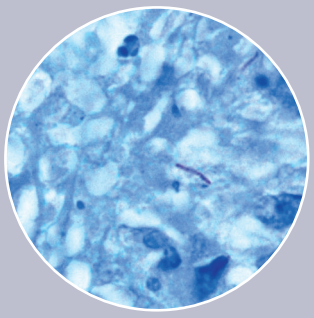
A PRACTICAL HANDBOOK ON THE PHARMACOVIGILANCE OF MEDICINES USED IN THE TREATMENT OF TUBERCULOSIS

ENHANCING THE SAFETY OF THE TB PATIENT



World Health Organization

A practical handbook on the pharmacovigilance of medicines used in the treatment of tuberculosis

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Contents

Abbreviations

ADRs	adverse drug reactions (to medicines, vaccines, herbal and traditional medicines)
AIDS	acquired immunodeficiency syndrome
ARV	antiretroviral
ATC	Anatomic Therapeutic Chemical Classification (for medicines)
BMI	body mass index
CEM	cohort event monitoring
CemFlow	electronic tool for data entry and analysis in cohort event monitoring
DD	(WHO) Drug dictionary
DF	dosage form (for combination therapy)
DOB	date of birth
DOTS	internationally agreed strategy for TB control
E	ethambutol
E2B	standardized data elements for transmission of ICSRs
FDC	fixed dose combination
GFATM	Global Fund to Fight AIDS, TB and Malaria
H	isoniazid
HIV	human immunodeficiency virus
IC	Information Component
ICD-10	WHO International Classification of Diseases version 10
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

ICSR	individual case safety report(s) (spontaneous reports)
IMMP	(New Zealand) Intensive Medicines Monitoring Programme
ISTC	international standards for tuberculosis care
MDR	multidrug resistance
MDR-TB	multidrug-resistant tuberculosis
MedDRA	Medical dictionary for drug regulatory activities
NCR	non-carbon copy paper
NTP	national tuberculosis control programme
PEM	prescription event monitoring
PTB	pulmonary tuberculosis
PvC	pharmacovigilance centre
R	rifampicin
SOP	standard operating procedure
S	streptomycin
TB	tuberculosis
TB/HIV	HIV-associated TB
TSR	targeted spontaneous reporting
UMC	Uppsala Monitoring Centre
VigiBase	WHO database of individual case safety (ADR) reports (ICSR)
VigiFlow	electronic tool for data entry and analysis of spontaneous reporting data
VigiLyze	tool that provides access to and analysis of the WHO worldwide database of adverse drug reactions (ISCRs), VigiBase
WHO	World Health Organization
WHO-ART	WHO adverse reactions terminology
XDR-TB	extensively drug resistant tuberculosis
Z	pyrazinamide

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Preface

Why pharmacovigilance for anti-TB medicines?

Most of the medicines used to treat tuberculosis (TB) today have been on the market for several decades. Clinicians treating TB patients around the world know these medicines well, and are usually well aware of their associated adverse drug reactions (ADRs). The occurrence of these reactions is known to be frequent. The TB patient on treatment is taking more than one anti-TB medicine simultaneously and regimens last from many months to 2 years or more. This increases the likelihood of ADRs, some of which are severe. Most patients on treatment for drug-resistant TB experience at least one side-effect, and a recent study has shown that two thirds of such patients have had at least one medicine stopped temporarily or permanently as a result of ADRs.[1] These events may damage public confidence in any national treatment programme and affect patient adherence. Patients who stop taking anti-TB medicines pose a risk to themselves and to others. The generation of drug resistance is a very real risk.

So why should TB practitioners today reflect on a more systematic approach to surveillance of drug-related problems, which is at the heart of pharmacovigilance? Firstly, while national TB programmes are generally well structured to monitor patients and have a long tradition of following up care using standardized indicators, they do not collect information on ADRs directly. It is therefore difficult to assess precisely the net benefit of a treatment programme if adversities related to the medicines used are not factored in. The contribution of ADRs to death, treatment default and failure can therefore only be conjectured. Secondly, the widespread recognition by health workers that anti-TB medicines often cause ADRs is poorly reflected in the published information on the subject. There is a dearth of published literature about anti-TB drug-induced mortality, morbidity and reduced quality of life, particularly in low-resource settings. The overall burden of adversity directly attributable to anti-TB medicines is poorly quantified and it is not usually well profiled in individual TB control programmes. Thirdly, with the increasing use worldwide of more extensive regimens for drug-resistant TB, the added

[1] Bloss E et al. Adverse events related to multidrug-resistant tuberculosis treatment, Latvia, 2000–2004. *International Journal of Tuberculosis and Lung Disease*, 2010, 14:275–281.

use of antiretrovirals (ARVs) in patients with HIV-associated TB, and the imminent advent of new classes of medicines to treat TB, the case for improved pharmacovigilance becomes even stronger. Pharmacovigilance needs to be an integral accompaniment to treatment programmes as they expand their geographical coverage, given that the frequency and expression of ADRs may be influenced by factors linked to the demographic, genetic and nutritional patterns, and to the background co-morbidity (e.g. TB/HIV) in a population.

The cornerstones of pharmacovigilance apply equally to TB as to any other disease amenable to medication. Events linked to medications, particularly novel medicines or new combinations thereof, need to be recognized in a timely fashion if the events are to provide benefit to the individual patient and enrich public knowledge. Appropriate measures need to be put in place to ensure that harm is reduced and symptoms relieved. Health-care workers need to be informed and trained about the methodology and routes for reporting ADRs. This handbook aims to satisfy the need for pharmacovigilance, which has been neglected in the domain of TB for too long.

Key messages

- ▶ Adverse drug reactions can lead to a patient interrupting tuberculosis treatment before completion, and thus contribute to avoidable morbidity, treatment failure, reduced quality of life, or death
- ▶ Pharmacovigilance is the "science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem"
- ▶ The increasing use of complex regimens for drug-resistant TB globally, the concomitant use of antiretroviral therapy in patients with HIV-associated TB, and the imminent release of new classes of medicines to treat TB on the market make the case for pharmacovigilance even stronger
- ▶ A signal is the reported information on a possible causal relationship between an adverse event and a medicine, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending on the seriousness of the event and the quality of the information.
- ▶ This handbook provides the practitioner with a step-by-step approach to implement pharmacovigilance activities as a standard of care for TB patients. It provides useful information on registering adverse events, and how to assess for causality in an association between an adverse event and a medicine
- ▶ Three methods of pharmacovigilance are identified and described in this handbook: spontaneous reporting, targeted spontaneous reporting (TSR) and cohort event monitoring (CEM). The first two methods can be built into national programmes of routine pharmacovigilance and/or tuberculosis control. CEM is an active form of surveillance and is similar in design and management to an epidemiological cohort study

A. Introduction

This is a detailed manual giving a step-by-step approach to undertaking the pharmacovigilance of anti-TB medicines. It is intended to be a source of practical advice for Pharmacovigilance Centres (PvCs) and health professionals involved in the national TB control programmes. Users who are not familiar with the principles of pharmacovigilance are referred to available WHO publications that provide a background to the subject. A list of these publications is annexed (see Annex 1, under Published resources, World Health Organization) with the respective Internet addresses from where they can be downloaded. Before embarking upon pharmacovigilance, TB practitioners, health officials, planners, the staff of PvCs, public health teams and other health workers should become familiar with these publications. This Handbook on the monitoring of anti-TB medicines is the third in a series on pharmacovigilance in public health programmes. The two already published are:

- *A practical handbook on the pharmacovigilance of antimalarial medicines* (2008)
- *A practical handbook on the pharmacovigilance of antiretroviral medicines* (2009)

1. Pharmacovigilance

Definition

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem (WHO).[1]

Explanation

Pharmacovigilance is an arm of patient care and surveillance. It aims at getting the best outcome from treatment with medicines. No one wants to harm patients, but unfortunately, for many different reasons, any medicine will

[1] www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/ (accessed January 2012).

sometimes do this. Good pharmacovigilance will identify the risks within the shortest possible time after the medicine has been marketed and will help to establish or identify risk factors. When communicated effectively, this information allows for intelligent, evidence-based prescribing with the potential for preventing many ADRs. Such information will ultimately help each patient to receive optimum therapy at a lower cost to the health system.

The organizers of a monitoring programme for the safety of medicines used to treat tuberculosis must have a clear sense of the questions they want to answer before developing their plan. It is only with clear goals in mind that one can design a proper data collection instrument and an analytical plan.

The following general and specific aims reflect the purposes of this Handbook and the potential outcomes of monitoring which can be prioritized for goal-setting and for selecting the most appropriate method(s) of safety surveillance in the programme.

2. General aims

This Handbook aims to improve patient care and safety in relation to the use of medicines and all medical and paramedical interventions, by collecting good information on the effects of medicines and providing early warning and communication of problems which might affect the success of the programme. It will thus support the safe, rational and more effective (and more cost-effective) use of medicines.

3. Specific aims

The sections of this Handbook will provide details on the

- rapid identification of events that are likely to affect adherence to treatment and determination of their rates, and identification of the risk factors that make these events more likely, with the aim of reducing their occurrence;
- identification of signals (i.e., possible causal relationships between an adverse event and a medicine; see Glossary) of ADRs of concern following the introduction of a new drug or drug combination;
- assessment of signals to evaluate causality, clinical relevance, frequency and distribution of ADRs in particular population groups;

- calculation of rates of events so that:
  — risk can be measured;
  — the safety of different medicines can be compared and informed choices made;
  — risk factors can be clearly identified;
- contribution to the assessment of benefit, harm, effectiveness and risk of medicines, leading to the prevention of harm and maximization of benefit;
- appropriate response or action in terms of drug registration, drug use and/or training and education for health professionals and the public;
- measurement and evaluation of the outcome of the response or of action taken (e.g. reduction in risk, improved medicine use, or improved outcome for patients experiencing a particular ADR);
- timely communication with and recommendations to authorities and the public; and
- feedback to the clinicians who provided the information.

4. Pharmacovigilance centre (PvC)

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

BOX 1

The Global Fund and minimum requirements for a national pharmacovigilance centre

In 2010 WHO, the Global Fund to Fight AIDS, TB and Malaria (GFATM) and other partners agreed on a set of minimum requirements that should be met in any national pharmacovigilance system:[a]

1. A national pharmacovigilance centre with designated staff (at least one full-time), stable basic funding, clear mandates, well-defined structures and roles and collaborating with the WHO Programme for International Drug Monitoring.
2. The existence of a national spontaneous reporting system (see below) with a national individual case safety report (ICSR) form i.e. an ADR reporting form.
3. A national database or system for collating and managing ADR reports.
4. A national ADR or pharmacovigilance advisory committee able to provide technical assistance on causality assessment, risk assessment, risk management, case investigation and, where necessary, crisis management including crisis communication.
5. A clear strategy for routine communication and for communication about a crisis.

Countries applying for grants to support anti-TB treatment should include pharmacovigilance as a core component of their prevention and treatment programmes. The minimum requirements are expected to become mandatory for countries benefiting from GFATM grants for HIV, tuberculosis and malaria treatment programmes.

In the absence of a functional PvC, the National TB Control programme (NTP) should include in its budget, funding for catalysing and facilitating the establishment of a PvC which fulfils as a minimum the conditions listed above, or for improving resources if an established PvC is incapable of coping with the demands of the pharmacovigilance of anti-TB medicines. This would be a legitimate and wise call on the funds of the programme because pharmacovigilance should result in better therapeutic management, as well as more acceptable and safer treatment.

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[a] World Health Organization and GFATM Meeting to Determine Minimum Requirements for Pharmacovigilance, Geneva, Switzerland, 14–15 January 2010 (www.who.int/medicines/areas/quality_safety/safety_efficacy/).

B. Which approach to pharmacovigilance?

As with other branches of surveillance, in pharmacovigilance there are three main streams.

1. Spontaneous reporting

Spontaneous (or voluntary) reporting means that no active measures are taken to look for adverse effects other than the encouragement of health professionals and others to report safety concerns. Reporting is entirely dependent on the initiative and motivation of the potential reporters. This is the most common form of pharmacovigilance, sometimes termed passive reporting. In some countries this form of reporting is mandatory. Clinicians, pharmacists and community members should be trained on how, when, what and where to report.

2. Targeted spontaneous reporting (TSR)

TSR is a variant of spontaneous reporting. It focuses on capturing ADRs in a well-defined group of patients on treatment. Health professionals in charge of the patients are sensitized to report specific safety concerns. TSR is intended to ensure that patients are monitored and that ADRs are reported as a normal component of routine patient monitoring and to achieve the requisite standard of care. This focused approach has the same objectives and flow of information as for spontaneous reporting. The reporting requires no active measures to look for the particular syndromes. Its construct would thus differ from cohort event monitoring (CEM) explained below.

3. Active surveillance

Active (or proactive) safety surveillance means that active measures are taken to detect adverse events. This is achieved by active follow-up after treatment and the events may be detected by asking patients directly or screening patient records. It is best done prospectively. Active pharmacovigilance is sometimes

very descriptively referred to as "hot pursuit". The most comprehensive method is CEM. It is an adaptable and powerful method of getting good comprehensive data. Other methods of active monitoring include the use of registers, record linkage and screening of laboratory results in medical laboratories.

The critical stages of causality assessment and signal identification are applicable to all three methods of surveillance and will be covered in detail after the individual methods have been discussed (see Section G and Section I).

C. Spontaneous reporting

1. Introduction

A spontaneous report is an unsolicited communication by health-care professionals or consumers that describes one or more ADRs in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection scheme.

2. Objectives and methodology

It should be noted that spontaneous reporting is for the reporting of suspected *adverse drug reactions* and not adverse drug events in general (see Glossary). In TB treatment programmes, this would include reporting any ADR of concern, all suspected serious reactions, and persistent ADRs that can threaten adherence. It is designed to detect ADRs not previously observed in preclinical or clinical studies, to improve understanding of the potential risks, including reactions resulting from drug interactions or drug effects in particular populations, and to help provide a basis for effective drug regulation, education and consequent changes in practices by prescribers and consumers. Spontaneous reporting is the most common method of surveillance worldwide. It has played a major role in the identification of safety signals throughout the marketed lifetime of medicines in general. It is the easiest system to establish and the cheapest to run. However, reporting is generally very low and subject to strong biases; and there is no database of all users or information on overall medicine utilization. These problems prevent the accurate assessment of risk and risk factors or making comparisons between medicines. A new term has been introduced that will replace "spontaneous reports": this is individual case safety reports (ICSRs). ICSRs play a major role in the identification of signals of risk once a medicine is marketed. ICSRs can also provide important information on at-risk groups, risk factors (to a limited degree), and clinical features of known serious ADRs. Spontaneous reporting is dependent on clinicians and other health professionals, who need to be trained and encouraged to report details of suspected ADRs in patients on TB treatment. Underreporting is a serious drawback of this method, but reporting can be intensified in selected units e.g. hospitals. There is no standard global reporting form for ICSRs as the needs of countries differ and it is important that national

staff are involved in developing their own form. If a national pharmacovigilance system is in place, then it is preferable to use the reporting form already in use (see Annex 2 for an example of a national form). Health professionals will need advice on what types of suspected ADRs to report. Most pharmacovigilance programmes request reports of all serious reactions (see Glossary) which include death and congenital abnormalities and, in addition, all suspected reactions to new medicines. The particular requirements for reporting suspected ADRs to TB treatment would need to be specified, for example:

- reactions that affect adherence;
- reactions that necessitate hospitalization;
- reactions of special interest; and
- all suspected reactions in children and pregnant women.

Programme managers should decide if certain other circumstances would be deemed serious, even when they do not lead to hospitalization or death, but are events that may require intervention to prevent a serious outcome: for example, convulsions, drug dependence or drug abuse.

All ICSRs should first be sent to the PvC in the country for evaluation. Spontaneous reporting for TB medicines should be integrated with the national pharmacovigilance programme and regarded as an ongoing monitoring method which continues after any special studies are completed. The reports should then be forwarded by the PvC to the WHO Collaborating Centre for International Drug Monitoring (the Uppsala Monitoring Centre (UMC)) for entry into Vigibase, a global database that uses systematic methods for the detection of safety signals from ICSRs.

3. Minimum reporting requirements

WHO criteria

According to WHO criteria, the following basic information is required before a report is acceptable:

- an identifiable source of information or reporter;
- an identifiable patient;
- name(s) of the suspected product(s);
- a description of the suspected reaction(s).

The system depends on written records created using a standard reporting form. For this reason the reporter must be literate and the reporting system

extends only to the clinic and dispensary level of the health-care system. Informal health-care providers, because of their varying degrees of literacy, cannot act as reporters, but should play an important role in referring patients to health facilities where reports can be made.

4. How to report

Countries that have set up a PvC have developed their own reporting forms and more than 100 national versions of these documents are available today. To be effective, a reporting form needs to be available in the local language(s) and have features relating it to the responsible authority e.g. a logo, and the address and contact details of the issuing institution. The form in use in Ghana (Annex 2) is a good example.

Forms should be simple and easy to complete. They should not request too much information, particularly information that is difficult to find and record, or information that is unlikely to be used. There should be sufficient space in which to describe the suspected reaction(s). The forms should be widely distributed to all health professionals including those who are working in TB control programmes, and those who are working privately. Difficulty in obtaining a reporting form is a common barrier to reporting. The forms should be printed on a single page and easily folded and sealed. To facilitate postage, the return address should be printed on the outside, with postage pre-paid. It is desirable to have only one type of reporting form available in each country for use for reports on all medicines including antituberculosis therapy. Reports should be sent to the PvC. If it is not practical to send the forms directly to the centre, it may be necessary to arrange points of collection at other sites, for example at specific hospitals or clinics. The reports should be stored securely to maintain confidentiality.

Reporting to the centre needs to be made as convenient as possible. If other methods are available, they may be preferred by some health professionals, but full confidentiality needs to be ensured. Preferences may vary between clinics and hospitals, private or government facilities and public health programmes. Suitable methods might include:

Telephone. The person receiving the report should have a reporting form to record the details and make sure that no essential data are missing.

Fax. Sending reports by fax is equivalent to mailing the report, but faster. A fax machine is a very important asset for a national PvC and its major monitoring sites.

E-mail. A written case-report submitted by e-mail may be acceptable. Further details can be obtained by follow-up. Reporting forms can be sent to reporters as e-mail attachments and e-mailed, faxed or posted to the PvC when completed.

The Internet. An Internet site is a valuable asset for a PvC and a reporting form could be made available for downloading or for completion online (entering data through web-based data entry) if the site is secure. Entering data through a web-based data system could be a very efficient means to transmit information to a PvC. A secure site and reliable Internet connectivity are basic requirements.

5. What to report

Patient details

- Health number: this may be a national identifier (preferred), hospital, clinic, or programme number.
- Name: full name is preferable as an accurate identifier, for follow-up purposes and to avoid duplication. In some jurisdictions only initials may be acceptable.
- Address: to allow for follow-up and accurate identification. This may take various forms depending on the location.
- Sex.
- Date of birth (DOB) (preferred) or age, if DOB is unknown (add "est" if age is estimated).
- Weight and height.

Patient medical history of significance

This section may include details on pathology which is relevant to TB or anti-TB medication. The information could include end-organ disease (e.g. of the lung, kidney, or liver), malnutrition and HIV/AIDS status.

Details of medicines

- All medicines that were taken at the time preceding the reaction should be listed. Each suspect medicine can be indicated by an asterisk.
- Name(s) of medicines: (this may be the brand or generic name, preferably brand) and formulation (e.g. tablets, syrup, or injection). Recording the

brand name gives more specific information. Standard abbreviations for TB medicines would simplify recording. Recommendations on how best to record TB therapy would need to be part of a standard operating procedure (SOP) for completion of the reports.

- Mode of administration (e.g. oral, rectal, or injection).
- Indication(s) for use.
- Dose: e.g. for most medicines with fixed dosing, recording the total daily dose is appropriate. Fixed dose combination formulations are pertinent for TB therapy and recommendations for recording dose should be part of an SOP. This could include codes for the appropriate age groups. It is important to simplify recording as much as possible without sacrificing accuracy.
- Date treatment was started.
- Date treatment was stopped.
- Duration of use, if "start" and "stop" dates are not available.

Reaction details

- Date of onset.
- Reporters should be asked to give a brief clinical description. They should not be asked to give the official pharmacovigilance reaction term.
- Laboratory test results if available, together with units of measurement.
- Outcome of event: resolved, resolving, no change, disabling, worsening, death (with date), or congenital anomaly.[1]
- Effect of rechallenge (see Glossary).

Reporter details

The reporter details should include the name, contact details and profession: e.g. physician, nurse, or patient. This information will be kept confidential but is important to include in case it is necessary to contact the reporter for additional information on the case.

Date and place of report

[1] These are standard E2B terms which should be adhered to (see ICH website : www.ich.org).

6. When to report

A report should be completed as soon as possible after the reaction. It is better not to wait until final results and information such as hospital letters are received, because the report may be forgotten. These additional details can be sent to the PvC later.

7. Who should report

Reporters may be in the public or private health sector. They include physicians, pharmacists, and nurses. Other reporters include public health professionals, staff in medical laboratories and pathology departments, and pharmaceutical companies. Health and community workers (who are literate) should be encouraged to report, preferably to the clinician who prescribed the treatment, or directly to the PvC. Patients or patient representatives may also report.

8. Follow-up

All reports of serious events should be followed up if details are incomplete. This may require the involvement of health professionals in a clinical setting who have been trained and appointed for this type of work. Occasionally follow-up information is required to fully assess reports of non-serious events. Follow-up requests should be kept to a minimum as they can discourage further reporting. Examples of follow-up information might be: essential missing details, information on the final outcome, the result of rechallenge, the results of laboratory tests, and post-mortem results from health facilities where autopsy is undertaken.

9. Sharing the results

Individual, immediate

Anyone who sends in a report should, as a minimum, receive an acknowledgement and thanks from the PvC and additional reporting forms to encourage further reporting. If resources allow, the PvC should also provide some brief information about the reaction reported, such as, but not normally including all, of the following:

- number of reports of the reaction in the centre's database;
- number of reports of the reaction in the WHO database;

- information from the literature;
- the importance of the reaction in the treatment of patients with TB;
- the safety or risk of further administration to the patient;
- the possibility of preventing the reaction in other patients by indicating potential risk factors.

Relevant summaries or reviews

At agreed intervals, the centre should prepare a summary of the reactions reported and/or safety reviews of the anti-TB medicines being used. These should be distributed widely as bulletins or newsletters, including to national programme managers. News items should be prepared for the local media on overall effectiveness and safety, or about particular issues that have arisen.

Regular transmission to the WHO database

Details of reports should be sent for international analysis to the WHO Collaborating Centre for International Drug Monitoring (UMC; see Annex 1 for contact details), preferably using a special software package, VigiFlow, as described below.

10. Data entry

The UMC can provide the PvCs with access to VigiFlow, a web-based tool which can fulfil the data entry, storage and analysis requirements in the course of pharmacovigilance work. VigiFlow requires no local support or maintenance. It provides an online national database for the use of the PvC. The database is automatically backed up. Data entered are kept confidential. National data are owned by and can be accessed and used by the national PvC. VigiFlow provides a system for standardized entry of data from reports, as well as search functionalities. It has built-in error avoidance features. It provides live access to up-to-date terminologies: the WHO Drug dictionary (DD), MedDRA and the WHO Adverse reactions terminology (WHO-ART). Standardized outputs are available for summary tabulations and a range of standard statistical analyses. The data can be exported to a local country database (e.g. Excel) for ad hoc searches and to meet local analytical requirements. The completed reaction reports can also be easily exported to the WHO database (VigiBase). The PvC decides what data can be transferred to the international WHO database and when these will be transferred.

D. Targeted spontaneous reporting (TSR)

1. Introduction

Targeted spontaneous reporting (TSR) is a methodology that builds on the principles of both spontaneous reporting (described above) and CEM (described below). Health professionals in charge of a well-defined group of patients (e.g. patients on treatment for drug-resistant TB) would be sensitized to report specific safety concerns suspected to be medicine related. It provides a comprehensive monitoring method which is affordable, feasible and sustainable in settings with limited financial and human resources and will promote the role of pharmacovigilance as a best practice that improves quality of care.

2. Objectives and methodology

TSR may be adapted either to measure all adverse reactions in the defined population or to focus only on specific reactions of particular concern. It would be particularly suitable for the management of TB patients. For many years, national TB control programmes have been used to monitor TB patient outcomes in well circumscribed groups termed "cohorts" defined in time (e.g. a calendar quarter or a year). The monitoring of ADRs could be integrated as a standard of care, to accompany the routine practice of monitoring success, death, default or failure of treatment within the cohort.

One benefit of monitoring for safety within a treatment cohort is that the number and profiles of the exposed patients are known. To measure the burden of medicine-related problems accurately, recording and reporting of observed events needs to be as complete as possible. The steps required to meet the objectives of TSR include the following:

- Monitoring for suspected drug-related problems should be part of normal patient care. At every encounter, the responsible health-care professional should screen for any suspected ADRs. During patient investigation the possibility of a medicine-related problem should always be considered.
- Suspicion of the possibility of a causal relationship between drug treatment and the event should trigger the completion of an ADR reporting form (like the example shown in Annex 2), depending on the agreed reporting protocol.

- All health-care professionals involved in patient care should be sensitized to the need to ask about and investigate adverse effects at every encounter.
- The forms and route for transmission of information are the same as those used in spontaneous reporting, but the forms should be supported by specific guidance (case definitions and written procedures) on when to complete them and details on standardized reporting of drug names and ADRs.
- The reporting may primarily target serious ADRs (see Glossary) rather than the notification of any suspected reaction. TSR can be adapted to the safety question at hand. If the total burden of drug-related problems in the exposed population is of interest, health professionals can be instructed to report any suspected drug-related problem. If, however, the frequency of a specific problem suspected to be associated with the therapy given is the important question, e.g. vision disorders, a case definition for reporting can be given in the instructions to health-care professionals.
- The reporting would last the whole length of a TB treatment episode, typically between 6 months to 2 years for a TB patient.
- Unlike CEM (Section E), there are no baseline measurements nor is there any active follow-up of the members of the cohort and thus fewer resources would be required.
- The number of TB patients in the treatment "cohort" who have been investigated would represent a denominator for calculation of simple frequencies of ADRs.
- The routine patient record should include the question "Suspected adverse drug reaction? YES or NO" ensuring that the possibility has always been considered. The extent to which this information is recorded will also indicate whether ADR monitoring has become a part of normal practice. If safety monitoring of each patient is truly part of best practice and recording of whether the patient has experienced a suspected problem or not is complete, the calculated reaction frequencies may be close estimates of true incidence rates.
- TSR provides the opportunity to monitor every single patient on treatment, as part of treatment and care. However, implementing it would depend on the willingness of health-care providers to participate in this monitoring exercise and to report their observations. TSR will thus suffer from its voluntary nature. For the surveillance of ADRs associated with new anti-TB drugs, expected to be launched on the market in the coming years, CEM would thus be preferred over TSR.

E. Cohort event monitoring

1. Introduction

CEM is a prospective, observational, cohort study of adverse **events** associated with one or more medicines. An adverse event is any untoward medical occurrence that may present during treatment with a pharmaceutical product, but which does not necessarily have a causal relationship with this treatment. This methodology is sometimes referred to as prescription event monitoring (PEM), but this term is inappropriate when individual prescription with subsequent dispensing by pharmacists is not part of the process of supplying medicines to patients. In most resource-limited countries, the treatment of TB and other important diseases is not provided on a prescription basis. A CEM programme is essentially an observational study in normal clinical practice of a new medicine in the early post-marketing phase, but it can be used for older medicines.[1] Its basic function is to act as an *early warning system* of problems with new medicines, although it will provide much more information.

Event monitoring

An event is any new clinical experience that occurs after commencing treatment with a medicine regardless of its severity or seriousness and without judgement on its causality. Favourable events may be recorded as an indication of an unexpected therapeutic effect. CEM records all clinical events and not just suspected ADRs. It involves actively and systematically asking for reports of any and all events and provides a method that facilitates reporting.

2. Objectives and methodology

The objectives of spontaneous reporting (see Section C.2) are also the objectives of CEM. These are:

- To characterize known ADRs.
- To ensure the earliest possible recognition of new ADRs, including inter-

[1] See PEM in Mann R, Andrews E, eds. *Pharmacovigilance*, 2nd ed. Chichester, John Wiley, 2007.

actions with other medicines, complementary and alternative medicines, foods and concomitant diseases.

- To detect inefficacy, which might be due to:
  - — faulty administration;
  - — poor storage conditions;
  - — poor quality product;
  - — counterfeit product; or
  - — interactions.
- To measure risk (incidence), including comparative risk of different anti-TB regimens or individual medicines.
- To identify risk factors for the important reactions so that appropriate risk management can be applied and the risk of harm minimized.
- To assess safety during pregnancy and lactation.
- To provide evidence for:
  - — effective risk prevention and management;
  - — safer use of anti-TB therapy;
  - — the benefits versus harm of different regimens or products;
  - — evidence-based regulatory action.
- To provide potential cohorts for further study of safety issues if required in the future. These can include:
  - — nested case–control studies to determine risk factors (e.g. genetic polymorphism) for ADRs of interest;
  - — follow-up studies for long-term outcomes or more detailed information on events of interest;
  - — follow-up of sub-populations of particular interest; and
  - — measurement of changes in medicine utilization or prescribing practice.

Selection of medicines to monitor

The intention is that each of the different anti-TB regimens (combination TB therapies) in use for the prevention and treatment of TB will be monitored as a single treatment entity. However, there will be a need to attribute important reactions to individual medicines. This can be done by appropriate analyses at a later date.

Changes to individual medicines in any regimen creates a new treatment entity.

Basic processes

- A patient cohort is established for each drug regimen.
- Adverse events experienced by patients in the cohort(s) are recorded.
- Patient ID and demographic data together with details of medicines, events and other relevant information are recorded on questionnaires: a *Treatment initiation form* and a *Treatment review form*.

Programme duration

For most medicines the duration of monitoring is limited. It is determined by the length of treatment to be monitored in individual patients, and the time it takes to reach the desired cohort size. For TB therapy, treatment of individual patients is monitored for a period that is considered to be appropriate for the identification of both short- and long-term effects (e.g. for drug-resistant TB this might be 3–4 years). Enrolment will continue until the target cohort population is reached (see Section E.4).

The duration of treatment for TB patients is usually from 6 months to 2 years. This period may be longer if adjustments to therapy have been necessary because of multidrug resistance (MDR). TB patients should be monitored throughout the duration of their therapy. In patients who show signs of potentially serious reactions, such as renal or thyroid toxicity, it may be desirable to continue monitoring after therapy ceases in order to assess the late outcome of these problems. For individual patients with HIV-associated TB, treatment is lifelong. It has been observed that serious toxicities can develop after prolonged exposure to antiretroviral therapy (ARV) in terms of years. It is important to understand the natural history of serious toxicities and monitoring will therefore need to be aligned accordingly, at least for particular subgroups of the cohort who are at risk.

If there is special interest in certain subgroups e.g. pregnant women, or children, or more information is needed on a type of event of particular concern, then the programme may need to continue for a longer period to get sufficient numbers to evaluate these subgroups at a satisfactory level of statistical significance.

A practical approach is to review the data at regular intervals (e.g. 3-monthly). Trends may then be observed that indicate the need for an extension of monitoring.

Joint monitoring of treatment for two diseases

With the frequent joint occurrence of the two diseases TB and HIV/AIDS in the same population, there may be occasions when CEM programmes for both can run simultaneously. This would provide the opportunity for sharing resources and improving the cost–benefit ratio over both programmes. If it seemed to offer an advantage logistically in the local situation, the same set of questionnaires could be used. These would need to be adapted to meet the needs of both treatment programmes.

3. Implementation

Context

Examples of CEM methodology based on prescription records are the Intensive Medicines Monitoring Programme (IMMP) in New Zealand and Prescription Event Monitoring (PEM) run by the Drug Safety Research Unit in England. CEM has been used in a United Nations Children's Fund (UNICEF) programme in three African countries and is currently being used for antimalarials in Nigeria, the United Republic of Tanzania and Zimbabwe. A similar method is being used successfully in the People's Republic of China to monitor contraceptives and includes monitoring in rural areas.

The decision to undertake CEM activities will have been taken within the PvC, the regulatory authority or at ministerial level, or may be instigated by the TB Control Programme. This decision will be accompanied by the appropriate budgetary allocation. CEM activities should be undertaken by a special unit within the PvC. The proposed structure for a CEM programme is described in Section M.3. This will be understood better after the specific activities have been described. The implementation step has to be performed well if a CEM study is to succeed. To ensure success it is necessary to do the following:

- Appoint a manager as administrative head for the CEM unit. This person will undertake staff appointments, arrange office facilities and be responsible for administering finances, in consultation with the head of the PvC. He or she should seek to develop a team spirit and, although staff members will all have designated functions, to use the particular strengths of the individuals wisely.
- Aim at running an initial pilot programme. Select appropriate monitoring sites, with trained teams and adequate resources to perform CEM.

Advocacy

(See also Section M.4 for more information on communication.)

Using the most appropriate means, all stakeholders must be fully informed of the reasons for monitoring, the methodology as far as it involves them, the value of safety monitoring and the advantages of CEM, the contribution it will make to the health of the population (improving benefit and reducing risk); its potential for increasing the effectiveness of public health programmes; its potential for reducing health costs for the community and government; and the contribution CEM programmes can make to the knowledge of TB medicines and their safety in any particular country and internationally.

4. Establishing the cohort(s)

4.1 Numbers of patients

A cohort of 10 000 patients is usually recommended for CEM. This gives a 95% chance of identifying a specific event that has an incidence of 1:3000 (uncommon or rare). Normally several events are needed to alert to a signal, or to help evaluate a problem. A cohort of 3000 patients gives a 95% chance of identifying a single event with an incidence of 1:1000 (see Annex 3). For a meaningful assessment, at least three events need to be identified. Hence the higher objective of 10 000 patients. However, the identification of one serious event can be clinically significant. If a comparator study is being undertaken, greater numbers of patients will be needed if the background incidence of a particular event in the community is high (as with diarrhoea) and the aim is to detect statistically significant differences between the comparators. Larger numbers might be needed

- to detect differences between patients on specific medicines (e.g. ARVs) and other patients; and
- to detect differences between patients with and without other health problems such as malnutrition.

Taking the above factors into consideration, and because of the often complex issues surrounding the clinical care of patients with TB, some of whom, for example, have HIV/AIDS as well, it would seem desirable to aim for a cohort of 15 000–20 000 patients.

Software packages are available that will facilitate sample size calculations, as well as statistical analyses. The CDC Epi Info™ package, which can be downloaded free of charge (www.cdc.gov/epiinfo), includes a sample size calculator ("StatCalc") as well as other utilities for statistical analysis.

4.2 Selection of patients

4.2.1 Logistics

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

- The patients might be recruited from all health facilities involved in treatment of TB.
- Patients might be recruited from selected health facilities that are representative of the whole country, designated as *monitoring sites*.
- From a practical point of view, monitoring sites may be selected where there is good infrastructure, facilities and record-keeping.

4.2.2 Onset of monitoring

Patients must be monitored from the start (inception) of treatment. Subjects may include patients whose drug regimen has changed. Patients should not be enrolled part way through a stable course of treatment because this might introduce bias or confounding factors into the analysis.

4.2.3 Subgroups of interest

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

Patients with HIV/AIDS or another specific co-morbidity: To determine any risk factors specific to patients with HIV/AIDS or another specific co-morbidity, the whole population of users will still need to be monitored to enable comparison with the cohort members who do not have HIV/AIDS or another disease of interest.

Pregnancy: If the only interest in monitoring was in outcomes for pregnant women, then patient selection could be restricted to women with child-bearing potential.

4.3 Patient identification

It is vital that patients can be identified accurately. Inaccurate identification will result in duplicate entries in the database leading to inflated numbers in the cohort and inaccurate statistics and then to difficulties in follow-up.

4.4 Other required patient data

- Date of birth (preferred) or age at the time of treatment.
- Sex.
- Weight and height for calculation of body mass index (BMI).
- Clinic identification number on patient's file or card.

4.5 Background data

- History of significant illness (e.g. liver disease, or kidney disease).
- Other conditions present at the time of treatment (e.g. anaemia, and HIV/AIDS).

4.6 Controls or comparators

4.6.1 Comparator cohorts

A CEM programme involving two (or more) TB treatment regimens, given to patients in the same population, and which took into account drug substitution, might provide a useful comparison of the medicines involved. Comparisons could be made of two regimens in two groups of the same population over the same period, or of consecutive treatments in the same patients who have had drug substitutions or changed regimens. Because the patients in the different cohorts are not strict controls, comparisons would have to be made with caution due to the likely presence of confounders.

4.6.2 Pretreatment comparator period.

It is important to be able to differentiate background morbidity in the cohort from ADRs that might occur as a result of treatment. It is therefore recommended that at the time treatment is initiated any health events (including those due to the TB) that occurred in the previous month are recorded as "control" events. If a patient is seen for assessment with a view to treatment, he or she should be given a notebook in which to record any events in the period before treatment begins.

5. Acquiring the data

5.1 Details of administration of anti-TB medicines

The following data will be recorded on the questionnaires for later entry into the database.

5.1.1 Treatment details

- The name of each medicine (brand name is more specific). The standard abbreviations should be used for each medicine e.g. H for isoniazid, or E for ethambutol. Brand names and lot numbers should be recorded if available (see Annex 4 Table 4.1).
- The standard abbreviations for regimens may be recorded to expedite completion of the CEM questionnaires; e.g. HRZE in the intensive phase, or HR in the continuation phase (see Annex 4 Table 4.2).
- The total daily dose should be recorded for each medicine, or if the regimen only is recorded. Use of fixed dose combination (FDC) formulations should be recorded.
- The date of commencement of treatment with each medicine or regimen.
- The date of withdrawal or cessation of any medicine or regimen.

If any, or all of the medicines were stopped temporarily for any reason, a stop date and a restart date should be recorded.

5.1.2 Treatment adherence

- Record adherence (> 80% of doses taken or ≤ 80% doses taken).

5.1.3 Reasons for stopping TB therapy

The reasons for stopping therapy are coded as 1, adverse event; 2, poor adherence; 3, course completed; 4, planned interruption; 5, planned medication change; 6, no longer needed; 7, treatment failure; 8, pregnancy; 9, drug out of stock; 10, cost; 11, patient decision; 12, died; 13, lost to follow-up; 14, other (please specify).

5.1.4 Effectiveness

- Did the patient's condition improve as expected? Yes or No.
- If the patient's condition did not improve as expected, please comment.

5.2 Concomitant medicines

All short- or long-term medicines taken during anti-TB therapy should be listed. This includes vaccines. Standard abbreviations for ARVs, which are at times given concomitantly, can be found in *A practical handbook on the pharmacovigilance of antiretroviral medicines* (pages 97–98 at apps.who.int/medicinedocs/documents/s16882e/s16882e.pdf).

Record the following information on each concomitant medicine:

- name of medicine;
- any traditional medicine(s) ("yes" or "no");
- indication for use;
- dose and frequency of administration;
- date started; if long-term and the date is uncertain, record, "long term";
- date stopped (record "continues" if not stopped).

A note should be made of whether traditional medicines were taken or not. This is because many patients would not know the name of the traditional medicine they were taking. Many of these medicines have a number of poorly defined constituents of variable quality and quantity and a similar name may be used for quite different products. If the analysis of results did show an important event associated with the use of a traditional medicine, then elucidating the problem would necessitate a special research study. However, if CEM staff and the clinicians believe that patients would know about the traditional medicines that are well recognized and commonly used, then these could be recorded. This would add some specificity, but the decision on whether to record them would need to be a local one.

It is important to record vaccines as concomitant medicines, because of the possibility of adverse interactions with medicines. Also, it is worthy of note that the response to vaccines in immunocompromised patients who have HIV/AIDS or who are otherwise severely ill, is somewhat unpredictable.

5.3 Principles of event reporting

A number of ADRs to anti-TB medication have been well documented over the past few decades (Annex 5). While many clinicians will be fully aware of these, it should be emphasized that all adverse events need to be recorded and not just suspected ADRs. Clinicians or recorders should be asked to make no judgement on causality. These events will be recorded on the *Treatment initiation form* and the *Treatment review form* (Annexes 6 and 7). Normal clinical terms or descriptions should be used. There should be no attempt to apply the official adverse event terminology (see Section E.9). These terms will then be entered into the database as meeting the definition. Any other use of the same term not qualified as "defined", will be entered and qualified as "not defined".

5.3.1 Adverse events

Clinic staff or CEM recorders are asked to record events rather than suspected reactions because there are *always* unexpected or unrecognized ADRs. If only suspected reactions are reported, then those which are unexpected and unrecognized are likely to be missed.

5.3.2 Clinical events

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

5.3.3 Pretreatment comparator period

All events occurring in a pretreatment period should be recorded. If it has been possible to arrange for patients to keep diaries of health events before initiation of TB treatment, those events should be recorded. In some public health programmes patients have been given exercise books in which to keep a dated record of any health events and they are asked to make an entry of this at the end of each day. In the absence of a patient diary, this recent medical history-taking will need to rely on patient recall, or if the patient has needed to attend the clinic for the event(s) (e.g. malaria), clinic records should be used as well. These control events will be recorded on the *Treatment initiation form*. The length of the comparator period will need to be decided by the clinic staff. If good clinic records are available and patients are able to maintain health diaries, a period of a month or more would be desirable.

5.3.4 Treatment review

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

5.4 Types of events

Health professionals or CEM recorders should be asked to record the following types of events:

- all **new** events even if minor;
- **change** in a pre-existing condition;
- abnormal **changes** in laboratory tests compared with a previous examination;

- lack of **effectiveness**;
- **admission** to hospital, or prolongation of hospitalization, with date and cause;
- the first observation of **pregnancy** of any duration;
- an infant breastfed by a mother being treated for TB (**lactation exposure**);
- **accidents**;
- all **deaths** with date and cause;
- possible **interactions**:
  - — Include pharmaceutical and traditional medicines.
  - — Remember hormonal contraceptives and alcohol.
  - — Be aware of the possibility of food–drug interactions.

5.5 Recording event details

A brief description of each event is usually all that is necessary. These event descriptions will be reviewed later by a clinical reviewer and standard adverse event terminology will be applied then. The clinician does not need to know, or refer to, the standard event terminology.

5.6 Reporting forms (questionnaires)

There are two questionnaires for routine monitoring (Annexes 6 and 7). The *Treatment initiation form* (Annex 6) records patient details, past conditions of importance, any current treatment and anti-TB treatment prescribed, comorbid conditions, laboratory test results, and any events during the pretreatment control period.

The *Treatment review form* (Annex 7) is for recording any events that have occurred or are still present from the previous review. A new follow-up questionnaire should be completed at each follow-up visit. A persistent event might be recorded on more than one questionnaire, but in the analysis it is not counted twice unless it resolved and there was another episode later (e.g. relapse of a TB case). Recording it a further time enables information on outcome to be entered into the database. If a woman reports being pregnant at a follow-up visit, this may be recorded on the follow-up form.

The questionnaires may need to be adapted for local use, in particular, they should carry an appropriate logo and use the local language. Although the format of the questionnaires may be adapted to local preferences, it is impor-

tant that the data fields remain unchanged. This will allow aggregation of data across regions or countries to enable valid comparisons. The international aggregation of data will also allow more powerful statistical analyses from the larger numbers in the combined cohorts.

5.7 Data recording

TB clinics and other clinics that treat TB patients are frequently under-resourced and over-busy. It is therefore crucial to avoid adding to the already burdensome demands on the clinicians and other health workers running the clinics. This is achieved by the provision of data that will allow:

- the identification of risk factors for serious reactions. This will enable better selection of medicines for individual patients and avoidance of troublesome and costly ADRs;
- the early identification of previously unrecognized ADRs and thus will enable preventive action to be taken that will minimize the effect of these problems in the patient population and the adverse publicity that can arise from delay in recognition;
- the measurement of the comparative safety of different medicines and regimens.

5.7.1 Planning

- Administrators and programme managers need to be aware of these advantages and provide for the resources to undertake adequate pharmacovigilance.
- CEM can provide the necessary data better than spontaneous reporting and do so relatively quickly.

5.7.2 The recording of data

With CEM, the data are commonly recorded from existing records following each patient visit. Where clinics have an adequate system for recording events, this could be done with the monitoring of TB therapy. This may require the recording of types of events that are not normally recorded (see requirements for event recording Section E.1). Clinical staff would need to be trained to perform this more comprehensive recording and would need to understand that this process goes beyond the advice often found in guidelines to keep the recording of data to an essential minimum. All events data are necessary.

- Recording data from a patient diary should be done in the presence of the patient. This also provides the opportunity for clarifying the meaning of any entries.
- Recording of events from existing records should be performed as soon as possible after the patient consultation.
- The recording should be done by a health professional who is familiar with clinical terminology (e.g. a nurse) and this person should be trained and employed for this work (with the title of "data recorder").
- At sites where data are computerized, it may be possible to record or extract the required data electronically. Digital records are strongly recommended as they facilitate storage and access.

Where clinic records are inadequate for the data extraction required, the local workflow may need to be adapted to divert the task of extensive recording from the clinicians and/or support may need to be provided to suit the local site. This should be done in consultation with clinic staff. Some possibilities are:

- the recording of non-clinical data (e.g. patient ID and demographics) by support staff with the recording of clinical data being done by the clinicians;
- the recording of non-clinical data by support staff and the recording of clinical data, given orally by the clinician during the consultation process, by a trained data recorder;
- the recording of all data on medicines by the pharmacist or a pharmacist assistant;
- patients interviewed by a trained support worker while they are waiting to be seen by the clinician. Standard checklists could be developed so that the interviewers do not overlook important questions.

Where the workload of a clinic cannot cope with daily recording, it might be preferable to undertake monitoring only at certain clinic sessions e.g. every morning, or on specific days of the week such as Tuesdays and Thursdays, or for the first 20 patients each day.

5.7.3 Data capture questionnaires

Consideration should be given to printing the questionnaires in pads on duplicate self-copying (NCR) paper bearing in mind the following:

- Separate pads would be needed for the two questionnaires.

- It would be an advantage to have the pads colour-coded.
- The forms should look as attractive and professional as possible. This communicates that the system is professionally organized and encourages compliance with the programme.
- When the forms are completed in the clinic, the top copy of each form should be sent by the CEM Focal Person at the clinic to the PvC for data processing and the duplicate copy retained in the health facility with the patient's record, where possible, or in another specified location.
- A standard operating procedure (SOP) would need to be developed for collecting, storing and forwarding the forms. An SOP, properly supervised, should result in:

  — a reduced likelihood that forms will be lost;
  — copies of the questionnaires being retained in the health facility for reference;
  — the questionnaires reaching the PvC soon after completion and offering the data manager for the CEM programme the opportunity to instigate procedures for checking on follow-up questionnaires not received at the expected time.

5.8 Frequency and duration of monitoring

5.8.1 Routine monitoring

- The frequency of recording monitoring data will depend on the normal schedule of assessment and follow-up at the clinic.
- If patients are requested to return monthly or at other intervals, then events should be recorded at these scheduled visits, on the *Treatment review forms*.
- Variations to this procedure could be agreed in consultation between the CEM team and the clinical team. Consideration should be given to a local policy on completion of questionnaires at unscheduled visits for acute conditions. Rather than complete questionnaires in these circumstances, it should be possible to identify and record the events which occurred at these times during a later, normal scheduled appointment.

5.8.2 Termination of routine monitoring

- The monitoring programme should continue until the agreed cohort size is reached and patients have been monitored until the end of their treatment.
- Data from monitoring should be analysed and reviewed at regular intervals, preferably no less frequently than every 3 months. Trends can then be iden-

tified and any particular concerns addressed (e.g. to determine the ultimate outcome of a serious toxicity).

- In view of the possibility of late-onset reactions, it is suggested that routine monitoring continue throughout the whole period of treatment for individual patients, even if this is prolonged.

5.8.3 Extending the monitoring programme

There are a number of reasons why it might be desirable to extend the monitoring programme. If more information on certain subgroups of the cohort is needed, a decision could be made to extend the programme in order to increase the numbers in these subgroups and thus gain better statistical power for the analyses. This might apply, for example, to the following:

- Patients with specific **co-morbidities** of particular interest e.g. HIV/AIDS and hepatitis. This would give greater opportunity for detecting interactions between therapies and provide more data on outcomes for the patients.
- **Children**: to define ADRs and the risk factors specific to children more clearly. Comparison with the adults in the cohort may not be definitive if the number of children in the original cohort is small.
- For the comparison of the safety of different **regimens**.
- Women of **child-bearing** potential: extended monitoring of this group may be required to record greater numbers of pregnant women on therapy and for subsequent assessment of the outcomes.

5.8.4 Non-attenders

Good coordination between the CEM team and the clinic health workers needs to be established in order to obtain information on any events experienced by patients who have lost mobility and are unable to attend the clinic, have been admitted to hospital, have died, or have been lost to follow-up for some other reason, which could include severe or serious ADRs. An SOP should be developed to facilitate this work.

5.9 How and where to send the completed questionnaires

The completed questionnaires need to be sent to the National or Regional PvC, or if neither of these exist, to the CEM unit within the national tuberculosis control programme (NTP), according to a locally agreed procedure. There the events will be assessed and the information entered into a database.

The method of sending the questionnaires needs to be planned with each health facility, ranging from hospitals to rural clinics, and an SOP should be prepared for each facility. It may be desirable for rural clinics to send their reports to district hospitals and for district hospitals to send them to reference hospitals which will then send them to the PvC. However, some other method may suit local circumstances better. An appropriate chain of communication needs to be established and everyone involved should be well informed about it. The questionnaires should be stored securely so that they cannot be accessed by unauthorized people. An appropriate frequency for sending the reports needs to be established, e.g. weekly, and the role of checking on the transfer of the reports along the chain needs to be assigned to a suitable person (e.g. the Field Coordinator). An SOP should be prepared and made known to everyone involved.

5.10 Record linkage

Record linkage, if available, can be used to supplement or check information received on the CEM questionnaires. This is a method of searching different health databases electronically using unique patient identifiers. The unique patient identifiers (or national health numbers) must be in use nationally to enable national registers of deaths or diseases to be searched. The identifying health number must be recorded with the patient details in the cohort database. Examples of databases that may be available for searching using the health identifiers are:

- register of deaths
- register of congenital abnormalities
- cancer registers
- other specialist registers, e.g. TB or AIDS registers.

In the absence of national numbers, other identifying numbers (e.g. hospital numbers) if available, can be recorded in the patient cohort data. It would then be possible to use these numbers to search registers maintained by the hospital (e.g. a teaching hospital) or another facility that has health (or disease) registers.

6. Database for CEM

6.1 Choice of database

CemFlow

The UMC has developed CemFlow as a tool for data entry into an online database maintained by the UMC for CEM. In situations with unreliable Internet connection or low bandwidth the tool allows data to be entered offline. Data may be uploaded to the CEM database at times when or at places where the connection is functioning well. The same principles apply to the use of CemFlow as to VigiFlow, which is used for spontaneous reporting (see Section C.10). In addition to the advantages listed for VigiFlow, the following are of particular value:

- CemFlow provides for entry of cohort data as well as the events.
- CemFlow also provides programs for standardized collation of data and statistical analyses which have been identified as essential for CEM data.
- CemFlow has the essential terminologies built in, including the CEM events terminology. These are necessary for working within the WHO Collaborating Programme.
- CemFlow has an Assessment screen which brings together all the data elements necessary for relationship assessment. This ensures that drug–event relationships are assessed in a standardized way.
- CemFlow is designed for use with the CEM questionnaires.
- Using CemFlow it is possible to aggregate data internationally and make valid and valuable comparisons.
- This aggregated data also allows for analyses with greater statistical power and more reliable signal detection using data mining.
- CemFlow provides a documents section which includes the questionnaires and instructions for using them.

For those without Internet connections:

- A relational database like Microsoft Access can be used, but requires special expertise
- Purpose-built databases can be programmed using a software such as SAS©. This requires a person with expertise in this software.

6.2 Data elements and fields

6.2.1 About data elements and fields

Fields required in the database need to allow for entry of all the data elements included in the questionnaires. Some of the data from the questionnaires require the application of dictionary terms and codes and also relationship assessment (see Section G).

6.2.2 Patient demographics and identifiers

Treatment provider

- district
- health unit
- clinician or clinical team
- patient file number
- interview site (e.g. clinic, home visit, telephone).

Patient

- name, first name and family name
- unique ID number
- address or contact details
- contact telephone number
- sex
- date (preferred) or year of birth, or age if DOB is not available
- weight and height
- pregnancy status, if applicable.

Patient ID numbers

There are usually two or more patient ID numbers available which allow patients to be identified accurately. This helps to avoid confusion between the identity of patients in the database and to ensure that the correct data are assigned to the correct patient. Use of ID numbers also helps to keep the cohort numbers and hence the statistics derived from the data accurate.

Unique country ID number

It is desirable to use a unique ID number. Many countries already have a unique ID that is permanently assigned to a person and used for administra-

tive purposes. This should be used if available because it will identify patients accurately and enable record linkage. This will be a number that will not change according to where a patient happens to attend for treatment. Ideally, a national health number should be used if there is one. If not, some other form of national ID should be used if possible, e.g. the number from a national identity card, or birth certificate. A decision should be made by country programme administrators as to what kind of unique ID will be used.

Clinic file number

The clinic file number is a number that is used for the clinical records in health facilities. It may be different in each hospital or clinic that the patient attends. This number is required so that the correct patient records can be found easily for any follow-up enquiry.

- Both numbers should be recorded on the questionnaires.
- In analyses and in information shared within the country, use of the ID numbers without personal data, helps to preserve patient identity and ensure privacy. The ID numbers are not used in published data.

6.2.3 Medicine(s)

- name: brand or generic name; the brand name is sometimes more useful;
- indication for use: for TB, indicate whether for treatment or prevention;
- adherence (for anti-TB treatment);
- dose: the total daily dose (or number of dosage forms per day) and number of days per week on which it is given;
- date of commencement;
- date of stopping or interrupting treatment;
- date of dose reduction;
- date of rechallenge (if performed); and
- concomitant medicines with details of administration, dates and indications.

6.2.4 Events

- description of the event (in free text)
- date of onset
- effect of dechallenge (withdrawal of medicine)

- effect of rechallenge (if performed)
- severity[1]
- seriousness of the event
- outcome of the event (coded).[2]

6.2.5 Contact details of the CEM focal person

The CEM focal person is the key CEM person at the health facility;

- name
- status (doctor, nurse, etc)
- telephone number.

6.2.6 Other data

All the above refer to those data elements entered on the questionnaires in the clinics. Other data are recorded at the PvC at the time of data entry and during the assessment of the events later. These include the following:

- report number. Each *Treatment review form* that has events recorded should be given a report number and this number should be recorded with the events in the database. The report numbers for CEM should link with the report numbering system given for ICSRs in the PvC;
- the appropriate terms selected from the events dictionary when the events are reviewed by the assessor;
- relationship assessment.

7. Maximizing the reporting rate

7.1 Prepare the ground

In all the planning phases and communications with health professionals, health workers and public health staff, it is important to try to develop a culture of collaboration: working together for the successful management of TB therapy in the safest possible way for the patients.

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[1] Severity is coded as mild, moderate, or severe (see also Section E.9.6).

[2] R1, recovered/resolved; R2, recovering/resolving; S, recovered with sequelae; N, not recovered/not resolved; D, died; U, unknown.

7.2 Removing barriers to reporting

The following means of removing barriers need to be considered:

- Ensure an adequate supply of readily available questionnaires.
- Make sure everyone is adequately briefed on the importance and value of CEM and understands the basic methodology.
- Arrange the completion of the forms in such a way as to minimize any disruption to the normal flow of clinical procedures in the clinic.
- Do not ask for information that is not absolutely necessary for pharmacovigilance purposes.
- Do not ask for information that might take a long time to find, e.g. batch numbers, unless it is very important. Batch numbers are included on the questionnaires, but if they prove an obstacle to recording, a programme decision should be made not to record them.

7.3 Other health facilities

Patients may need to visit health facilities other than the clinic they regularly attend for their TB treatment. For event reporting to be complete, reports of all health events are needed from these other facilities. It is suggested that patients be given an ID card or "CEM card" with instructions to any other health professionals to contact the patient's regular clinic and advise them of the problem(s), so that they can be recorded in the patient's data and included in the monitoring programme. The tuberculosis identity card can be adapted for this purpose (see Annex 8). The card should be designed locally and printed in the local language.

7.4 Feedback

Good feedback to the health professionals and health workers will encourage good participation. The health personnel will need regular information to be sent to them by the PvC or CEM centre. This information needs to be relevant and helpful to their work. Occasional meetings to discuss the results are valuable.

8. Practical advice and information

8.1 Don't ask for too much

- The more you ask for the less you will get.
- Whereas the reporting of all events is essential, the necessity for additional information needs to be weighed carefully.
- Increased data raise the workload and the cost. Only collect data which are going to be analysed.
- Some information is best requested by follow-up when the necessity for it can be explained and interest created by the problem being explored.

8.2 Non-serious events

It is important to include non-serious events because:

- They might indicate an underlying serious problem.
- They might affect adherence, e.g. nausea.
- If common, they might be more important to public health than rare, but serious problems.
- Clinicians often find it easier to record all events than to remember selective instructions and if they don't remember, they don't record.

8.3 Be open-minded

- Predictions of safety, if based only on spontaneous reporting, are unreliable.
- Unexpected reactions will occur.
- Avoid preconceived ideas on safety.
- **All events data** should be collected and analysed in a totally **objective** manner.

8.4 Privacy

Given basic precautions to maintain confidentiality, patients will give greater priority to safety concerns. Security and confidentiality of data are essential requirements. Other ethical requirements should not prevent CEM taking place or reduce its functionality, because it is unethical not to pursue those methods that are essential to safety assessment and the protection of patients. Ethical issues are discussed in Section M.2.

9. Clinical review

Clinical review involves the following activities in the monitoring centre:

- assessing the clinical details of the events and determining the appropriate event terms;
- determining the duration to onset of each event;
- noting data on dechallenge and rechallenge (if any);
- assessing severity and seriousness;
- checking the outcome of each event;
- undertaking a relationship assessment for each event as the first step in establishing causality.

9.1 The event should be specific to be acceptable for recording

For example, sometimes a "stomach upset" is reported, but this description is too vague. It could mean dyspepsia, nausea, vomiting, diarrhoea, or some other specific event. "Dizziness" is an event frequently recorded, but it can mean either vertigo or faintness which are quite different and because of this lack of specificity, it should not be used.

9.2 Determining the event term

A person with clinical expertise (the CEM Clinical Supervisor) in the CEM unit of the PvC should review the details of the events described on the questionnaires. The first decision to be made is which clinical category(s) (equivalent to system organ class), would be the most appropriate in which to record the event(s) e.g. alimentary or respiratory. The most appropriate term should then be selected from the particular clinical category in the CEM events dictionary. With CemFlow the event terms are available online and are easily displayed and selected. If, however, there seems to be no appropriate term for a reported event, a new term can be entered. In choosing a new term, a standard medical term should be selected from ICD-10, another dictionary (e.g. MedDRA or WHO-ART) or from a textbook or the literature. This additional term is reviewed during dictionary maintenance and added to the dictionary if approved, or else another appropriate term is applied. Definitions will be added as necessary. If it is not possible to use CemFlow, the selected terms should be recorded manually on a coding sheet for later data entry (see Section F and Annex 9).

9.3 The events dictionary

The need for an **events** dictionary arises because the readily available dictionaries are *reaction* dictionaries related to the spontaneous reporting of suspected ADRs rather than of *events*. It is important to use standard terms so that data can be compared between CEM programmes run in different regions or countries and/or at different times. A specific events dictionary is needed because many events will not be reactions. Many event terms are not found in standard reaction dictionaries (e.g. WHO-ART and MedDRA). Clinical events rather than suspected reactions need to be recorded in order to identify unexpected reactions.

Event monitoring of new medicines in developing countries will require many new event terms that are not in standard (western) reaction dictionaries because of:

- combinations of anti-TB medicines used in standardized regimens particularly in resource-limited countries;
- different medicines in common use in medical practice which are given concomitantly with anti-TB therapy, e.g. artemisinin combination therapies for malaria;
- different co-morbid conditions e.g. malnutrition or parasitic infestations;
- the common use of traditional medicines;
- different ethnicity, diet and living conditions.

An event dictionary for CEM needs to be rapidly adaptable to meet the above needs.

9.3.1 The structure of the dictionary

Event terms are organized in a hierarchical structure of five levels that arrange the terms in clinically related groupings through to the lowest level. The first three levels are grouping terms (clinical category, anatomical/functional change, clinical subgroup). The actual event terms fit into these groups as primary event terms and secondary event terms. The second grouping term (anatomical/functional change) includes the term "change" because CEM is not simply recording the presence of an event, but a change from the previous condition. The structure is used to collate and display the events in a clinically meaningful manner. The major clinical categories are listed in Annex 10. The clinical categories include deaths, pregnancy exposure, lactation exposure and concomitant medicines, so that these will be displayed routinely after automated collation.

9.3.2 The clinical and epidemiological value of the dictionary

Events data are sorted by the dictionary codes to create a clinical collation of events that enables a visualization of the pattern of morbidity in the cohort.

Because related events are grouped together, the collation presents a clinical perspective that provides a key to rapid signal identification. The listings of collated events can be presented with rates for individual events and for their groupings. The collation of events from the control period provides a picture of the background morbidity in the community and this can be used to assist in the evaluation of events recorded after treatment has begun.

9.4 Dictionary maintenance

New terms may be added to the country CEM database by the clinical reviewers of the reports, but when the reports with new terms are forwarded to the UMC, these new terms will be flagged for consideration by a central standardizing committee, which will give feed-back on the terms approved. This committee will consult with WHO TB experts as appropriate, to help determine the best term. The dictionary will be rapidly adaptable to meet the day-to-day needs of the event monitoring programmes. Some definitions are built into the dictionary and these will be added to keep the terms as specific as possible. For TB-specific terms, definitions will be sought from the WHO TB specialists. Any new reaction terms (as opposed to terms for incidents) found necessary will be included in WHO-ART and mapped to MedDRA. Where there are no matching terms in MedDRA, a request will be made for their inclusion.

9.5 Seriousness

Each event should be routinely recorded as either not serious or coded for the reason for its grading as serious. Standard codes are N, not serious; H, hospitalization (caused or prolonged); P, permanent disability; C, congenital anomaly; L, life threatening; D, death (see Annex 9).

9.6 Severity

Severity does not have the same meaning as seriousness. The degree of severity reflects the intensity of the event. A patient can experience a severe event that is not serious, e.g. pruritus. Severity is a subjective assessment made by the patient and/or the clinician. Although subjective, it is nevertheless useful in identifying reactions that may affect adherence. There is no international agreement on the use of the term severity, but the grading adopted for some WHO public health programmes and CEM uses the terms “mild”, “moderate”, or “severe”. The US Centers for Disease Control has a scheme for grading the severity for adverse events and this may be used. It grades the severity

of adverse events that can be measured using laboratory investigations e.g. anaemia.

9.7 Outcome of the event

Normally recording the outcome is a matter of copying the outcome as entered on the questionnaire, but at times clinical judgement is required, e.g. when recording deaths. The types of outcome to be recorded, together with their respective codes, are R1, recovered/resolved; R2, recovering/resolving; S, recovered with sequelae; N, not recovered/not resolved; D, died; U, unknown (see also Annex 7).

9.8 Standard Operating Procedures for CEM

The drafting of the SOPs needs to take into account the following:

- **what** needs to be done
- **who** will do it
- **where** it will be done
- **when** it will be done
- **how** it will be done.

The following list should not be perceived as a complete list. There are other tasks and functions in the local situation that will need SOPs if they are to be performed satisfactorily (see also Annex 11):

- distributing and returning completed spontaneous reporting forms;
- distributing the CEM questionnaires (for standard follow-up) to the monitoring sites, management of the questionnaires at the sites (including secure storage of completed questionnaires) and the return of the questionnaires to the CEM unit;
- the standard recording of TB therapy (including doses) on the spontaneous reporting forms and CEM questionnaires. The aim is to make recording easy, but also very clear;
- the numbering, completion and checking of the questionnaires at the clinics;
- the follow-up of non-attenders at the TB clinic and the recording of any events;
- for pregnant women, the recording of details needs to include notification of when a baby is born to a mother on TB therapy;

- the longer term follow-up of babies at 3 months and 1 year;
- receiving the questionnaires at the CEM unit, giving each one a report number and the data entry;
- checking with the health facilities when follow-up questionnaires for particular patients do not come through at the expected times;
- collating and reviewing the events;
- reviewing and acting on data for the special categories: serious events, pregnancies, lactation exposure, deaths, lack of efficacy;
- good communication and coordination between CEM staff and PvC staff (if they are different) at the central office and incorporating the reactions identified by CEM into the national database;
- clinical review of the events;
- reporting the results to the regulatory authority, advisory committee, health workers involved in the programme and health professionals generally.

F. Data processing

Data must be accurate ("clean"). A process of validation is often needed to ensure that the quality of the data is as good as possible. Data operators must be trained and supervised until their level of skill is acceptable. They need to be given good tools (a good computer and suitable office furniture) for this exacting job. They must also share the vision and the results so that they feel that they are a vital part of the team.

The use of standard formats is a means of reducing error. Input masks will only allow predetermined terms and values to be entered. Drop-down lists are preferred to free text entry to speed data entry and also to limit standard response options. Common examples include standard date format (dd/mm/yyyy), restriction of number of digits to what is appropriate (e.g. 2 digits for age), use of WHO Drug Dictionary codes for medicines and ICD-10 codes for diseases, drop-down lists for names of hospitals and clinics; units for laboratory values.

VigiFlow and CemFlow, two tools developed and maintained by the UMC for database management in pharmacovigilance, both have built-in error avoidance and other features listed above to facilitate data entry.

Systematic checks of data entered may be done by printing and "eyeballing" lists of data regularly. Checks should look for dates that are improbable, male sex with female name and similar names (e.g. Joe and Joseph) with the same date of birth who could be the same patient. Some of these checks may be automated.

Coding of medicines and diseases: Drug names or codes may be entered from the WHO Drug Dictionary; ICD-10 codes are used for diseases that are recorded as indications for treatment or diseases recorded in the medical history. The ICD is also a useful source of acceptable event names. The terms are accessible in VigiFlow and CemFlow and it is not necessary to look up the codes.

Standardized recording of event details: Use of CemFlow or a coding sheet by reviewers ensures a systematic and standard approach to reviewing the events reported on the questionnaires. With CemFlow, the clinical reviewer can enter clinical details directly on the "assessment screen" during the review process. In the absence of CemFlow, a coding sheet is a useful tool for facilitating

review and recording of the clinical details in a report. An example is provided in Annex 9. The coding sheet should be completed before data entry. This speeds up data entry and reduces error. With a completed coding sheet a data processor is able to enter the clinical details the clinical reviewer has recorded.

Collating and summarizing the events: The collation will provide the earliest means of identifying signals simply by observing the clinical patterns of events. This method of signal identification is very sensitive and should be performed for each drug or drug combination. Collation and search for signals should be seen as regular functions of the data manager and performed at least monthly during CEM. The events are sorted by the event dictionary codes (print codes). When a printout is made, the events listing will reveal the clinical pattern of the events that have occurred in the local environment. This collated events listing is one of the programmed reports on CemFlow and can be produced at any stage. The events collation should incorporate the event, sex, age at the time of the event onset, dose, duration to onset (in days, hours or minutes), relationship (coded as 1 (certain), 2 (probable), 3 (possible), 4 (unlikely), 5 (unclassified), 6 (unassessable); see Section G), report ID number, death and withdrawal of medicine.

Event/risk profiles can be displayed graphically to represent the rates of events in each clinical category, or of groups of related events within a category. It is particularly useful for comparing two or more medicines or regimens. To develop a risk profile, only those events coded as having a relationship of 1, 2 or 3 should be included. This results in a profile of those events with a plausible relationship to the medicine and illustrates the actual risk pattern better than an events profile which includes all events, including those with an "unlikely" relationship. In other words, this selection of events helps to remove unwanted "noise".

G. Relationship and causality assessment

1. Background

Establishing causality is a process which begins by examining the relationship between the medicine and the event. Two basic questions need to be addressed separately:

- Is there a convincing relationship between the drug and the event?
- Did the drug actually cause the event?

The relationship of a single case-report can be established, but it may not be possible to establish a firm opinion on causality until a collection of such reports is assessed or new knowledge is gained. *Causality* for individual reports, even those with a close relationship, can seldom be established beyond doubt and our assessments are based on probability. A causality assessment should be seen as provisional and subject to change in the light of further information on the case, or new knowledge coming from other sources.

2. Relationship ("objective phase")

Factors to consider when assessing the relationship between drug and event are listed below.

2.1 Did the event begin *before* the patient started taking the medicine?

This may seem an obvious consideration, but reports are received in which this has not been taken into account, and a careful check has then revealed that the event preceded the use of the suspect medicine and therefore there was no relationship.

2.2 Is the duration to onset of the event plausible?

- Is the event likely to have occurred in the time frame in question?
- Did it occur too quickly to be related to the particular medicine, taking into account its pharmacological action?

- Did the patient take the medicine for a long time without any problems? (Delayed reactions after long-term exposure do occur, but most reactions will occur soon after the patient starts to take the medicine.)
- The nature of the event should be considered when assessing the significance of the period of exposure, e.g.
  - — Some events take time to develop (e.g. deafness).
  - — Some develop quickly (e.g. nausea and vomiting).
  - — Allergic reactions to first-time exposure to a drug generally take around 10 days to appear. On repeat exposure they may occur immediately.

2.3 Did the event occur after the commencement of some other medicine?

If the event began shortly after commencing to take another medicine, then two possibilities should be considered:

- The new medicine may have caused the event.
- There may have been an interaction between the two medicines and the interaction caused the event.

2.4 Did the event occur after the onset of some new illness?

If so, the event may be due to the new illness.

2.5 Is there any other possible cause for the event?

- Could the event be due to the illness being treated?
- Could it be due to some other co-existing disease?
- Could it be due to some other medicine being used concurrently?

2.6 What is the response to withdrawal of the medicine (dechallenge)?

- Did the patient recover?
- Did the patient improve?
- Was there no change?
- Did the patient get worse?
- Is the response to dechallenge unknown? If this is the case, then it should always be recorded as "unknown".

If more than one medicine has been withdrawn, and if rechallenge is considered appropriate, it should be performed with only one medicine at a time.

2.7 What is the response to rechallenge?

A positive rechallenge means that the same event occurred again after re-administration of the same medicine. Conditions for a positive rechallenge are:

- The patient recovered on initial withdrawal.
- The patient developed the same problem again when re-exposed to the same medicine alone, although it may be of different severity.
- The patient recovered when the medicine was withdrawn once again.
- It should be noted that it is not always safe to subject the patient to a rechallenge. However, many rechallenges occur inadvertently and data recorders, data processors and assessors should be alert to this possibility.
- If the response to rechallenge is unknown, this should be recorded.

3. Categories of relationship

There are six standard categories of relationship between drug and event. These are the same as the causality categories in the WHO International Drug Monitoring Programme.

The following are requirements for inclusion of an event in a specific category. Not all events can fit easily into the following categories and some exceptions are given below.

3.1 Certain

- The event is an identifiable clinical or laboratory phenomenon.
- The time elapsed between the administration of the drug and the occurrence of the event is plausible. (*Requirement:* dates of drug administration and date of onset of the event must be known.)
- The event cannot be explained by concomitant disease or any other drug or chemical. (*Requirement:* Details of other medicines taken must be known. The report must also state if there were no other medicines in use. If this is unknown, then doubt exists and the event cannot be included in this category.)

- The patient recovered within a plausible length of time following withdrawal of the drug. (*Requirement:* The date of withdrawal of the drug and the time taken for recovery should be known. If these dates are unknown, then doubt exists and the event cannot be included in this category.)
- The same event recurred following rechallenge with the same drug alone. (*Requirement:* The report must state the outcome of rechallenge. If this is unknown, then doubt exists and the event cannot be included in this category.)

Exceptions

Acute anaphylaxis immediately following an injection. Here there is an obvious direct relationship, which needs to be viewed as "certain", but the usual parameters for establishing a relationship, e.g. dechallenge do not apply. Immediate reactions to other forms of administration (e.g. inhalation) should also be included in this category, as also should severe reactions to oral medication which occur within the time of expected onset of pharmacological effect.

3.2 Probable

- The event is an identifiable clinical or laboratory phenomenon.
- The time elapsed between the administration of the drug and the occurrence of the event is plausible. (*Requirement:* The dates of drug administration and date of onset of the event must be known.)
- The event cannot be explained by concurrent disease or any other drug or chemical. (*Requirement:* Details of other medicines taken must be known. The report must also state if there were no other medicines in use. If this is unknown, then doubt exists and the event cannot be included in this category.)
- The patient recovered within a plausible length of time following withdrawal of the drug. (*Requirement:* The date of drug withdrawal and the time taken for recovery should be known.)
- Rechallenge did not occur, or the result is unknown.

3.3 Possible

- The time elapsed between the administration of the drug and the occurrence of the event is plausible. (*Requirement:* The dates of drug administration and date of onset of the event must be known.)

- The outcome of withdrawal of the suspect medicine is not known, and/or the medicine might have been continued and the final outcome is not known; and/or
- there might be no information on withdrawal of the medicine; and/or
- the event could be explained by concomitant disease or use of other drugs or chemicals; and/or
- there might be no information on the presence or absence of other medicines.

It is important to point out that "deaths" cannot be coded as probable because there is no opportunity to see the effect of withdrawal of the drug. If there is a plausible time relationship, a death could be coded as possible.

3.4 Unlikely

- The event occurred with a duration to onset that makes a causal effect improbable with the drug being considered. (The pharmacology of the drug and nature of the event should be considered in arriving at this conclusion.); and/or
- the event commenced before the first administration of the drug; and/or
- the drug was withdrawn and this made no difference to the event when, clinically, recovery would be expected. (This would not apply for some serious events such as myocardial infarction, or events causing permanent damage.); and/or
- it is strongly suggestive of a non-causal relationship if the drug was continued and the event resolved.

3.5 Unclassified (or conditional)

These are reports with insufficient data to establish a relationship and more data are expected. This is a temporary repository, and the category for these events will be finalized when the new data become available.

3.6 Unassessable

- An event has occurred in association with a drug, but there is insufficient data to make an assessment.
- Some of the data may be contradictory or inconsistent.
- Details of the report cannot be supplemented or verified.

Difficult to categorize events

Deaths

Relationships to death cannot be coded as probable or certain because there is no opportunity to see the effect of dechallenge or rechallenge. If there is a plausible time relationship and other causes can be excluded, a relationship to death should be coded as possible. If there is no plausible time to onset and other causes are evident, then the relationship should be coded as unlikely. If there is doubt, then they should be coded as unclassified and they can be reassessed as a group after an epidemiological analysis.

Myocardial infarction

Many patients recover from this event as part of the evolution of the disease and, with very few exceptions, recovery is not a response to withdrawal of a drug. Hence the result of "dechallenge" is meaningless. This type of reaction may be coded as "unclassified" for the individual event. If there is an aggregation of similar events, epidemiological assessment may clarify the issue, as described for deaths.

Stroke

Some patients recover fully, some partially, some remain severely disabled and some die. All these outcomes are part of the natural history of the disease and cannot be subjected to the dechallenge test. This type of event should be coded as unclassified following the same approach as taken as for deaths.

Acute liver necrosis requiring transplant

Consideration of dechallenge (and of course rechallenge) is also meaningless here, because there is no opportunity to assess the effect of withdrawal or rechallenge on the same organ. The individual case should be coded as possible if other causes can be excluded and the duration to onset was not implausible, or unclassified if there is doubt, for reassessment later.

Renal transplant

If renal transplant for irreversible renal failure has been undertaken, the same considerations apply as for liver transplant above.

4. Processes for establishing the relationship

The use of CemFlow ensures a methodical approach to relationship assessment. If CemFlow cannot be used because of a poor Internet connection, use of a coding sheet before data entry is very helpful (see Annex 9 for an exam-

ple). If the Internet connection is poor or unreliable, data can be downloaded from the CemFlow database to a spreadsheet format (MS Excel) and can be analysed locally. The following should be recorded systematically:

4.1 Outcome of event

Enter the code for the most appropriate outcome. These are described in Section E.9.

4.2 Result of rechallenge with the same medicine by itself

Enter the code for the most appropriate outcome:

N: no rechallenge;

+ve: recurrence of the same event;

−ve: no recurrence;

U: result unknown.

4.3 Clinical details

- Consider concomitant disease(s).
- Assess relevant patient history, e.g. liver disease, renal disease.
- Previous exposure to same medicine(s).

As a quick check after assigning a relationship, and bar the exceptions mentioned earlier:

- You should not have a relationship of "certain" if there has been no rechallenge, or the outcome of rechallenge is unknown.
- You should not have a relationship of "probable" if there has been no dechallenge or the result of dechallenge is unknown.
- You should not have a relationship of "probable" if the outcome of the event is unknown.
- You should not have a relationship of "probable" if there are other possible causes of the event.

It is useful for analytical purposes to divide the events into two groups:

1. *Reactions:* those events with a relationship coding of *definite*, *probable* or *possible* can be aggregated and referred to as "reactions" because the event is likely to be related to the medicine(s).

2. *Incidents:* Those events with a relationship coding of *unlikely*, can be referred to as "incidents" because they appear to be incidental to the use of the medicine. They should be retained as a separate group because they can prove to be of considerable value (see Section J.4).

Events with a coding of *unassessable*, should not be considered further and should be removed from analyses. Those with a coding of *unclassified* are in an interim category and should be reassessed when further information becomes available.

5. Causality ("subjective phase")

Having considered the parameters in assessing relationship the next step is to address the question, "Did the medicines actually cause the event?" In other words, "Is the event a reaction?"

It is possible that the administration of a medicine and the occurrence of an event may have a close relationship, but still not be a reaction e.g. death from myocardial infarction.

In actual practice the assessment of relationship and causality frequently merge, particularly when an event is a well-known reaction and the relationship is close. The two phases occur without conscious deliberation, but should be there nevertheless.

However, it is often necessary to gather other knowledge about the medicine, the patient and the event to undertake a deliberate evaluation of these factors which are actually external to the drug–event association that occurred. This is the methodological approach for evaluating a signal, described in Section I.

The same categories are used for causality as for relationship ("probable" etc.), but after the subjective evaluation of external factors, the category assigned provisionally with the relationship assessment may need to be changed.

H. Special types of event

1. Serious events

Details of serious events should be sent immediately to the CEM Clinical Reviewer in the PvC where they will be fully assessed and appropriate action taken. This will include urgent notification to the NTP manager.

A process needs to be defined for each health facility to follow so that there is no delay. National medicine regulatory authorities often have in place SOPs and clear timelines for transmission of case-report forms in case of serious adverse drug events. Regulatory requirements for reporting should be integrated into the procedures for CEM.

2. Pregnancy

2.1 Background

A very important aspect of pharmacovigilance, including that of TB medicines, is obtaining more information on safety in pregnancy, particularly with new medicines and those for which there has been limited experience in new populations. The success of obtaining outcomes of exposure during pregnancy depends on the vigour of follow-up.

2.2 CEM in pregnancy

The forms for treatment initiation and treatment review (Annexes 6 and 7) also facilitate the gathering of outcome information following exposure to anti-TB drugs during pregnancy. The review form should be completed at intervals during a woman's pregnancy, either at each follow-up visit to the treatment clinic for her TB, or at the antenatal clinic, according to the protocol established locally. It is recommended that the infant is examined at birth or postnatally, at 3 months and at 1 year. Ideally, an examination by a paediatrician at 1 year should be undertaken with the aim of detecting any major internal abnormalities e.g. cardiac pathology. The examinations at 3 months and at 1 year serve as additional checks, which will be of value because some congenital abnormalities are not obvious at birth, or if missed at birth, should be identified later.

All women who are known to be pregnant and on anti-TB medicines should be followed up to find out the outcome of the pregnancy and the health status of the infant. An SOP needs to be developed for each site where monitoring is taking place to ensure that every woman known to be pregnant is followed up by a health worker. Infants of women with TB will be given prophylactic treatment and will be readily available for follow-up checks.

2.3 Pregnancy register

Pregnancy is an event and should be recorded as such at the time of data entry. For this purpose and for the entry of pregnancy details, a special clinical category called *Pregnancy exposures* should be created and this can form the basis of the pregnancy register. CemFlow produces this automatically.

The fields that should be incorporated in the pregnancy register are:

- report number;
- age of mother;
- duration of pregnancy on first date of exposure to anti-TB medicines;
- outcome of pregnancy, including miscarriage or stillbirth;
- duration of pregnancy at parturition;
- outcome for fetus or newborn.

Any congenital abnormalities should be reported immediately to the clinical coordinator or reviewer for CEM at the PvC who should in turn, advise the NTP manager. Further evaluation and investigation by a specialist team should follow.

The CEM clinical reviewer in the PvC should review the register regularly and ensure that all follow-up procedures have been undertaken, or attempted. An SOP should be developed for this.

2.4 Expectations from CEM monitoring of pregnancies

CEM should signal common problems, which, of course, are more important than uncommon problems, because they affect more infants. Rates of any congenital abnormality can be compared with background rates for that country or region, if these are available. The absence of any apparent congenital abnormalities is reassuring, but is not conclusive of safety, particularly from uncommon problems. Cases found of unknown significance, could signal the need for a controlled investigation by a specialist team. All morbidities and drug therapy will be recorded in CEM and can be analysed as risk factors for congenital malformations or spontaneous abortion or fetal death. The find-

ing of congenital abnormalities of concern should be referred for consultation by the Expert Safety Review Panel[1] (Advisory Committee), the PvC and the NTP.

3. Lactation exposure

At follow-up, women on anti-TB therapy who are breastfeeding an infant need to be asked about any events they have observed in the infant. The outcome for every infant exposed during lactation should be recorded. If there have been no events, it is important to record, "*no effect*" as the outcome. The age of the infant should be recorded. Details of exposure during lactation should be incorporated in the special Clinical Category called *Lactation exposure* at the time of data entry in order to establish a register with outcomes.

4. Deaths

All deaths should be followed up to assess the cause, even if it seems most unlikely that death was related to the medicine. Deaths should be entered in the Died clinical category at data entry to compile a register for regular review with each collation of events. This facilitates assessment. With CEM, death rates can be calculated. This has particular advantages as rates can be used to measure changes in outcomes and can be compared between comparators. Differences may demonstrate greater effectiveness or greater safety. Numbers need to be adequate to make valid comparisons.

5. Lack of efficacy

Lack of expected efficacy should always be recorded as an event. The event terms "medicine ineffective" and "therapeutic response decreased" should be used as appropriate.

Reasons for lack of efficacy may be:

- medication not retained because of vomiting or severe diarrhoea;
- lack of patient adherence to treatment schedule;

[1] The Expert Safety Review Panel (or Advisory Committee) is a committee of experts that considers important safety issues and gives advice to the PvC and the regulatory authority. The committee's composition and role is described in *The safety of medicines in public health programmes: pharmacovigilance an essential tool*. Geneva, World Health Organization, 2006: p. 38.

- inadequate dose;
- poor quality medication;
- counterfeit medication;
- incorrect diagnosis;
- interactions reducing blood levels;
- drug resistance.

6. Late onset reactions

A number of important and serious ADRs are late in onset or progressively worsen over time e.g. deafness after treatment with injectables. For some of the reactions that require further characterization, the programme managers may decide to continue monitoring the patients being treated without withdrawing the suspected medication until the natural history of the problem becomes clearer or until the risks to the patients become unacceptable. In the latter case a decision may be made to monitor these patients after the suspect treatment is withdrawn in order to develop an understanding of the degree of reversibility of the problem. Special event terms and definitions may be needed to record changes as a toxicity progresses. The clinical experts should suggest what terms are needed and they can be added to the event dictionary.

7. Co-morbid conditions

Patients may be more susceptible to particular ADRs if they also have other health problems, either because of the concomitant condition or from the interaction of the medicines being used to treat the other condition(s). HIV/AIDS, malnutrition, and malaria are examples of concomitant illnesses that may result in such problems. Concomitant conditions should therefore always be recorded and they can then be tested statistically as risk factors for events of interest.

I. Signal identification

(For spontaneous reporting, targeted spontaneous reporting or cohort event monitoring.)

1. Introduction

A signal is defined as: *Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously* (WHO).[1]

Usually more than a single report is required. Alternatively, several similar events have been identified with a strong relationship to a medicine ("certain" or "probable") and there does not seem to be good evidence anywhere of these events being recognized as a reaction. Events coded as "possible" can be used as supporting evidence. A group of unexpected deaths coded as "possible" forms an exception to this general rule and will need to be taken seriously. Occasionally a single event (certain or probable), notable for its severity, seriousness or distinctiveness, can be regarded as a signal. There may be one or two case-reports in the literature, but this is insufficient as validation and the signal needs to be strengthened.

The identification of signals in the PvC's database (or another database) of adverse events or suspected ADRs requires careful review of individual reports and events. Careful, informed, routine, systematic and standardized clinical review of the Centre's reports with the recording and appropriate collation of good data is the surest way of identifying previously unsuspected ADRs. Following through the whole process from relationship assessment, to signal identification, to signal strengthening, to communicating the findings is essential.

The data in the report(s) need to be of good quality if a signal of a new ADR is to be considered. There should be sufficient data to fully assess the relationship of the drug to the event. Selecting only those reports with a certain

[1] Safety Monitoring of Medicinal Products: Guidelines for Setting Up and Running a Pharmacovigilance Centre (see Annex 1).

or probable relationship ensures this. The strongest signals will have several reports with a certain or probable relationship. A signal may possibly be identified from one distinctive "certain" report. If there are no "certain" reports, at least three "probable" reports would be necessary for a signal. The first reports in a signal with a certain or "probable" relationship are called "**index cases**". Cases coded as "unclassified" or "unassessable" should not be considered in the investigation of a signal.

The "unlikely" events should be scrutinized on a regular basis because they may contain hidden or unrecognized reactions. A cluster of similar events of significance may suggest an unexpected reaction that was not recognized at the time of clinical assessment. However, they should not be included in the assessment of a signal for which there are reports with certain, probable or possible relationships because differences could mask the characteristics of the signal being investigated.

2. Selection criteria for events to investigate

- There are good data.
- The event is clinically relevant.
- There have been several reports of the event that show a credible and strong relationship with the drug (certain or probable).
- If validated, the event is of sufficient importance or interest to:
  - require regulatory action;
  - require advice to prescribers;
  - be of scientific importance.

3. Methods of signal identification

There are four methods for identifying signals:

1. Clinical assessment of individual events
2. Clinical review of collated events
3. Record linkage
4. Automated signal detection.

1. Clinical assessment of individual events

Careful, routine, standardized clinical assessment of individual reports with alertness to the possibility of a signal, offers the quickest method of identifying signals.

During routine assessment of incoming reports, if an assessor identifies an event and thinks that it could be a new type of ADR, a search should be undertaken for records of other similar events to confirm the opinion.

- First, the database should be checked for other similar reports or clinically related terms.
- References should be checked for information on ADRs (Annexes 1 and 5). *Martindale, The complete drug reference* and *Micromedex online drug reference* are reliable references. *The Physicians Desk Reference (PDR)* is useful although entries consist of data sheets provided by pharmaceutical companies and contain many references to possible reactions that are not validated and the information is often difficult to interpret.
- If there is no reference to the occurrence of the event as an ADR, proceed with its investigation.

2. Clinical review of collated events

All the events in the database for the drug(s) of interest (or class of drugs) should be reviewed at regular intervals e.g. each month.

This review is facilitated by collating (sorting) the events, using a computer program, into a clinically oriented structure so that the overall clinical picture of events occurring with the drug or regimen can be viewed. This is accomplished by sorting the event terms by the events dictionary codes (see Section E.6.2.6).

To collate the events:

- Each event should have had a term applied to it that is selected from the events dictionary and the individual events should have been assessed. There is a dictionary code ("print code") for each of these terms and this should be added to the database with the terms during data entry. Using CemFlow the application of the code is automated.
- The dictionary terms are coded in such a way that clinically related events appear together when the events are sorted by code.
- The events can then be printed out or viewed on the computer monitor in a systematic clinical structure. Groups of related events are then seen clearly.

For instance in the investigation of a skin eruption as a possible signal, all possibly related events and conditions should be considered together, such as dermatitis, dermatitis exfoliative, Stevens Johnson syndrome, rash, and rash erythematous. The events dictionary terms are coded in this clinically relevant way. An illustration of how to develop and validate a signal can be consulted at Coulter DM, Clark DWJ. Disturbance of vision by COX-2 inhibitors. *Expert Opinion on Drug Safety*, 2004, 3:607–614.

At the point of collation of all the events in the database into their clinical categories and sub-groups, using CemFlow, four special reports will be produced in addition to the general collation. These should also be reviewed for potential signals.

1. Concomitant medicines
   These are listed in the report together with the events reported while they were in use. This listing can signal interactions.
2. Pregnancy register
3. Lactation exposure
4. Died

This perhaps unusual term is used to indicate that the patients died from whatever cause (and the causes will be listed) without any implication of an adverse effect of the medicine. This is necessary for event monitoring where the recording of events implies no cause and effect relationship. The use of the terms "Fatal" or "Deaths" might carry the implication that the death was caused by the medicine or regimen being monitored and should be avoided because of the risk of creating a drug scare.

Deaths should be entered with the cause(s) given. The causes of death should be collated within this category in the same way as events generally, using the dictionary code, so that they appear in clinically meaningful groupings. Any clinical patterns associated with death can then be seen easily. Rigorous validation procedures should then be applied to any suspicious patterns forming a signal.

Signals of interactions

All medicines used in association with the monitored medicines or regimen will be entered into the database and listed in a special report called "Concomitant medicines" at the time of the general collation. Each additional medicine is listed together with the events that occurred while it was being used, in order to facilitate visual identification of signals of possible interactions. It is a record of events occurring when more than one medicine is being used.

There is the possibility that unexpected reactions may have been coded as "unlikely" and represent missed signals. Records of these events should be examined regularly for any unexpected patterns. If unexpected patterns emerge, they should be treated as signals and investigated as described in Section I.

3. Record linkage

Record linkage depends on the availability of a unique identifier for patients in the health system or in hospital records. This same identifier must also be recorded with the patient details in the cohort database. It can then be used as a tool to gather additional events data such as details of hospital admission. The process involves matching the patient identifiers in the cohort with patient identifiers in any available databases or registers (e.g. register of deaths or hospital admissions). When the patient records are linked in this way, it is possible to see, for example, if the patient has died and the date and cause of death; if the patient has been admitted to hospital and the diagnoses; or if the patient has been diagnosed with a disease of special interest, for which a register has been created (e.g. drug-resistant TB).

The results of the linkage are then added to the records of events for the patients in the cohort. An unexpectedly high rate of a particular event (e.g. dystonic reactions or liver damage identified from hospital discharge diagnoses), may represent a signal.

Identifying signals in "real time" by clinical evaluation during routine assessment and regular review of the events in the database for a drug, will find most signals earlier than automated methods will.

4. Automated signal detection

The UMC regularly scans the WHO database for potential signals using advanced methods of data mining (see www.who-umc.org/graphics/25294.pdf). Automated methods can strengthen a signal identified by clinical evaluation. They may identify signals that were missed during assessment of the reports and later review. The analysis runs on all reported ICSRs worldwide and therefore offers a greater chance of finding more reports of the suspect drug–event combination.

J. Evaluating a signal

1. General approach

Validating a signal is generally a process of gradual strengthening arising from new findings in pharmacovigilance or research. The process entails examining other available data and also examining your own data in greater depth according to the following principles:

- reviewing other experience;
- searching for non-random patterns;
- comparison with control events;
- reviewing the pharmacology;
- undertaking epidemiological studies;
- communication and feedback.

2. Other experience

- Look for similar reports in the database, of **related clinical events** within the same clinical category (CEM) or system organ class (spontaneous reporting), for the suspect drug and not simply a single event term. Also, look at **related drugs** in the same ATC classification grouping.
- You can also search the worldwide WHO database using VigiBase. You can request the Information Component (IC) value for the drug-event combination from the WHO database at the UMC. This will indicate if the particular drug–event combination has been reported more often than would be expected. It is available to users of VigiFlow or CemFlow as one of the analysis tools. The IC value for a drug–event combination can be obtained through the online VigiLyze tool provided by the UMC.
- You can also ask for information held by other National Centres through the VigiMed e-mail network coordinated by the UMC.
- Search the literature for similar reports, using search tools such as PubMed or Micromedex.

- Ask the pharmaceutical company if they have identified the problem in trials data or received similar ICSR reports and ask for details. Were similar events identified in preclinical studies? Has this event or have any similar events been identified in postmarketing CEM (prescription event monitoring – PEM – or IMMP) programmes?

3. Searching for non-random patterns

Examination of data on a group of reports may show patterns that are not random and, in the absence of biases, non-random patterns suggest that the events may be related to the medicine. Several of the following can only be assessed using CEM.

Onset times

Does the range of onset times cluster around a particular period (e.g. 5 days or 3 weeks), or are the onset times scattered randomly over time? Life-table or survival analysis are useful tools for confirming this. Survival analysis is also useful for examining the difference in onset times between patients on the medicine of interest and a comparator; e.g. if the event occurs earlier in patients on the medicine of interest than in those on the comparator a drug-event effect needs to be considered.

Mean dose

Is the mean dose significantly higher in those who experienced the event being studied than in those in whom the event did not occur?

Mean age

Is the mean age of patients in whom the event occurred significantly different from that of those who did not experience the event?

Sex differences

When compared with the cohort, are the rates of the event in men and women significantly different? A drug effect could be one reason for this.

4. Comparison with control events

Should a group of events in the post-treatment group be suspected of signalling a reaction, the rate should be compared with the same event terms

from the pre-treatment data. A higher rate for the suspect events in the post-treatment group which is statistically significant would provide confirmatory evidence of a causal relationship with the monitored medicine(s).

Those events coded as incidents (non-reactions) (see Section G.4) should represent the background morbidity and can be used as an internal control. If, for example, the suspect events showed different characteristics from the incidents, this would suggest a causal relationship with the monitored medicine(s).

5. Pharmacology

Is there a plausible pharmacological mechanism by which the medicine could cause the event?

Have other drugs in the same class caused a similar problem and has a mechanism been described for the related drug(s)?

Note that with a new medicine there may not be a known mechanism for a new ADR. Sometimes the study of a previously unidentified ADR brings to light new knowledge about the pharmacology of the medicine.

6. Undertaking epidemiological studies

Investigative epidemiological studies may be needed if the event seems important. These studies may require collaboration with others who have expertise in this field. Such studies include cohort studies, case–control studies, record linkage studies or population database studies.

7. Communication and feedback

Effective, well-presented communication of a signal to the various stakeholders will supply information and give you feedback on its validity and its importance. The following stakeholders can provide invaluable advice:

- Expert Safety Review Panel and/or regulatory authority;
- health practitioners;
- the UMC;
- the pharmaceutical company;
- country ADR bulletin;
- letter or report to a medical journal.

K. Identifying risk factors

1. Introduction

A risk factor is a characteristic associated with an increased probability of occurrence of an event. In the presence of a risk factor, a patient is more likely to develop an ADR. Knowledge of risk factors provides a means of avoiding or minimizing the number of ADRs they relate to. Risk factors may be associated with the patient (e.g. age, weight, height, BMI, genetic polymorphism (CYP 450 enzymes), pregnancy, concomitant illness (e.g. HIV/AIDS), renal or liver damage) or the medicine, including dose, duration of therapy, previous exposure (allergic type reactions), and concomitant medicines. Other substances in the patient's environment, such as tobacco, alcohol, diet (e.g. grapefruit juice), and traditional medicines may also influence the outcomes.

2. Identification

Knowledge of the pharmacodynamics and pharmacokinetics of a drug may allow certain ADRs to be predicted, but does not identify them.

Risk factors for certain ADRs might be identified in clinical trials. However, these trials are not designed to examine safety issues and the opportunity to do so is limited because of small numbers of participants and the lack of potential confounders (e.g. concomitant medicines).

Clinical experience might create the impression that certain characteristics are risk factors, but these impressions are unreliable. It is necessary to compare rates of the characteristics between those with and without the reaction.

Risk factors cannot be identified with certainty from spontaneous reporting because of the absence of rates. For instance, an observed association of an event with age may be due to the age distribution of the population from which the patients who experienced the event came.

In CEM, knowledge of the characteristics of the whole cohort makes it possible to measure the differences between patients in whom ADRs occur and those in whom they do not and thus to identify risk factors. The simplest approach is to measure the rate of a characteristic in patients from the cohort

who have experienced the ADR under investigation, and compare it with the rate in patients in the cohort in whom the reaction did not occur. The relative risk (RR) can then be calculated by dividing the rate in those who did have the reaction by the rate in those who did not have the reaction.

Confidence intervals (CI) should also be calculated in order to assess the statistical significance of any difference found. This method is subject to biases or confounders because of possible differences between the two groups e.g. concomitant medicines or prescribing bias. These differences might be multiple e.g. concomitant disease plus cigarette smoking.

Multiple logistic regression is a powerful statistical method that will control for several characteristics (e.g. age, dose, concomitant medicines) in one calculation and identify risk factors reliably. If you wish to employ this method it is best to consult a biostatistician.

Case–control studies can be undertaken to examine characteristics for which no data have been collected. As an example, abnormal renal function might be suspected as a risk factor. To investigate this, a sample of patients who have had the ADR under investigation is selected together with a matching sample of patients in the cohort who did not have the ADR. Renal function tests are then undertaken and the rates of abnormal function calculated for each group. The RR for the reaction group is then calculated. Confidence intervals for the RR will reveal whether any difference found is statistically significant and if abnormal renal function is a risk factor. (This is called a "nested" case–control study.) This type of study can be used to identify the influence of any genetic polymorphism. The risk of bias may be high, particularly if controls are not selected properly.

L. Data description and analysis

Different methods to describe and analyse data have been mentioned in this handbook. CemFlow and VigiFlow have built-in analytical programs.

Data tabulation is the simplest way to summarize reporting frequencies by sex, age-groupings, treatment centre or site. Events collation consists of tabulation of events by suspected drug or clinical category showing individual patient data on sex, age, dose, duration to onset, relationship, and outcome. Tables may compare relative risks for important events pre- and post-treatment. Aggregated information can also be presented helpfully as bar graphs.

Simple statistical techniques will suffice for the types of analyses needed:

- Means of variables such as age may be compared using the t-test.
- The risk can be calculated as a rate for any event or group of events.
- The attributable risk is the difference between the absolute risk (rate in the treated group) and the rate when the cohort was not exposed to the medicines (the control period). The difference represents the risk associated with exposure to the monitored medicine(s). This does not apply to events of late onset in the context of the protocol outlined in this handbook. Rates are usually expressed with their confidence intervals to reflect uncertainty of estimates.
- Life-table (or survival) analysis may be used to identify the duration to onset for every patient who experienced the event and it calculates the rates for patients in whom the event has occurred (or the survivors) at specified points in time. This can be used to measure the range of onset times of any event and to assess if there is a non-random relationship with the drug.
- Multiple logistic regression is used to adjust estimates of effect related to different risk factors.

BOX 2

Advantages and disadvantages of different types of pharmacovigilance

Spontaneous reporting

Advantages

- It is administratively simpler and less labour-intensive than cohort event monitoring (CEM).
- It is less costly than CEM.
- Pharmacovigilance centres (PvCs) and health professionals are more likely to be familiar with this method as it is the most common method of pharmacovigilance used.
- It provides safety surveillance throughout the marketed life of all medicines.

Disadvantages

- The data collected by this method are incomplete. In developed countries, fewer than 5% of reactions are reported.
- Reliable rates cannot be calculated and so risk cannot be measured and risk factors cannot be established with confidence.
- There are strong biases in reporting.
- Deaths are poorly reported.
- Special studies will need to be set up to obtain accurate information on areas of particular interest e.g. pregnancy, children and specific events of concern. These special studies add to the cost and in turn reduce the cost advantage of spontaneous reporting.

Targeted spontaneous reporting (TSR)

Advantages

- It is simpler and less labour-intensive than CEM.
- There is no baseline measurement as in CEM.
- TSR represents an "add-on" to the routine monitoring of outcomes of TB patients.
- It can be focused on priority ADRs.
- The forms and routes for reporting are similar to those for routine spontaneous reporting.

Disadvantages

- The method is subject to individual willingness to monitor and report. Thus numerator (number of individuals with the adverse reaction) may not be accurate.

- Completeness of reporting is therefore crucial.
- There is limited experience with TSR and the technique needs to be field-tested.

Cohort event monitoring

Advantages

- the ability to produce rates;
- the ability to produce a near complete profile of the adverse events and/or adverse drug reactions for the medicines of interest;
- very effective in identifying signals at an early stage;
- the ability to associate reactions with risk factors;
- the ability to make accurate comparisons between medicines;
- the ability to establish a pregnancy register and identify problems with pregnancy and common congenital abnormalities;
- the method, using routine follow-up, can detect reduced or failed therapeutic effect and thus raise suspicion of inaccurate diagnosis of disease, poor prescribing, inadequate adherence to treatment, emerging resistance or poor quality or counterfeit medicines;
- the ability to record and examine details of all deaths and provide rates of death;
- the ability to produce rapid results in a defined population;
- because the method looks intensively at drugs of great interest in a specific area of need, and provides clinically significant results rapidly, it stimulates interest in drug safety in general;
- the method provides sound evidence with which to deal with any drug scares, give early warning of interactions with concomitant medicines (e.g. antiretrovirals) and the need to undertake any necessary regulatory changes.
- the characterization of the reactions allows for better risk management and a reduction in non-adherence. Overall there should be a better outcome for the patients and for the TB programme which should be cost-effective.

Disadvantages

- The method is more labour-intensive and more costly than spontaneous reporting.
- It will be new to health professionals and PvCs, and training in its use will be necessary.

M. Organization

1. Legislation

1.1 Legal authorization

Spontaneous reporting and CEM programmes form the data collection backbone of pharmacovigilance activities. Pharmacovigilance is non-interventional and will not create any physical risk to patients. Spontaneous reporting and CEM programmes are not clinical trials. They are methods of public health surveillance requiring the collection of certain types of data in the public interest. Public health surveillance is frequently conducted under specific laws authorizing or requiring the collection of certain types of data. In some countries, reporting on the risks associated with medicines is mandatory. All medicines are subject to spontaneous reporting. Selected medicines, that are to be used widely and are of public health importance should be subject to CEM where possible, particularly new medicines or medicines being introduced to a previously unexposed population. Anti-TB treatment and ARVs are prime examples. National leaders of public health programmes and pharmacovigilance should advocate the legal endorsement or requirement for pharmacovigilance activities.

1.2 Conditional registration

The legal status of collection of data for pharmacovigilance can be reinforced by further legal requirements or regulations that require specified new medicines of public health importance to be subject to CEM before full registration is granted. Conditional registration can be offered until the outcome of a CEM programme is known, at which time full registration can be approved or declined on the grounds of safety.

1.3 Regulation of professional standards

In many countries the standards of health professionals are maintained and improved by compulsory continuing medical education (CME). It is justifiable for CME credits to be given for pharmacovigilance activities. Sending spontaneous reports or CEM questionnaires to the PvC displays, on the part of the health professional concerned, professional responsibility, good medical practice and involvement in activities that improve the standard of patient care

and safety. In addition, the activity provides a learning process both through the completion of the forms, which requires thinking about safety issues, and through the feedback received from the PvC. Professional associations should be encouraged to include spontaneous reporting and CEM in their approved CME activities.

2. Ethical issues

Ethical principles must be applied consistently to all types of pharmacovigilance methods. The ethics of collecting data for CEM, in particular, have special features since it is a methodology which requires the collection of detailed personal data and sometimes stores these data for indefinite periods. There may often be a need for follow-up at a later date for the further study of any safety concerns identified, at which time there will be a need to conduct investigations such as a more detailed cohort study, nested case–control studies, comparative safety studies, subgroup investigations (e.g. in children) or even a full clinical trial.

Before starting a CEM programme, there must be open discussions with all the stakeholders including patients. Most importantly, early in the planning stage, endorsement must be sought from the health ministry without whose support little will be achieved. Open communication must follow with professional organizations, all health providers, the pharmaceutical industry, the general public, community leaders and the media.

2.1 Prerequisites to collecting patient data

It is important to seek the approval of the highest appropriate authority in the country. This may be the Minister of Health or the regulatory authority.

It is important to declare publicly what data are being collected and why. The stated purposes should be broad enough to include:

- long-term follow-up looking for signals of delayed reactions;
- use of the data to enable follow-up investigations such as nested case–control studies to be undertaken to identify risk factors. It is not always possible to predict what additional studies might be needed for the investigation of safety issues that are identified during monitoring, and so approval should be sought for storage of the data to enable further investigations if necessary;
- follow-up studies required to validate signals;
- comparative studies with new anti-TB agents or regimens.

Security and confidentiality arrangements should be publicized and should conform with any national legislative requirements.

2.2 Training of staff

Staff members responsible for pharmacovigilance need to be trained in the strict maintenance of security and confidentiality.

After appropriate instruction they should be required to sign a document saying that they understand the privacy issues and agree to maintain security and confidentiality.

2.3 Security issues

Because it is essential to record personal identifiers, the security, privacy and confidentiality of personal data need to be strenuously maintained. Pharmacovigilance will not work properly if personal identifiers are not available. With both spontaneous reporting and CEM programmes, the ability to follow up specific patients on important outcomes is essential. With CEM, which can measure risk (incidence) and identify risk factors, it is essential that duplicate entries are avoided so that the accuracy of these findings is not compromised by an inflated denominator, and this can only be done if patients can be correctly identified. This necessity for recording patient identifiers therefore imposes strict conditions on maintaining data security. These are outlined below:

- Data that might identify patients should be stored on computers with no Internet link. This prevents access by hackers. This precaution will be impractical and unnecessary for those using VigiFlow or CemFlow.
- Access to a computer that has data on it that might identify patients should be controlled by password.
- Password access should be given only to those people involved in the particular pharmacovigilance activity.
- Access to the premises should be security controlled.

2.4 Use of data

- The data collected should be used only for the purposes declared.
- Personal identifiable data should not be given to any other parties including pharmaceutical companies, government or ministry officials, agencies and research groups. This includes personal details of patients or reporters. Only anonymized data may be shared.

2.5 Confidentiality

- No published data, including reports, should contain any information that could identify patients.
- Staff should not take any identifiable data home or to other places outside the PvC or monitoring centre.
- Staff should not discuss information outside the monitoring centre that could lead to the identification of any patient.

2.6 Informed consent

If pharmacovigilance activities, spontaneous reporting and CEM, are authorized or required by law, informed consent from individual patients is not required for the collection of data required for safety monitoring. However all the privacy conditions outlined above should be strictly observed.

Programme managers should avoid attempting to obtain individual informed consent if at all possible because it will be time-consuming to try to explain the concepts of pharmacovigilance (which will often be culturally strange) to each patient, will increase complexity and add to the cost, and could potentially compromise the validity of the results if many patients refuse to be enrolled. A CEM programme is **not** a clinical trial or research study and does not interfere with treatment in any way. It is simply a process of observation of normal practice and data collection in the interests of public health.

An alternative to obtaining informed consent from individual patients is to provide information publicly and to give patients leaflets which they can study, or have explained to them away from the pressure of the clinics, and which provide them with contact details for the health facility and PvC so that they can object to having their data stored if this is their decision. Their data can then not be entered or if they have already been entered, they will be deleted. This is called the "opt out principle" which operates in a number of countries and, if needed, is much more practical than individual informed consent.

This approach has been endorsed by competent authorities internationally.[1]

[1] Council for International Organizations of Medical Sciences. *International ethical guidelines for epidemiological studies*. Geneva, CIOMS, 2009: pp. 37, 42–43.

3. Structure

3.1 Pharmacovigilance centre (PvC)

The development of a PvC and its relationship to public health programmes is discussed fully in other WHO publications – *Safety monitoring of medicinal products: Guidelines for setting up and running a Pharmacovigilance Centre*, WHO, 2000 and *The safety of medicines in public health programmes: Pharmacovigilance an essential tool*, WHO, 2006 (see Annex 1).

3.2 CEM centre staff

It is essential that the PvC has sufficient additional capacity to run CEM studies. Clearly defined roles to suit local conditions would need to be formulated. For two parallel CEM studies (i.e. a comparator study of two medicines or regimens) to be undertaken, it is suggested that the following personnel would be necessary.

Secretary/manager

This person would function as an administrator (see Section E.3). There would be additional administrative duties to those described, including the printing, supply and distribution of stationery.

Clinical supervisor/reviewer

A full-time clinical supervisor who would be in charge of the monitoring, reviewing and clinically related activities. This person would:

- review the events reported on the questionnaires and would undertake relationship assessment, arrange follow-up of reports as required, liaise with the NTP manager, request appropriate data analysis, report regularly to the Expert Safety Review Panel in conjunction with the TB programme manager and consult them about any concerns arising from the data, any reports of serious events, any signals of new ADRs and issues of risk management;
- be responsible for communication in collaboration with the NTP manager. This would involve promotional activities as outlined in Section E.3;
- be responsible for the training of Centre and peripheral staff.

Data manager

A full-time data manager would maintain the database, be responsible for quality assurance, ensure security and confidentiality of data, be responsible for collating the data at agreed intervals and producing reports as required,

ensure the supply of questionnaires to all health facilities, train and supervise the data processors and generally assist the clinical supervisor.

Data processor(s)

One or two full-time data processors (operators) need to be employed for the duration of the monitoring programme. They would be responsible for data entry and certain other tasks under the supervision of the data manager.

3.3 Field staff for CEM

Field coordinator

Field staff will be under the supervision of a person with the role of field coordinator who will be responsible to the clinical supervisor of the CEM programme and may need to interact with the TB programme manager.

A CEM focal person

A CEM focal person will need to be appointed to each monitoring site to be responsible for the following:

- to ensure the collection of the data required for the CEM programme using whatever method is agreed to for the TB clinic at that site (see Section E.5);
- to ensure collection and delivery of completed questionnaires;
- to maintain a local register of patients included in the CEM activity, to note appointments made for follow-up at the TB clinic and, in liaison with staff at the TB clinic, to help ensure follow-up of patients who miss their return appointment;
- to maintain a register of pregnant women on TB treatment and to note their return appointment times;
- to ensure follow-up of pregnant women if they miss their follow-up visit to the TB clinic. The focal person will also need to liaise with antenatal clinics and birthing facilities to collect follow-up data on the pregnancy and the outcome of childbirth.
- to ensure follow-up of all deaths in order to find out the history of events leading to death, the cause of death and the date of death.

Data recorder

A data recorder will need to be appointed to each monitoring site if the clinic staff cannot cope with this work. The data recorder will be responsible to the

CEM focal person and will use the methodology agreed locally for completing the questionnaires.

Support

The field coordinator will be available to facilitate the work of the CEM focal person and data recorder at the monitoring sites. This may include soliciting the help and coordination of the staff at the PvC, TB programme personnel, and staff at the antenatal, paediatric and birthing units.

4. Communication[1]

Throughout this manual effective communication has been mentioned as being an essential part of good pharmacovigilance. This brief section gives an overview of some of the most important knowledge and skills in communication, without which even the best system will not fulfil its potential. The method and quality of professional communication is as important as the message itself.

The approaches need to be adapted for the target audience and can include personal meetings with people with influence in government and the ministry of health, regulatory authorities, academic institutions, hospitals, public health programmes, WHO offices, professional associations, the pharmaceutical industry, the privacy commissioner, the community and the media; presentations at meetings of professional groups e.g. hospital doctors, nurses and pharmacists (this is best arranged at one of their regular meetings); producing and distributing leaflets for health professionals and patients; producing posters for patients and the community and distributing them to pharmacies, hospitals and clinics; cultivating good relationships with key media journalists on newspapers, magazines, radio and television; promoting CEM as a newsworthy activity that will create a culture of safe use of medicines in civil society; encouraging a feeling of collegiality and collaboration among health professionals in the interests of the health of the community, rather than taking an authoritarian approach; and developing the detailed application of CEM methodology in consultation with the health workers in the hospitals and clinics.

4.1 Know your audience

It is critical to tailor all your materials and activities closely to the abilities and preferences of your many audiences. These days, even very serious people

[1] Contributed by Bruce Hugman: mail@brucehugman.net

have little time or short attention spans for printed materials especially, and everything needs to be as brief, clear and persuasive as possible. Not everyone will share your priorities and values, understand them or care about them, so it is important to know the state of mind of your recipients so that you deliver your message in a way that really does get under their skin. Remember that within just one audience (pharmacists, for example) there will be a very wide range of ability, literacy, motivation and so on. Get to know your audiences through direct engagement and exchange with them: such knowledge will pay dividends. One message in one format will never be suitable for all your audiences.

4.2 Seek feedback

One of the best ways to understand your audiences is to actively seek feedback from them about your materials and what you are doing. Always pilot test a project like the production of a reporting form or a new explanatory leaflet: find out what a range of recipients think about your work and then modify the content and the approach in the light of their views. Those of us working at desks in centralized offices often misjudge the minds of our recipients and so our messages don't get the attention they deserve or the response we hope for. Involve your audiences and constantly seek their views.

4.3 Give feedback and provide benefits

To stimulate collaboration and motivate colleagues, there needs to be some degree of real benefit from making the effort to report ICSRs, or to monitor public health programmes, or take part in other activities. At the lowest level, appreciation (a "pat on the back") is an essential, powerful motivator, but feedback about how information has helped improve patient safety, or a special newsletter for reporters and collaborators, or any other acceptable incentive will make a difference. There are still too many systems in which doctors, nurses and pharmacists are expected to help, but get no acknowledgement, appreciation or feedback at all. We cannot simply rely on people helping us without active encouragement.

4.4 Make your communications stand out

The competition for everyone's attention at every moment of the day is extreme, and health-care professionals the world over are buried in printed materials of all kinds – many of them attractive, impressive and influential, but many of them are still put in the bin without so much as a glance.

We need to be sure that our materials look attractive and professional and, as far as possible, irresistible! Reporting forms need to look engaging and

inviting, not merely produced amateurishly on a word processor in black and white. Some input from a graphic designer will make all the difference to the quality (and success) of forms and of every other piece of printed or electronic material. There may be a small initial cost, but that will be offset by the reduction in forms wasted and thrown away, and in increased interest and involvement. We are competing for people's attention, and need to take that challenge seriously. (Just look in any decent magazine and see how elegantly and powerfully commercial messages are promoted. Notice how important are pictures and visual quality in successful communications.)

4.5 Writing style

Writing is another of those advanced skills which every pharmacovigilance professional is expected to be born with. Good writing is hard work and is essential for effective communication. Try to use people whose writing skills are advanced already, but if there is no such person, follow these rules:

- Write in the simplest, clearest language suitable for the task.
- Get your main points over at the beginning, and repeat them at the end.
- Keep sentences and paragraphs short.
- Use subheadings and bullet points as much as you can.
- When there is a lot of subsidiary or supporting material, try to separate it from the main message, and put it at the end.
- Read your writing aloud to see how it sounds – this is one of the best tests possible.
- Get some members of your intended audience to read and comment on what you have written.
- Try to use pictures and simple graphics to support your words.

4.6 Repeat the message

Remember that in the hurly-burly of workaday life, many people will miss a message which is sent only once. *One communication is no communication*. Repeat your message again and again, in different forms and through different channels, until you know that people have received it and are being influenced by it – and that might take years rather than months. And then keep going: if people are not constantly reminded, they will forget. Changing people's attitudes, values and behaviour takes an immense amount of time and effort.

4.7 Get personal

The closer your communications get to being one-to-one, face-to-face, the more effective they will be. A mailing of a thousand leaflets will have far less effect than ten mailings of ten leaflets carefully tailored to subgroups of the audience. And, of course, mailings will have far less effect than meeting people in small groups or individually. Within the limits of your budget and resources, get as personally close to your recipients as you can.

4.8 Journalists

The media in all its forms can become powerful allies of health-care and patient safety if journalists are dealt with personally and professionally. Most bad press comes from alienated journalists who have never been contacted, briefed, or educated in the complexities of medicine. Get some training in media relations; meet some of your local editors and health journalists; explore what you can achieve together. Suspicion and avoidance simply generate more suspicion and hostility. (The UMC publication *Dialogue in Pharmacovigilance* contains guidance on media relations, and there are lots of books and useful websites). And – never say, "No comment".

4.9 Meetings

Meetings are the form of group communication which probably cause more anxiety and frustration, and waste more time than any other single activity. While they are sometimes productive, they are often depressing and demoralizing. Meetings can be well-run, short, effective and uplifting. Running effective meetings requires a very specific set of knowledge and skills which can be learnt by anyone keen enough to reduce the percentage of their own and other people's lives wasted sitting pointlessly in meeting-rooms. Again, there are lots of good books and websites which will reveal how staff meetings, seminars, conferences, and consultations can be made stimulating and productive. At the beginning of a meeting always ask these two questions:

- What are we hoping to achieve?
- How long will this meeting last?

4.10 The message

The safety of patients worldwide is served by dedicated professionals doing their work well, but that work will never reach its considerable potential without excellent supporting communications. Excellent communications require a degree of expertise, creativity and skill which not all officials and scientists have as a matter of course. In every organization there is likely to be someone

with a communications gift: look for them and use them if you can; otherwise put communications on your regular agenda as a high priority and give the activity of communicating as much attention as the content of what you wish to communicate. Failure to pay attention to the complexity and demands of effective communication lies at the heart of many of the most serious failures throughout health-care and regulation.

Annexes

Annex 1. Useful websites and other resources

1. World Health Organization

A great deal of information is available here, including access to WHO publications.

1.1 http://www.who.int/

1.2 http://www.who.int/medicines/areas/quality_safety/safety_efficacy/en/index.html

1.3 Anti-TB Programme

http://www.who.int/tb/
http://www.who.int/tb/challenges/pharmacovigilance/en/index.html

2. Uppsala Monitoring Centre (UMC)

This site provides very useful information about practical pharmacovigilance including definitions and advice on pharmacovigilance policy and access to various web based tools, some of which are listed below. The "Links" section provides links to the web sites of most of the existing national pharmacovigilance centres.

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

VigiFlow™

This is a web-based tool maintained by the UMC for database management of individual case safety reports (ICSRs) (spontaneous reports). It provides for data entry in an internationally standardized way.

Access requires an agreement with UMC and registration.

Contact: info@who-umc.org

VigiLyze

Provides access to and analysis of the WHO worldwide database of ADRs (ISCRs), VigiBase and its associated dictionaries: WHO Drug Dictionary, WHO Adverse Reaction Terminology and MedDRA. Access requires an agreement with the UMC. Contact info@who-umc.org

CemFlow™

CemFlow is a tool maintained by the UMC for database management in cohort event monitoring (CEM). It is web based and the fields match the data elements on the questionnaires. There are screens for patient demographics, treatment initiation, treatment review and assessment of events as well as

details of all medicines. Access is available to the appropriate terminologies and a search and statistics section.

Contact: info@who-umc.org (registration is necessary).

3. WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance

This centre is designed to promote and assist pharmacovigilance in Africa and elsewhere. A pharmacovigilance toolkit for countries is one resource that is offered to countries on this site (UMC-Africa).

http://www.pvafrica.org
http://www.pvtoolkit.org

4. European Medicines Agency

This is a useful resource on product information, current issues and regulatory actions.

http://www.ema.europa.eu/

5. Food and Drug Administration (FDA), USA

This is a useful resource on product information, current issues and regulatory actions.

http://www.fda.gov/

6. Communicable Diseases Centre, USA

This site has a lot of information and statistics on communicable diseases and medicines related to their treatment.

http://www.cdc.gov/

7. New Zealand regulatory web site

This is a good resource for data sheets for medicines and patient leaflets. It also has articles in *Prescriber Update*, many of which come from the National Pharmacovigilance Centre.

http://www.medsafe.govt.nz/

8. Natural Standard

The best and most authoritative web site available on herbal medicines. Users are required to register and pay a fee.

http://www.naturalstandard.com/

9. British National Formulary

A good and reliable resource for information on medicines.

http://bnf.org/bnf/

10. Low cost literature resource

The WHO Health Inter-Network Access to Research Initiative (HINARI). This provides free or very low-cost online access to the major journals in biomedical and related social sciences to local, not-for-profit institutions in developing countries.

http://www.who.int/hinari/about/en

11. Micromedex/Drugdex/Martindale

This is probably the most convenient and comprehensive source of information on medicines. Users are required to register and pay a fee. All three are available through this web site.

https://www.thomsonhc.com/home/dispatch/PFDefaultActionId/pf.

12. PubMed

This is a good literature resource. Abstracts are available free.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?CMD=search&DB=pubmed

13. Anatomical Therapeutic Chemical (ATC) Classification and codes

The ATC classification system of medicines is maintained by the WHO Collaborating Centre for Drug Statistics Methodology.

http://www.whocc.no/atcddd/

14. Defined Daily Dose (DDD)

This is a WHO statistical method for estimating patient drug consumption maintained by the WHO Collaborating Centre for Drug Statistics Methodology. It can be useful for estimating denominators with spontaneous reporting.

http://www.whocc.no/atcddd/

15. International Society of Pharmacovigilance (ISOP)

This is an important international society. Their web site gives information about meetings and training courses.

http://www.isoponline.org

16. International Society for Pharmacoepidemiology (ISPE)

This site is a useful source of information on the activities of the society and for guidelines on risk management and links to relevant information.

http://www.pharmacoepi.org

17. International Uniform Requirements for Manuscripts Submitted to Biomedical Journals

An essential resource when writing articles, this site gives guidance on structure of articles and formats for references.

http://www.icmje.org/

18. Reactions Weekly

http://adisonline.com/reactions/Pages/default.aspx

19. Pharmacoepidemiology and Drug Safety

http://www.interscience.wiley.com/journals/pds

20. Drug Safety

http://adisonline.com/drugsafety/Pages/default.aspx

21. *International Journal of Risk & Safety in Medicine*

http://www.iospress.nl/journal/the-international-journal-of-risk-safety-in-medicine/

22. *BMJ* (British Medical Journal)

Free access to some articles is available and the table of contents for each issue can be seen.

http://bmj.bmjjournals.com

23. Medline

This site gives access to a list of journal abbreviations. It is an essential resource for compiling literature references and checking the details of journals referred to in articles in the literature.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Journals&itool=toolbar

24. Cytochrome P450 enzymes

A listing of the enzymes with the medicines affected is provided. This is a useful resource when researching possible interactions.

http://medicine.iupui.edu/flockhart/table.htm

25. International Classification of Diseases (ICD-10)

An electronic searchable version of ICD-10 is available on this web site.

http://www.who.int/classifications/apps/icd/icd10online/

Published resources

1. World Health Organization

Safety monitoring of medicinal products: Guidelines for setting up and running a Pharmacovigilance Centre. Uppsala, Sweden, The Uppsala Monitoring Centre, 2000.

http://apps.who.int/medicinedocs/en/d/Jh2934e/

Safety of medicines: A guide to detecting and reporting adverse drug reactions. Geneva, World Health Organization, 2002.

http://apps.who.int/medicinedocs/en/d/Jh2992e/#Jh2992e

The importance of pharmacovigilance: Safety monitoring of medicinal products. Geneva, World Health Organization, 2002.

http://apps.who.int/medicinedocs/en/d/Js4893e/#Js4893e

The safety of medicines in public health programmes: Pharmacovigilance an essential tool. Geneva, World Health Organization, 2006.

http://apps.who.int/medicinedocs/documents/s14085e/s14085e.pdf

A practical handbook on the pharmacovigilance of antimalarial medicines. Geneva, World Health Organization, 2008.

http://apps.who.int/medicinedocs/en/m/abstract/Js16881e/

A practical handbook on the pharmacovigilance of antiretroviral medicines. Geneva, World Health Organization, 2009.

http://apps.who.int/medicinedocs/en/m/abstract/Js16882e/

Treatment of tuberculosis guidelines, 4th ed. Geneva, World Health Organization, 2010.

http://www.who.int/tb/publications/tb_treatmentguidelines/

Guidelines for the programmatic management of drug-resistant tuberculosis. Geneva, World Health Organization, 2008. WHO/HTM/TB/2008.402.

http://whqlibdoc.who.int/publications/2008/9789241547581_eng.pdf

Management of MDR-TB: a field guide – a companion document to guidelines for programmatic management of drug-resistant tuberculosis: integrated management of adolescent and adult illness (IMAI). Geneva, World Health Organization, 2008 (WHO/HTM/TB/2008.402a).

http://whqlibdoc.who.int/publications/2009/9789241547765_eng.pdf

Guidelines for the programmatic management of drug-resistant tuberculosis, 2011 update. Geneva, World Health Organization, 2011 (WHO/HTM/TB/2011.6).

http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf

2. Other

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Harrison-Woolrych M, Coulter DM. PEM in New Zealand. In: Mann R, Andrews E, eds. *Pharmacovigilance*, 2nd ed. Chichester, John Wiley, 2007:317–332.

Shakir Saad AW. PEM in the UK. In: Mann R, Andrews E, eds. *Pharmacovigilance*, 2nd ed. Chichester, John Wiley, 2007.

Coulter DM. Signal generation in the New Zealand Intensive Medicines Monitoring Programme. *Drug Safety*, 2002, 25:433–439.

Coulter DM. Privacy issues and the monitoring of sumatriptan in the NZ IMMP. *Pharmacoepidemiology and Drug Safety*, 2001, 10:663–667.

Hugman Bruce. *Healthcare communication*. Pharmaceutical Press, London, 2009. www.pharmpress.com

Reporting adverse drug reactions: Definitions of terms and criteria for their use. Geneva, Council for International Organizations of Medical Sciences (CIOMS), 1999.

Contacts for pharmacovigilance and TB

1. World Health Organization, Geneva, Switzerland

Quality Assurance and Safety: Medicines

Dr Shanthi Pal
Department of Essential Medicines and Pharmaceutical Policies
Email: pals@who.int

Stop TB Department

Dr Dennis Falzon
Stop TB Department
Email: falzond@who.int

2. WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden

Dr Marie Lindquist
Email: info@who-umc.org

Mr Sten Olsson
Email: sten.olsson@who-umc.org

Mr Magnus Wallberg, VigiFlow & CemFlow
Email: Magnus.Wallberg@who-umc.org

3. WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance, Ghana

Dr Alex Dodoo
University of Ghana Medical School
PO Box GP4236, Accra, Ghana
Website: www.pvafrica.org
Email: alex.dodoo@who-umc.org

4. Cohort Event Monitoring advice

Dr David Coulter
264 Highgate
Dunedin 9010
New Zealand
Email: dmcoulter@xtra.co.nz

Annex 2. Form for spontaneous reports of suspected ADRs (Ghana)

PATIENT DETAILS

Last name:	Other names:	Title:	Sex: ☐ M ☐ F
Address:		Town/City:	Region:
District:	Region:		
Date of birth: … /… /…..	Age: …… years …… months	Weight (kg):	Height (m)

SUSPECTED DRUG(S) Please add details of additional suspected medicines on a separate sheet if necessary

Brand name	Dose & frequency	Date	Source of drug
Generic name	Total no. of tablets or doses taken	Started	☐ Hospital pharmacy ☐ Community pharmacy ☐ Chemical sellers shop ☐ Herbalist/street seller ☐ Friend/relative ☐ Other, please specify .....
Batch no. (if known)			
Indications for use	Strength of tablet or dose (mg):	Stopped	Was the drug prescribed ☐ Yes ☐ No ☐ Do not know

DETAILS OF ADVERSE EVENT

Date event started: …/…/….. Date event stopped: …/…/…..

Description of event

Treatment or action taken

Outcome (please tick all that apply)
☐ Recovered without sequelae (Please describe sequelae) .....
☐ Ongoing
Do you consider reaction to be serious?
☐ Yes ☐ No ☐ Recovered with sequelae
☐ Other

Do you consider reaction to be serious? ☐ Yes ☐ No
If yes, please indicate why the reaction is serious by ticking one of the boxes below:
☐ Patient died due to reaction ☐ Life threatening
☐ Congenital anomaly ☐ Permanent disability
☐ Required/prolonged hospitalization
Date admitted: …/…/….. Date discharged: …/…/…..
☐ Other outcome, please specify .....

Has the patient taken the suspected medicine before? ☐ Yes ☐ No ☐ Do not know
If yes, was this event observed? ☐ Yes ☐ No ☐ Do not know

LIST OF ALL OTHER MEDICINES TAKEN IN THE LAST 3 MONTHS ☐ NO OTHER MEDICINES Please include medicines not prescribed by a doctor, and any herbal or natural drugs. Continue on a separate sheet if necessary.

Name of drug	Indication (Why was the medicine taken)	Dose & frequency	Date started	Date stopped	Was the drug prescribed?
					☐ Yes ☐ No
					☐ Yes ☐ No
					☐ Yes ☐ No
					☐ Yes ☐ No
					☐ Yes ☐ No

ANY OTHER RELEVANT DETAIL
(e.g. Laboratory test results, allergies or other medical history.) Continue on a separate sheet if necessary.

REPORTER ☐ Doctor ☐ Pharmacist ☐ Nurse ☐ Other (please specify)

Last Name:	Other Name(s):	Title:
Address:		Town/City
Telephone number:	Fax:	Email:
Signature:		Date:

Please return this form to: The National Centre for Pharmacovigilance, CTCPT, University of Ghana Medical School, 2nd Floor Medical Block Building, Korle-Bu Teaching Hospital, Box 4236, Accra, Ghana Tel: 021-675885; Fax: 021-668219

Annex 3. Relationship between sample size and probability of observing an adverse event (AE)

Per cent probability of observing at least one AE in the sample by expected incidence of AE

	expected AE incidence: 1 event out of … patients						
sample size	**100**	**200**	**500**	**1 000**	**2 000**	**5 000**	**10 000**
200	86.47	63.21	32.97	18.13	9.52	3.92	1.98
300	95.02	77.69	45.12	25.92	13.93	5.82	2.96
500	99.33	91.79	63.21	39.35	22.12	9.52	4.88
700	99.91	96.98	75.34	50.34	29.53	13.06	6.76
1000	100.00	99.33	86.47	63.21	39.35	18.13	9.52
1500	100.00	99.94	95.02	77.69	52.76	25.92	13.93
2000	100.00	100.00	98.17	86.47	63.21	32.97	18.13
3000	100.00	100.00	99.75	95.02	77.69	45.12	25.92
5000	100.00	100.00	100.00	99.33	91.79	63.21	39.35
7000	100.00	100.00	100.00	99.91	96.98	75.34	50.34
10 000	100.00	100.00	100.00	100.00	99.33	86.47	63.21
12 000	100.00	100.00	100.00	100.00	99.75	90.93	69.88
15 000	100.00	100.00	100.00	100.00	99.94	95.02	77.69
20 000	100.00	100.00	100.00	100.00	100.00	98.17	86.47
20 000[a]	100.00	100.00	100.00	100.00	99.72	76.19	32.33

[a] Per cent probability of observing at least 3 AEs in the sample by AE expected incidence

Comment: The per cent probabilities of observing at least 1 AE and 3 AEs were calculated using binomial distribution.

Annex 4. Abbreviations for tuberculosis (TB) medicines and regimens

TABLE 4.1

Individual medicines for TB therapy

Am	amikacin	Lfx	levofloxacin
Amx/Clv	amoxicillin/clavulanate	Lzd	linezolid
Cm	capreomycin	Mfx	moxifloxacin
Cfx	ciprofloxacin	Ofx	ofloxacin
Clr	clarithromycin	PAS	*p*-aminosalicylic acid
Cfz	clofazimine	Pto	prothionamide
Cs	cycloserine	Z	pyrazinamide
E	ethambutol	Rfb	rifabutin
Eto	ethionamide	R	rifampicin
Gfx	gatifloxacin	S	streptomycin
Ipm	imipenem	Trd	terizidone
H	isoniazid	Thz	thioacetazone
Km	kanamycin		

TABLE 4.2

Usual anti-TB drug combinations

HRZE	isoniazid-rifampicin-pyrazinamide-ethambutol
HR	isoniazid-rifampicin
HRE	isoniazid-rifampicin-ethambutol
HRZES	isoniazid-rifampicin-pyrazinamide-ethambutol-streptomycin
SHRE	streptomycin-isoniazid-rifampicin-ethambutol
Fixed dose combinations	
EHZR	ethambutol 275 mg + isoniazid 75 mg + pyrazinamide 400 mg + rifampicin 150 mg
EHR	ethambutol 275 mg + isoniazid 75 mg + rifampicin 150 mg
HZR 75/400/150	isoniazid 75 mg + pyrazinamide 400 mg + rifampicin 150 mg
HZR 150/500/150	isoniazid 150 mg + pyrazinamide 500 mg + rifampicin 150 mg
HR 75/150	isoniazid 75 mg + rifampicin 150 mg
HR 150/300	isoniazid 150 mg + rifampicin 300 mg
HR 60/60	isoniazid 60 mg + rifampicin 60 mg
HR 150/150	isoniazid 150 mg + rifampicin 150 mg

Annex 5. List of adverse drug reactions (ADRs) commonly associated with anti-tuberculosis medication

First-line drugs[a]	Second-line drugs[b]
hepatitis	nausea, vomiting
nausea, vomiting, gastrointestinal upset	diarrhoea
rash	arthralgia
weakness, fatigue	dizziness, vertigo
arthralgia	hearing disturbances
fever	headache
pruritus	sleep disturbances
headache	electrolyte disturbances
vertigo, tinnitus	abdominal pain
visual disturbances	anorexia
paraesthesia	gastritis
anorexia, weight loss	peripheral neuropathy
abdominal pain	depression
swelling	tinnitus
palpitations	allergic reaction
dyspnoea	rash
seizures	visual disturbances
neutrophilia	seizures
	hypothyroidism
	psychosis
	hepatitis
	renal failure, nephrotoxicity

[a] Ordered by frequency of occurrence in one published series: Marra F et al. Adverse drug reactions associated with first-line anti-tuberculosis drug regimens. *International Journal of Tuberculosis and Lung Disease*, 2007, 11:868–875.

[b] Ordered by frequency of occurrence in one published series: Nathanson E et al. Adverse events in the treatment of multidrug-resistant tuberculosis: results from the DOTS-Plus initiative. *International Journal of Tuberculosis and Lung Disease*, 2004, 8:1382–1384.

Annex 6. Treatment initiation form

LOGO

Cohort event monitoring antituberculosis therapy
Treatment initiation

Patient ID: ……..…..
Interview date: dd/mm/yy

PATIENT DETAILS

Patient Initials: ..... Date of birth: dd/mm/yy Age: ..... Sex at birth ☐ male ☐ female

TREATMENT PROVIDER

District Health Unit

Clinician/ Team Patient File number

Interview site ☐ Health Centre ☐ Hospital Clinic ☐ Phone interview ☐ Home visit ☐ Other

MEDICAL DETAILS

Weight (kg) Height (cm)

Indication for treatment ☐ Pulmonary TB ☐ Extra-pulmonary TB ☐ MDR-TB ☐ Prophylaxis

Prior exposure to anti-TB medicines ☐ No ☐ Yes ☐ Unknown

Pregnant ☐ Yes Date of LMP: dd/mm/yy *or* estimated current gestation (weeks):

☐ Uncertain If PREGNANT record patient details in PREGNANCY REGISTER for follow-up

☐ No

Breastfeeding an infant ☐ No ☐ Yes

		EXCLUDE all medical conditions that began in PAST 30 DAYS as these will be recorded below			
Pre-existing & past medical conditions		**Country-specific list of pre-existing medical conditions of particular interest**	**Date onset**	**Date resolved**	**Continues**
Past TB infection	☐				☐
HIV/AIDS	☐				☐
Smoker (tobacco)	☐				☐
Alcohol abuse	☐				☐
Intravenous drug user	☐				☐
Anaemia	☐				☐
Malnutrition	☐				☐
Diabetes	☐				☐
Other					☐
Other					☐
Other					☐
Other					☐

NEW EVENTS in PAST 30 DAYS	INCLUDE all NEW EVENTS or CHANGES in pre-existing conditions that BEGAN in PAST 30 DAYS			
Date onset	**Date resolved**	**Outcome***	**Severity†**	**Seriousness‡**

OUTCOME*
R1 Recovered/ resolved
R2 Recovering/resolving
S Recovered with sequelae
N Not recovered/not resolved
D Died
U Unknown

SEVERITY†
1 Mild
2 Moderate
3 Severe

SERIOUSNESS‡
N Not serious
H Hospitalization (caused or prolonged)
P Permanent disability
C Congenital abnormality
L Life threatening
D Death

LABORATORY TESTS. Include laboratory tests taken at any time during the PAST 30 DAYS

Test	Date	Result (units)	Test	Date	Result (units)
Sputum smear			ESR		
Sputum culture			Total WBC		
Drug susceptibility			Haemoglobin		
Line probe assay			ALT (SGPT)		
Nucleic acid testing			AST (SGOT)		
Tuberculin Test			Creatinine		
HIV Antibody			Creatinine Clearance		
CD4 Count			Glucose		
Other			Other		

MEDICINES

Medicines & traditional medicines taken at any time in PAST 30 DAYS	Indication	Dosage	Frequency	Route	Start date	Stop date	Continues
							☐
							☐
							☐
							☐
							☐
							☐
							☐
							☐

All NEW medicines (Anti-TB & other) prescribed at this interview	Indication	Dosage	Frequency	Route	Start date	Anticipated Stop date

Please give this form to the CEM Focal Person

Focal Person: ..... Phone: .....

Date of next appointment: dd/mm/yy

Instructions for the completion of the TREATMENT INITIATION FORM

A **Treatment Initiation Form** should be completed at treatment initiation: the interview at which anti-tuberculosis therapy is commenced and at which the patient is enrolled in the Cohort Event Monitoring programme.

Patient participation

It is important that monitoring begins at the commencement of therapy. Patients may be enrolled if they are beginning treatment with the monitored medicine(s) for the first time (i.e. treatment naïve) or if their regimen is being changed. Patients who have previously been exposed to anti-TB medicines may also be included in the cohort, but monitoring should begin at the commencement of a new course of treatment.

Patients should be informed about the purpose of the monitoring programme and their agreement to participate should be sought prior to enrolment. Patients who are unwilling to participate should not be enrolled in the monitoring programme.

Patient ID

Type of identification to be selected by country.

Tick boxes (✔)

Where there are tick boxes, please answer by placing a tick ✔ in the appropriate box.

Patient details

Patient initials

Please use initials of given name(s) and family name.

Date of birth

If DOB is unknown, record the patient's age (or estimated age, if true age is unknown).

Treatment provider

Patient file number

Record the file number used to identify the patient in your clinic.

Medical details

Weight & height

Record the patient's current weight and height.

Pregnant

If this patient is currently pregnant, please record her details in the **Pregnancy Register** to ensure outcome of pregnancy is followed up.

Indication for treatment

Please indicate whether the anti-tuberculosis therapy is to be used for the treatment of pulmonary TB, extra-pulmonary TB, MDR-TB or for prophylaxis. More than one box may be ticked.

PRE-EXISTING & PAST MEDICAL CONDITIONS

Please record any pre-existing or past medical conditions for this patient. A list of conditions has been provided: please *tick* ✔ any of the listed conditions that apply to this patient and record additional pre-existing or past medical conditions in the space provided. Record the date (or approximate date) of onset of each condition, if known, and indicate whether the condition has resolved (by recording date in '**Date resolved**' column) or continues (by ticking the box ✔ in the '**Continues**' column).

NEW EVENTS in PAST 30 DAYS

Please record any of the following types of events that started in the 30 days prior to the treatment initiation interview:

- All **new health events**
- Any **deterioration or improvement in pre-existing conditions**
- **Pregnancy-related conditions** including:
  - **Complications** (e.g. gestational diabetes, preeclampsia, threatened miscarriage)
  - **Type of Delivery** (e.g. normal delivery, caesarean section)
  - **Pregnancy Outcome** (e.g. miscarriage, abortion, still born, live infant, multiple birth).
- For **women who are breastfeeding**, record any new health events in the infant during this same period (e.g. '*infant: diarrhoea and vomiting*').

LABORATORY TESTS

Record the results (including *units*) of any laboratory tests taken in the PAST 30 DAYS. A list of commonly performed tests has been provided; the details of any additional tests may be recorded in the rows marked '**Other**'.

MEDICINES

Medicines & traditional medicines taken at any time in PAST 30 DAYS

Record the details of any prescription or over-the counter medicines and any traditional medicines, herbal remedies or health supplements taken at any time during the PAST 30 DAYS. Include the *units* the '**Dosage**' column. If a medicine is given as a fixed dose combination (FDC), either as a co-formulation or in a co-blister pack, record the number of dosage forms (DF) given.

All new medicines (ART and other) prescribed at this interview

Please record the details of all medicines prescribed at this interview.

Annex 7. Treatment review form

LOGO

Cohort event monitoring antituberculosis therapy
Treatment initiation

Patient ID: ……..…..
Interview date: dd/mm/yy

PATIENT DETAILS

Patient Initials: ..... Date of birth: dd/mm/yy Age: ..... Sex at birth ☐ male ☐ female

TREATMENT PROVIDER

District Health Unit

Clinician/ Team Patient File number

Interview site ☐ Health Centre ☐ Hospital Clinic ☐ Phone interview ☐ Home visit ☐ Other

MEDICAL DETAILS

Weight (kg) Height (cm)

Indication for treatment ☐ Pulmonary TB ☐ Extra-pulmonary TB ☐ MDR-TB ☐ Prophylaxis

Pregnant ☐ Yes Date of LMP: dd/mm/yy *or* estimated current gestation (weeks):

☐ Uncertain If PREGNANT record patient details in PREGNANCY REGISTER for follow-up

☐ No

Breastfeeding an infant ☐ No ☐ Yes

Events	Record all NEW EVENTS or CHANGES in pre-existing conditions since last interview					
	Date onset	Date resolved	Outcome*	Severity†	Seriousness‡	Rechallenge§

OUTCOME*
R1 Recovered/ resolved
R2 Recovering/resolving
S Recovered with sequelae
N Not recovered/not resolved
D Died
U Unknown

SEVERITY†
1 Mild
2 Moderate
3 Severe

SERIOUSNESS‡
N Not serious
H Hospitalization (caused or prolonged)
P Permanent disability
C Congenital abnormality
L Life threatening
D Death

RECHALLENGE§
1 No rechallenge
2 Recurrence of event
3 No recurrence
4 Result unknown

LABORATORY TESTS

Test	Date	Result (units)	Test	Date	Result (units)
HIV Antibody			ALT (SGPT)		
CD4 Count			AST (SGOT)		
ESR			Lactic acid		
Total WBC			Lipase		
Haemoglobin			Other		
Creatinine			Other		
Creatinine Clearance			Other		
Glucose			Other		
TSH			Other		

MEDICINES

Anti-TB medicines taken since last interview	Dosage	Frequency	Route	Start date	Stop date	Continues	Reason(s) for stopping #	Adher-ence**
						☐		
						☐		
						☐		
						☐		
						☐		
						☐		

Other medicines & traditional medicines taken since last interview	Dosage	Frequency	Route	Start date	Stop date	Continues	Reason(s) for stopping #	Indication
						☐		
						☐		
						☐		
						☐		
						☐		
						☐		
						☐		

All NEW medicines (anti-TB & other) prescribed at this interview	Dosage	Frequency	Route	Start date	Expected stop date	Indication

REASON FOR STOPPING #
1 Adverse event
2 Poor adherence
3 Course completed
4 Planned interruption
5 Planned medication change
6 No longer needed
7 Treatment failure
8 Pregnancy
9 Drug out of stock
10 Cost
11 Patient decision
12 Died
13 Lost to follow-up
14 Other (please specify)

ADHERENCE **
A > 80 % doses taken
N ≤ 80 % of doses taken.

Please give this form to the CEM Focal Person

Focal Person: ..... Phone: .....

Date of next appointment: dd/mm/yy

Instructions for the completion of the TREATMENT REVIEW FORM

A Treatment Review Form should be completed each time the patient is interviewed following commencement of treatment with the monitored medicine(s).

Patient ID

Type of unique patient identification to be selected by country.

Tick boxes (✔)

Where there are tick boxes, please answer by placing a tick þ in the appropriate box.

PATIENT DETAILS

Patient initials

Please use initials of given name(s) and family name.

Date of birth

If DOB is unknown, record the patient's age (or estimated age, if true age is unknown)

TREATMENT PROVIDER

Patient file number

Record the file number used to identify this patient in your clinic

MEDICAL DETAILS

Weight & height

Record the patient's current weight. Height should be recorded for children at treatment review, but is unnecessary for adults.

Indication for treatment

Please indicate whether the anti-tuberculosis therapy is to be used for the treatment of pulmonary TB, extra-pulmonary TB, MDR TB or for prophylaxis. More than one box may be ticked.

Pregnant

Please indicate whether the patient is pregnant, uncertain or not pregnant. Women who are pregnant should be entered into a pregnancy register to ensure that the outcome of the pregnancy is followed-up.

EVENTS

Please record:

- All **new health events** that have occurred since the patient started the monitored medicine
- Any **deterioration or improvement in pre-existing conditions** (or previously recorded events)
- **Death** (including cause of death, if known)
- **Pregnancy-related conditions** including:
  - **Complications** (e.g. gestational diabetes, preeclampsia, threatened miscarriage)
  - **Type of Delivery** (e.g. normal delivery, caesarean section)
  - **Pregnancy Outcome** (e.g. miscarriage, abortion, still born, live infant, multiple birth).
- **For INFANTs exposed to ART in utero** please include the following EVENTS, if applicable:
  - **Congenital malformation** (describe)
  - **Condition of infant at birth** (e.g. low birth weight)
  - **Infant's wellbeing** (record any health concerns for the infant)
  - **Death** (including cause of death, if known)
- For each event, select the appropriate code for **Outcome**, **Severity**, **Seriousness** and **Rechallenge** from the shaded panel

LABORATORY TESTS

Record the results (including *units*) of any laboratory tests taken since the patient was last interviewed. Commonly performed tests have been listed; other tests may be recorded in the space provided.

MEDICINES

Anti-tuberculosis medicines or regimen taken since last interview

Anti-tuberculosis medicines may be recorded either as individual medicines or as fixed dose combinations (FDC). Include start and stop dates for medicines that were started or stopped during the interval since the patient was last interviewed and indicate which medicines continue to be taken (continues ✔). For medicines that have been stopped, please select the **reason(s) for stopping** from the list of codes provided (more than one code may be used). For Anti-tuberculosis medicines, please also select the appropriate **adherence code**.

Note: If a medicine was stopped and later restarted, include separate entries for each course. If the dose was changed, record the medicine again on a new line with the new dose and dates.

Other medicines & traditional medicines taken since last interview

Record the details of other medicines, including over-the-counter medicines and any traditional medicines, herbal remedies or health supplements taken since the last interview.

All new medicines (Anti-tuberculosis & other) prescribed at this interview

Record the details of all new medicines (Anti-tuberculosis and other medicines) prescribed at this interview.

Tuberculosis Identity Card

Name _____ BMU TB Register No. _____

Address _____ Date of registration: _____

Sex: ☐ M ☐ F Age _____ Date treatment start _____

Health facility: _____

Supporter (name and address) _____

Sputum smear microscopy				Weight (kg)
Month	Date	Lab No.	Result	
0				

Disease site (check one)

☐ Pulmonary ☐ Extrapulmonary, specify _____

Type of patient (check one)

☐ New ☐ Treatment after default
☐ Relapse ☐ Treatment after failure
☐ Transfer in ☐ Other specify _____

I. INITIAL PHASE

CAT (I, II , III): ☐	(RHZE)	S	Other
Drugs and dosage:			

II. CONTINUATION PHASE

	(RH)	(RHE)	Other
Drugs and dosage:			

Appointment dates: _____

_____

_____

_____

_____

_____

REMEMBER

From: Revised TB recording and reporting forms and registers – version 2006. World Health Organization, Geneva, Switzerland, 2006. (WHO/HTM/TB/2006.373)

Annex 9. Manual coding sheet

Coding sheet for reviewing of events before data entry

TYPE OF EVENTS

Events in control period ☐ Events on treatment ☐

For events in the control period, event terms will be determined, but no other assessment will be undertaken.

REPORT ID

Patient initials ☐ Unique # ☐ Report # ☐

(The report # is given by the PvC for events that occur on treatment)

MONITORED MEDICINES

Record the individual medicines or the TB regimen

1. .....
2. .....
3. .....

ASSESSMENT OF INDIVIDUAL EVENTS

Event terms are selected by the clinical reviewer from the events dictionary

Dechallenge and rechallenge details

This assessment will be made on the monitored medicine(s) or regimen only

Events	Outcome[1]	Rechallenge[2]	Died[3]
1			
2			
3			
4			
5			
6			

Coding for the above as follows:

1. R1, recovered/resolved; R2, recovering/resolving; S, recovered with sequelae; N, not recovered/not resolved; D, died; U, unknown
2. N, no rechallenge; +ve, recurrence; -ve, no recurrence; U, unknown outcome
3. Died: DR, due to adverse drug reaction; DC, medicine may be contributory; UN, unrelated to medicine; DU, cause of death unknown

Qualitative and relationship assessment

This assessment will be made only on the monitored medicine or regimen only.

For events in the control period, there will be no assessment – just a list.

Events	Severity[a]	Seriousness[b]	Duration[c]	Relationship[d]
1				
2				
3				
4				
5				

Coding for the above as follows:

a. severity: 1. mild; 2. moderate; 3. severe.

b. seriousness: N, not serious; H, hospitalization (caused or prolonged); P, permanent disability; C, congenital anomaly; L, life-threatening; D, death.

c. duration to onset: date medicine begun to date of onset of event, calculated in days

d. relationship: 1, certain; 2, probable; 3, possible; 4, unlikely; 5, unclassified; 6, unassessable

Clinical Groups for each event

Enter the appropriate Clinical Group for each event: this can be abbreviated to the first 3 letters of each group.

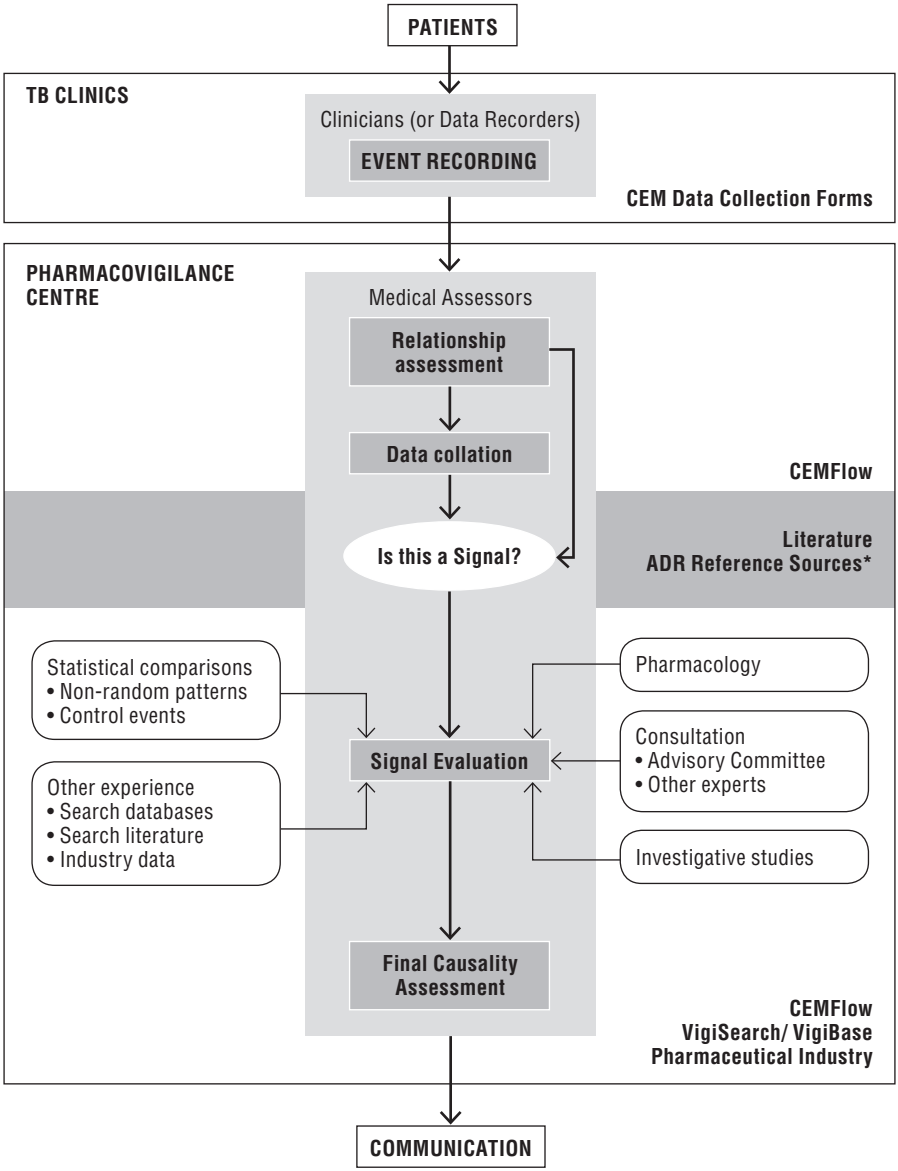
Clinical Group	1	2	3	4	5	6

Date of completion ...../...../..... **Clinical reviewer** .....

Annex 10. Major clinical categories in events dictionary

1. Accidents
2. Alimentary
3. Associations (of concomitant medicines and events)
4. Autonomic
5. Circulatory
6. Died
7. Device
8. Endocrine/metabolic
9. Ear, Nose and Throat
10. Eyes
11. Haematological
12. Hepatobiliary
13. Immunological
14. Infections
15. Lactation exposure
16. Musculoskeletal
17. Neoplasms
18. Neurological
19. Poisoning
20. Pregnancy register
21. Mental health disorders
22. Reproductive organs
23. Respiratory
24. Skin
25. Surgery
26. Unclassified
27. Urological

Annex 11. Decision tree for cohort event monitoring



* 'Martindale: The Complete Drug Reference', Micromedex®, 'Physicians Desk Reference' (PDR®).

Glossary

The definitions given below apply to the terms used in this guide. They may have different meanings in other contexts

adherence Active, voluntary and collaborative involvement of the patient in a mutually acceptable course of behaviour (including taking the prescribed dose of a particular medicine at the recommended time) to produce the desired therapeutic results

adverse event Any untoward medical occurrence that may present during treatment with a pharmaceutical product, but which does not necessarily have a causal relationship with this treatment

adverse (drug) reaction (ADR) A response to a medicine which is noxious and unintended, and which occurs at doses normally used in humans

causal relationship A relationship between one phenomenon or event (A) and another (B) in which A precedes and causes B. In pharmacovigilance, a medicine causing an adverse reaction

causality assessment The evaluation of the likelihood that a medicine was the causative agent of an observed adverse reaction

cohort event monitoring A prospective observational study of adverse events associated with one or more medicines

counterfeit medicine Medicines that are deliberately and fraudulently mislabelled with respect to identity and/or source

data mining A general term for computerized extraction of potentially interesting patterns from large datasets, often based on statistical algorithms

dechallenge The withdrawal of a drug from a patient; the point at which the continuation, reduction or disappearance of adverse effects may be observed

diary (patient) A dated record of health events recorded by the patient

event dictionary A standard listing of terms which describe health events for use in event monitoring

incident A health event which is believed to be incidental to the taking of a particular medicine

index case One of the first good descriptions of a specific adverse reaction to a medicine

individual case safety report (ICSR) A report that contains information describing a suspected adverse drug reaction related to the administration of one or more medicinal products to an individual patient

information component (IC) A measure of the disproportionality in the reporting of a drug–ADR pair in an ICSR database, relative to the reporting expected based on the overall reporting of the drug and the ADR. Positive IC values indicate higher reporting than expected

Medical dictionary for regulatory activities (MedDRA) Medical terminology developed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) with an emphasis on ease of use for data entry, retrieval, analysis and display

medication error An error which occurs during the prescribing, dispensing and/or use of a medication

pharmacovigilance The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem

rechallenge The voluntary or inadvertent re-administration of a medicine suspected of causing an adverse reaction. (The point at which a drug is again given to a patient after its previous withdrawal – see also dechallenge.)

record linkage Method of assembling information contained in two or more records, e.g. in different sets of medical charts, and in vital records such as birth and death certificates. This makes it possible to relate significant health events that are remote from one another in time and place

relationship assessment The objective evaluation of the relationship between the administration of a medicine and a health event, taking into consideration duration of therapy to onset of event, response to dechallenge and rechallenge (if performed) and the presence of other diseases or medicines that could have caused the event. This process stops short of attempting to establish a causal relationship, but is an essential preliminary

report A description provided to a monitoring authority of a health event which follows the use of a medicine

risk factor A characteristic associated with an increased probability of occurrence of an event. In the presence of a risk factor, a patient is more likely to develop an adverse reaction

serious reaction A serious reaction is an adverse drug reaction which involves any of the following: death or a life-threatening experience; hospitalization or prolongation of hospitalization; persistent significant disability; congenital anomaly

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

spontaneous reporting Unsolicited communication by health-care professionals or consumers that describes one or more suspected adverse drug reactions in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection scheme

targeted spontaneous reporting (TSR) A method that monitors and records all or a specific set of safety concerns in a defined population of treated patients, e.g. drug-resistant TB patients on treatment

WHO adverse reactions terminology (WHO-ART) The WHO terminology for coding clinical information in relation to medicinal product therapy

Adverse drug reactions (ADRs) can lead to the interruption of tuberculosis (TB) treatment, and contribute to regimen failure, morbidity, loss in quality of life or death. ADRs due to TB medicines are well known, but the overall contribution of anti-TB medicines to the burden of disease and patient mortality has been poorly studied. While many national TB programmes have a long tradition of monitoring patient care, the surveillance of drug-related problems, or pharmacovigilance, has not been systematic. Why should TB programmes today consider reinforcing pharmacovigilance? The increasing worldwide use of more extensive regimens for drug-resistant TB, the concomitant use of antiretroviral therapy in patients with HIV-associated TB, and the imminent release on the market of new classes of medicines to treat TB make the case for pharmacovigilance even stronger. This handbook provides the practitioner with a step-by-step approach to the different methodologies available to include pharmacovigilance activities as a standard of care for TB patients.

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