to please specify)***: _____ _____ _____ _____	

5) What position do you hold at this facility? ***(tick '✓' only ONE option)***

1 = Doctor	
2 = Pharmacist	
3 = Matron	
4 = Facility manager/CEO	

5 = Quality assurance manager	
6 = Professional nurse	

6) How long have you held this position at this facility? ***(tick '✓' only ONE option)***

1 = Less than a year	
2 = 1 to 5 years	
3 = 6 to 10 years	
4 = Longer than 10 years	

7) How many years of total working experience do you have in your current profession? ***(tick '✓' only ONE option)***

1 = Less than a year	
2 = 1 to 5 years	
3 = 6 to 10 years	
4 = Longer than 10 years	

B. TRAINING IN PHARMACOVIGILANCE/ADVERSE EFFECT REPORTING

8) Were you ever introduced to the concept of pharmacovigilance/adverse effect reporting during your tertiary education? ***(tick '✓' only ONE option)***

1 = Yes	
2 = No	

9) Have you had any additional training after your formal tertiary education (including refresher courses) in any of the following fields? ***(tick '✓' all that apply)***

1 = Adverse drug reactions and drug-related problems	
2 = Toxicology	
3 = Pharmacovigilance	
4 = None	

10) Have you received training in adverse effect reporting in the last 12 months? ***(tick '✓' only ONE option)***

1 = Yes	
2 = No	

11) Have you received training regarding any medication used to treat drug-resistant tuberculosis in the last 12 months? ***(tick '✓' only ONE option)***

1 = Yes	
2 = No	

12) Are you aware of a Standard Operating Procedure (SOP) within the facility or ward regarding adverse effect reporting? ***(tick '✓' only ONE option)***

1 = Yes	
2 = No	

13) In your opinion, is adverse effect reporting is necessary? *(tick '✓' only ONE option)*

1 = Yes	
2 = No	

14) Do you believe that it is your responsibility to report adverse effects? *(tick '✓' only ONE option)*

1 = Yes	
2 = No	

15) Whose responsibility do you think adverse effect reporting should be? *(tick '✓' all that apply)*

1 = Medical practitioner (doctor)	
2 = Pharmacist	
3 = Professional nurse	
4 = Dedicated person within the facility	
5 = Other ***(ask participant to please specify)*** _____	

16) To whom do you think in-patients should speak to concerning adverse drug reactions they may have experienced? *(tick '✓' all that apply)*

1 = Medical practitioner (doctor)	
2 = Pharmacist	
3 = Registered nurse	
4 = Dedicated person within the facility	
5 = Other ***(ask participant to please specify)*** _____	

17) To whom do you think outpatients do actually speak to concerning adverse drug reactions they may have experienced? *(tick '✓' all that apply)*

1 = Medical practitioner (doctor)	
2 = Pharmacist	
3 = Registered nurse	
4 = Dedicated person within the facility	
5 = Other ***(ask participant to please specify)*** _____	

C. ATTITUDES AND KNOWLEDGE OF PHARMACOVIGILANCE

18) In your opinion, the scope of pharmacovigilance includes *(answer yes or no; or unsure)*

1 = yes; 2 = no; 3 = unsure

a) Adverse reactions/effects	
b) Medication errors	
c) Counterfeit/fake medicines	

d) Lack of efficacy of medication (failure to produce the desired pharmaceutical outcome)	
e) Abuse and misuse of medicines	
f) Interactions between medicines	
g) Interactions between medicines and food	
h) Medical devices	

19) In your opinion, pharmacovigilance activities encompass the following products *(answer yes or no; or unsure)*

1 = yes; 2 = no; 3 = unsure

a) General medicines	
b) Herbal products	
c) Biological products	
d) Medical devices	
e) Blood products	
f) Vaccines	
g) Traditional and complementary medicine	

20) To what extent do you agree or disagree with the following statements?

1 = strongly agree 2 = agree 3 = neutral 4 = disagree 5 = strongly disagree

Policy making	
a) Reporting adverse effects can influence how a medicine is used (dose, frequency of dose, duration of use, etc)	
b) Reporting adverse effects can influence national treatment guidelines	
c) Reporting adverse effects can influence international treatment guidelines	
d) Reporting adverse effects can influence prescribing practices	
e) Reporting adverse effects can influence the registration of a medication	
f) Reporting of adverse effects directly influence patient safety	
Therapeutic drug monitoring	
a) Adverse effects can be detected through blood tests (full blood counts, liver enzyme levels, kidney function, drug concentration in the blood, etc)	
b) Efficacy of medication can be detected through blood tests (full blood counts, liver enzyme levels, kidney function, drug concentration in the blood, etc)	
Post-marketing surveillance	
a) Adverse effects only need to be reported if the medication has not yet been registered with the South African Health Product Regulation Authority (SAHPRA) (formerly known as Medicines Control Council (MCC))	
b) Adverse effects should only be reported for new medicines (less than 5 years old)	
c) Adverse effects do not have to be reported for medicines that have been on the market for many years (5 years or longer)	

d) Post-marketing pharmacovigilance is directly dependent on healthcare professionals	
Health care professional participation	
a) Health care professionals should report adverse effects as part of their professional responsibility	
b) Health care professionals should report adverse effects even if they doubt the relationship between the adverse effect and the medication	
c) Adverse effect reporting should be a compulsory part of any health care profession	
Broader influences	
a) Reporting adverse effects would have a positive influence on the economy	
b) Reporting adverse effects would have positive influence on financial status of public and private health care centres	
c) Reporting adverse effects would have a positive influence on South Africa's health care system	
Training	
a) More training on pharmacovigilance activities should be provided by pharmaceutical companies	
b) More training on pharmacovigilance activities should be provided by the Department of Health	
c) More training on pharmacovigilance activities should be provided by management staff at the facility	
d) I am willing to undergo further training to improve my understanding and practice of pharmacovigilance activities	

D. KNOWLEDGE AND ATTITUDES REGARDING TB PHARMACOVIGILANCE

21) Do you think that the medications used to treat drug-resistant TB pose a risk to patients and their safety? ***(tick '✓' only ONE option)***

1 = Yes	
2 = No	

22) Do you feel that you have sufficient knowledge of drug-resistant TB medication and their side effects to detect a side effect or adverse effect? ***(tick '✓' only ONE option)***

1 = Yes	
2 = No	

Types of adverse effects that are reported

23) **To what extent do you agree or disagree with the following statements:**

1 = strongly agree 2 = agree 3 = neutral 4 = disagree 5 = strongly disagree

All serious adverse drug reactions should be reported	
All adverse reactions that result in death should be reported	

All adverse reactions that result in congenital abnormalities or birth defect should be reported	
All adverse reactions that result in hospitalisation or prolongation of existing hospitalisation should be reported	
All adverse reactions that result in significant disability or incapacity should be reported	
Adverse reactions of well-known drugs that were unexpected should be reported	
Adverse reactions of well-known drugs that were expected should be reported	
Adverse reactions of new drugs that were unexpected should be reported	
Adverse reactions of new drugs that were expected should be reported	
If a drug demonstrates an unexpected therapeutic effect it should be reported	
Adverse reactions suspected to be caused by unscheduled medicines should be reported	
Adverse reactions caused by vaccines should be reported	
Adverse reactions suspected to be caused by traditional and herbal medicine should be reported	
If an adverse effect is not listed in the package insert of the medicine, it should be reported	
Interactions that occur between two or more drugs should be reported	
Interactions that occur between a drug and food should be reported	
Adverse reactions that occur due to a medication error should be reported	

24) Which of the following adverse effects would you expect to see as a result of drug-resistant TB medication? ***(tick '✓' all that apply)***

a) Anorexia/nausea/vomiting/diarrhoea	
b) Peripheral neuropathy	
c) Hepatic abnormalities (liver abnormalities/changes in liver enzyme levels)	
d) Diabetes	
e) Skin rashes/hypersensitivity reactions	
f) Stevens-Johnson syndrome	
g) Gynaecomastia (development of breasts in men)	
h) Seizures	
i) Hyperuricemia (gout)	
j) Ocular toxicity	
k) Headache	
l) Pigmentation	
m) Psychosis	
n) Electrolyte imbalances	
o) Anaemia	
p) Hypothyroidism	

q) Bronchospasm (tightening of the chest)	
r) Musculoskeletal pain	
s) Ototoxicity (deafness)	
t) Renal (kidney) abnormalities	

E. CURRENT PRACTISES: REPORTING ADVERSE EFFECTS

Methods of adverse effect reporting used

25) Have you reported an adverse effect in the last six months?

1 = Yes	
2 = No	

26) Did you use an adverse effect report form?

1 = Yes	
2= No	

27) Which adverse effect reporting form does your facility use?

1= Standard form from Department of Health	
2 = TB specific report form	
3 = Customised internal form	
4 = Digital form/application	
5 = Unsure	

28) Have you ever identified an adverse effect associated with TB medication at this facility through the following methods:

1=yes; 2=no

a) Patient reported adverse effect to you	
b) Detected adverse effect through physical examination of the patient	
c) Detected adverse effect through examination of clinical tests (e.g. blood results, blood pressure, glucose levels, microbiology tests, etc)	
d) Colleague reported an adverse effect to you	
e) Detected an adverse effect through examination of a patient's medical record	
f) Computerised system for adverse effect detection	
g) Other ***(ask participant to please specify)*** _____	

29) Have you ever had to consult a reference to confirm an adverse effect?

1 = Yes	
2 = No	

29a) If yes, of which references do you make use? *(tick '✓' all that apply)*

1 = Guidelines	
2 = Internet	

3 = Colleague(s)	
4 = Medical reference book	
5 = UCT Medicines Information Centre Helpline	
6 = Department of Health provided resources (example: posters, pamphlets)	
7 = None	
8 = Other ***(please ask participant to specify)*** _____	

Individual practises: Reporting an adverse effect

30) How many adverse effect forms have you completed in the last 6 months at this facility?

1 = Zero	
2 = 1 to 5	
3 = 6 to 10	
4 = More than 10	

Please indicate yes or no to the following statements
Self-efficacy

31) Once the adverse effect has been identified:
1=yes; 2=no

a) I know from where to obtain an adverse effect form	
b) I feel able to complete the adverse effect form with no assistance	
c) I feel able to complete the adverse effect form only with assistance	
d) I do not feel that I am able to complete an adverse effect form	
e) I am not allowed to complete the adverse effect form	
f) I report the adverse effect to another health care professional (doctor, nurse, pharmacist) to complete the adverse effect form	
g) I do not report adverse effects to anyone, nor do I complete a form	

32) What did you do after you completed the adverse effect form? *(tick '✓' all that apply)*

a) I insert the form into the patient's folder	
b) I hand the form to the ward manager	
c) I hand the form to the doctor overseeing the patient	
d) I hand the form to the medical staff supervisor/chief medical supervisor	
e) I hand the form to the hospital matron	
f) I hand the form to a designated person within the facility concerned with adverse effects/pharmacovigilance activities	
g) I have never completed an adverse effect form in this facility	

Facility-specific procedures

33) Are all adverse effect forms completed at this facility/in my department submitted to a central regulatory authority

1 = Yes	
2 = No	
3 = Unsure	

33a) How often are the forms submitted to the authorities mentioned?

1 = As soon as a report is available	
2 = Weekly	
3 = Monthly	
4 = Quarterly	
5 = Biannually (twice a year)	
6 = I did not know that we had to submit forms to a regulatory body	

33b) To which body are the forms submitted? ***(tick '✓' all that apply)***

a) South African Health Products Regulatory Authority (SAHPRA)	
b) The manufacturer of the suspected medication	
c) National Pharmacovigilance Centre	
d) National Department of Health	
e) National Adverse Drug Effect Monitoring Centre	
f) MEDUNSA Pharmacovigilance Centre	
g) Bloemfontein Pharmacovigilance Centre	
h) International regulatory bodies	
i) I am unsure	

Knowledge/attitudes/Feelings surrounding reporting

34) To what extent do you agree or disagree with the following statements:

1 = strongly agree 2 = agree 3 = neutral 4 = disagree 5 = strongly disagree

a) I feel that reporting adverse effects is good practice	
b) I feel that there is a benefit to the patient if I report adverse effects	
c) I feel that there is a benefit to healthcare professionals if I report adverse effects	
d) I feel that reporting to regulatory authorities is beneficial to myself and the institution	
e) I feel that the process of reporting an adverse effect in my facility is straightforward and easy to do	
f) I feel that practices in my facility have changed because I have reported adverse effects	

35) To what extent do you agree or disagree with the following statements:

1 = strongly agree 2 = agree 3 = neutral 4 = disagree 5 = strongly disagree

The following would encourage me to report adverse effects:

a) Training on pharmacovigilance relevance	
b) Training on completing adverse effect reporting forms	
c) Making adverse effect reporting compulsory on health care professionals	
d) Receiving feedback from regulatory bodies regarding reports submitted	
e) Seeing the impact of reporting in clinical management of patients	
f) Making forms easier to complete	

g) Availability of a digital reporting system	
h) Having a pharmacovigilance specialist available at the facility	
i) An anonymous reporting form	
j) Not being held personally liable for the information reported	
k) Incentive (financial or otherwise) to report adverse effects	

Self-efficacy in patient management

Managing the patient once an adverse effect has been identified

36) To what extent do you agree or disagree with the following statements:

1 = strongly agree 2 = agree 3 = neutral 4 = disagree 5 = strongly disagree

a) I feel that I am able to manage the patient appropriately without assistance	
b) I feel that I am able to manage the patient appropriately with assistance	
c) I do not feel that I am able to manage the patient – I refer the patient to another health professional within the facility	

37) To what extent do you agree or disagree with the following statements:

1 = strongly agree 2 = agree 3 = neutral 4 = disagree 5 = strongly disagree

The following resources assist me in determining how best to manage the patient:

a) Guidelines	
b) Consultation with colleagues	
c) Clinical judgement	
d) Other ***(please ask participant to specify)*** _____	

Reporting the management strategy and outcome

38) To what extent to you agree or disagree with the following statements:

1 = strongly agree 2 = agree 3 = neutral 4 = disagree 5 = strongly disagree

a) I feel that the management strategy and outcome of an adverse effect should be reported	
b) I feel that there is a benefit to reporting to the regulatory authorities	
c) I have reported management strategy and outcome of an adverse effect	
d) I have seen the impact of my reporting management strategies and outcomes of adverse effects	

If participant reported management and outcome

38a) If you have reported on management and outcome, how did you report it? *(tick '✓' only ONE option)*

1 = Updated the existing adverse effect form	
2 = Completed a second adverse effect report form	
3 = Other ***(please ask the participant to specify)*** _____ _____ _____	

_____ _____	
4 = I have never reported on management and outcome	

38b) Did your report reached a central regulatory body? ***(tick '✓' only ONE option)*** ***(if participant has not reported management and outcome, skip to question 39)***

1 = Yes	
2 = No	
3 = Unsure	

38c) Did you receive any feedback on your report either from your facility or the regulatory authority? ***(tick '✓' all that apply)***

1 = Yes, facility	
2 = Yes, regulatory authority	
3 = No	

38d) Will you continue to report your management and outcomes?

1 = Yes	
2 = No	

Pharmacovigilance within the facility

39) When reporting an adverse effect, to whom in the facility do you report? ***(tick '✓' all that apply)***

1 = The patients' medical practitioner	
2 = The quality assurance officer	
3 = The Pharmaceutical and Therapeutics Committee	
4 = The multidisciplinary team	
5 = I do not know to whom to report	

40) Is there an active Pharmaceutical and Therapeutics Committee (PTC) in your facility?

1 = Yes	
2 = No	

40a) If yes, are you a member of the PTC? ***(if no, skip to question 40g)***

1 = Yes	
2 = No	

40b) Are adverse effects/pharmacovigilance a standing part of the agenda?

1 = Yes	
2 = No	

40c) Are individual patient cases of adverse effects discussed at PTC meetings?

1 = Yes	
2 = No	

40d) Are clear procedures for follow up and reporting of the outcomes of adverse effects clearly outlined?

1 = Yes	
2 = No	

40e) Is the outcome of the adverse effect and intervention, if any, recorded in the minutes?

1 = Yes	
2 = No	

40f) Is there consensus between clinicians on how to manage various adverse effects?

1 = Yes	
2 = No	

40g) Are the minutes of PTC meetings shared with the larger staff body?

1 = Yes	
2 = No	

PLEASE COMPLETE

Interviewer name	
Date of interview	
Interviewer signature	

Appendix B: Adverse event record audit form

AUDIT FORM		
Province: _____ **1 = EC, 2 = WC, 3 = KZN, 4 = GP, 5 = MP, 6 = NC, 7 = NWP, 8 = LP, 9 = FS** **Facility:** _____		
Checklist	**YES**	**NO**
Facility name		
Sub-district/district		
Province		
PATIENT DETAILS		
Initials		
Age		
Gender		
Weight		
Height		
Allergies		
DR-TB registration number		
Hospital number		
Pregnant		
Gestational age		
HIV		
Status		
On ART		
ART start date		
Current ARV regimen		
CD4 count and date		
Viral load and date		
Concomitant conditions		
TB MEDICATION		
TB medicines listed		
Dose		
Route		
Date started		
Date stopped or dose reduced		
Reason for stopping or reduction		
Manufacturer		
Batch/expiry date		
Suspect herbal medication		

ADVERSE DRUG REACTION		
Date of onset of reaction		
Date reported		
Morbidity or mortality report		
Laboratory results		
Adverse drug reaction		
Date observed		
Suspected drug		
Intervention		
Patient outcome		
Narrative of ADR		
Reported by		

Appendix C: Interview sheet for NGOs

Informed consent

Interview

1) Which NGO are you part of? _____
2) In which district/s do you work?

   _____
3) In how many facilities in these districts do you work?

   _____
4) Are you involved in pharmacovigilance or adverse event reporting activities involving drug-resistant TB medication?

   _____
5) How long have these activities been occurring at the facilities?

   _____
6) What type of activities do you perform at the facilities regarding pharmacovigilance?

   _____

   _____

   _____
7) Do you make use of a standard or customised form for adverse event reporting?

   _____
8) Do you feel that there has been an improvement in the adverse event reporting practices in the facilities you are involved with?

   _____
9) Please describe these improvements.

   _____

   _____

   _____

   _____
10) How much longer will you be involved with these facilities?

    _____
11) What plans are in place to ensure ongoing adverse event reporting once the NGO is no longer present at the facilities?

    _____

    _____

    _____

    _____
12) Upon completing an adverse event report form, are facilities encouraged to escalate the forms to the relevant bodies?

    _____

12a) If yes, to whom?

_____

12b) If no, why not?

_____

_____

_____

_____

13) Who is responsible for this escalation?

_____

14) Do you feel that your continued presence at the facilities is required to maintain and improve pharmacovigilance activities? Please explain.

_____

_____

_____

_____

15) What other strategies do you feel could serve to improve pharmacovigilance activities among healthcare workers?

_____

_____

_____

_____

_____

_____

_____

Appendix D: Informed consent

Adverse event reporting in drug resistant tuberculosis facilities in South Africa

INFORMATION SHEET

Who we are

Hello, I am_____ from the Human Sciences Research Council.

What we are doing

The Human Sciences Research Council (HSRC) has been contracted by the United States Agency for International Development (USAID) to conduct a study into the adverse events reporting practices at DR-TB Centres of Excellence across South Africa. The study is conducted on behalf of the National Department of Health (NDoH). The aim of the study will be achieved through conducting interviews with hospital personnel including doctors, matrons, head nurses and pharmacists in addition to a review of randomly selected medical records to understand the extent of adverse event recording. Researchers will request consent to participate. We hope that this study will allow us to understand the adverse event reporting practices in DR-TB Centres of Excellence, and the potential challenges and successes experienced, in order to make recommendations for future interventions.

Your participation

You are being requested to participate in the study as you are a doctor/matron/nurse/pharmacist/ quality assurance manager working in a selected DR-TB Centre of Excellence. All similar categories of staff working in other selected DR-TB Centres of Excellence will be asked to participate.

Please understand that even though you have been approached to take part in the study, your participation is voluntary. The choice to participate or not is yours alone. However, if you do decide to participate, it would be greatly appreciated.

If you decide not to participate in the interview, you will not be affected in any way. If you do agree, you may indicate at any point that you no longer want to participate, and the interview will be stopped. There will be no penalties against you and your decision will not impact your current or future employment in any way. The partially completed interview will not be analysed, although it will help if you are willing to state why you have decided to no longer participate.

Confidentiality

Your name will not be recorded anywhere in the interview. You will not be linked to any answers that you give. Your responses will remain confidential, meaning that it will only be known to the researchers. No other interviewer or researcher will come back to you after the study to ask what you meant by certain answers. We hope that this information will put you at ease and encourage you to participate in the study.

The interview process and questions to be asked

The interview will last approximately 30 to 45 minutes. The interviews will be done individually by trained researchers or research assistants. You will be asked a variety of questions pertaining to the adverse event reporting policy and practices at the facility.

Remember that there is no right or wrong response. Your responses cannot and will not be used to make you feel bad about yourself or your profession. We would like your responses to eventually help us to understand the adverse event reporting practices at DR-TB Centres of Excellence across South Africa.

Benefits

There are no immediate benefits to you by participating in the interview. However, the study will be helpful for us to understand the adverse event reporting practices at the facility and the potential challenges you face or successes you have had.

Getting your permission to participate

If you agree to participate, we ask that you sign the separate consent form below. This is the only time that your name will be recorded. If you are not willing or unable to sign your name, but willing to be interviewed, my colleague and I will sign as witnesses to say that you have given us verbal consent. The consent form and your responses in the interview will be kept separate and your name cannot be linked to any responses you may give.

Feedback from the study

The researchers would like to provide feedback once the study has been completed. We will provide reports to each facility discussing our findings and what it means.

Who to contact if you have been harmed or have any concerns

This research has been approved by the HSRC Research Ethics Committee (REC) and has been assigned reference number 6/22/08/18. If you have any complaints about any ethical aspects of the research or feel that you have been harmed in any way by participating in this study, please call the HSRC's toll-free ethics hotline 0800 212 123 (when phoned from a landline from within South Africa) or contact the Human Sciences Research Council REC Administrator, on Tel 012 302 2012 between 08:00 – 16:30 or e-mail research.ethics@hsrc.ac.za.

CONSENT

I hereby agree to participate in the research study regarding the adverse event reporting practices in DR-TB Centres of Excellence across South Africa.
I understand that I am participating freely and that I may choose to stop the interview at any time should I not want to continue. I also understand that my decision will in no way affect me.
I understand that this is a research project whose purpose is not necessarily to benefit me personally.
I have received the telephone numbers of the persons whom I can contact should I need to speak about any issue which may arise during the interview.
I understand that the consent form will not be linked to the questionnaire and that my responses will remain confidential. I understand that, if possible, feedback will be given to my facility and district about the results once the study is completed.

_____ _____

Name and surname of participant Date

_____

Signature of participant

_____ _____

Name and surname of researcher Signature of researcher

Verbal consent

I hereby state that the participant has given verbal consent to participate in the study.

_____ _____

Name and surname of researcher Date

_____

Signature of researcher

_____ _____

Name and surname of witness Signature of witness

Appendix E: Letter to facility managers

Dear Sir/Madam

We are a group of researchers from the Human Sciences Research Council conducting a study entitled 'Adverse event reporting in drug resistant tuberculosis facilities across South Africa'. The study aims to understand both the processes and perceptions of healthcare professionals in terms of adverse event reporting as well as any challenges he/she may have encountered. We would also conduct a random audit of a small number of medical records to determine whether adverse events are recorded in these documents. Interviews will take approximately 30 to 45 minutes to complete and staff will not be kept away from their duties longer than is needed. All costs will be covered by the research group, no additional costs will be incurred by the facility.

The identities of the healthcare workers and managers who consent to participate in the study will be kept confidential. Feedback of the study findings will be provided to the relevant stakeholders and Departments of Health.

Ethical approval has been obtained from the Human Sciences Research Council [approval number], as well as the provincial health departments of the Eastern Cape [approval number], Free State [approval number], Gauteng [approval number], KwaZulu-Natal [approval number], Limpopo [approval number], Mpumalanga [approval number], North West Province [approval number], Northern Cape [approval number] and the Western Cape [approval number]. We would greatly appreciate your cooperation and assistance. If you have any queries, please feel free to contact me at the below details.

Sincerely,

_____

Dr Razia Gaida (Principal Investigator)
Tel: 041 393 9500
E-mail: rgaida@hsrc.ac.za