

SAFETY OF MEDICINES

A GUIDE TO DETECTING AND REPORTING ADVERSE DRUG REACTIONS

Why health professionals need to take action

**Ministry of Health
CIMed
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Introduction

The purpose of this Guide is to help health professionals to participate in the very important process of continuous surveillance of safety and efficacy of the pharmaceutical products which are used in their clinical practice. Continuous evaluation of their benefit and harm will help to achieve the ultimate goal to make safer and more effective treatment available to patients.

The objectives of the Guide are to raise awareness of the magnitude of the drug safety problem and to convince health professionals that reporting of adverse reactions is their moral and professional obligation.

The ultimate goal of the Guide is to reduce drug morbidity and drug mortality by early detection of drug safety problems in patients and improving selection and rational use of drugs by health professionals.

The Ministry of Health would be grateful to receive any comments on experience gained from the practical use of the Guide which would help in developing it further. Please contact CIMed with your comments:

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Glossary

The terms are from “Safety Monitoring of Medicinal Products”¹

1. **Pharmacovigilance** “the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.

2. An **adverse drug reaction (ADR)** is “a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man”.

In this description it is of importance that it concerns the response of a patient, in which individual factors may play an important role, and that the phenomenon is noxious (an unexpected therapeutic response, for example, may be a side effect but not an adverse reaction).

2. An **unexpected adverse reaction** is “an adverse reaction, the nature or severity of which is not consistent with domestic labelling or market authorisation, or expected from characteristics of the drug”.

3. A **drug** or **medicine** is “a pharmaceutical product, used in or on the human body for the prevention, diagnosis or treatment of disease, or for the modification of physiological function”.

4. A **side effect** is “any unintended effect of a pharmaceutical product occurring at doses normally used by a patient which is related to the pharmacological properties of the drug”.

Essential elements in this definition are the pharmacological nature of the effect, that the phenomenon is unintended, and that there is no deliberate overdose.

5. An **adverse event** or **experience** is defined as “any untoward medical occurrence that may present during treatment with a medicine but which does not necessarily have a causal relationship with this treatment”.

The basic point here is the coincidence in time without any suspicion of a causal relationship.

6. A **serious adverse event** is any event that:

. Is fatal

- . Is life-threatening
- . Is permanently/significantly disabling
- . Requires or prolongs hospitalization
- . Causes a congenital anomaly
- . Requires intervention to prevent permanent impairment or damage

7. A *signal* refers to “reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously”.

Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information.

The magnitude of the problem

During the last decades it has been demonstrated by a number of studies that medicine morbidity and mortality is one of the major health problems which is beginning to be recognized by health professionals and the public. It has been estimated that such adverse drug reactions (ADRs) are the 4th to 6th largest cause for mortality in the USA,². They result in the death of several thousands of patients each year, and many

more suffer from ADRs. The percentage of hospital admissions due to adverse drug reactions in some countries is about or more than 10% 3, 4, 5.

In addition suitable services to treat ADRs impose a high financial burden on health care due to the hospital care of patients with drug related problems. Some countries spend up to 15-20% of their hospital budget dealing with drug complications⁶.

Beside ADRs, medicine-related problems include also – drug abuse, misuse, poisoning, therapeutic failure and medication errors.

There is very limited information available on ADRs in Mozambique and other developing countries. However, one may expect that the situation is worse rather than better. This problem is also caused by a lack of an ADRs reporting system, a large number of substandard and counterfeit products circulating in our market, inadequate independent information and the irrational use of drugs.

Why postmarketing surveillance and reporting ADR is needed

The information collected during the pre-marketing phase of drug development is inevitably incomplete with regard to possible ADRs. This is mainly because :

- . Tests in animals are insufficient to predict human safety;
- . Patients used in clinical trials are selected and limited in number, the conditions of use differ from those in clinical practice and the duration

of trials is limited;

- . By the time of licensing exposure of less than 5000 human subjects to a drug allows only the more common ADR to be detected;
- . At least 30,000 people need to be treated with a drug to be sure that you do not miss at least one patient with an ADR which has an incidence of 1 in 10,000 exposed individuals⁷;
- . Information about rare but serious adverse reactions, chronic toxicity, use in special groups (such as children, the elderly or pregnant women) or drug interactions is often incomplete or not available;

Thus, post-marketing surveillance is important to permit detection of less common, but sometimes very serious ADRs.

Therefore health professionals worldwide should report on ADRs as it can save lives of their patients and others.

Why pharmacovigilance is needed in Mozambique

There are differences among countries (and even regions within our country) in the occurrence of ADRs and other drug-related problems. This may be due to differences in e.g.:

- . diseases and prescribing practices;
- . genetics, diet, traditions of the people;
- . drug manufacturing processes used which influence pharmaceutical quality and composition;

- . drug distribution and use including indications, dose and availability;
- . the use of traditional and complementary drugs (e.g. herbal remedies) which may pose specific toxicological problems, when used alone or in combination with other drugs.

Data derived from within the country or region may have greater relevance and educational value and may encourage national regulatory decision-making. Information obtained in one country (e.g. the country of origin of the drug) may not be relevant to other parts of the world, where circumstances may differ.

Therefore, drug monitoring is of tremendous value as a tool for detecting ADRs and specifically in relation to counterfeit and substandard quality products. ADR monitoring is to help ensure that patients obtain safe and efficacious products.

The results of ADR monitoring have also a very important educational value.

How voluntary reporting on ADRs can prevent new medicine tragedies from developing

It took many decades before the deleterious effects of aspirin on the gastro-intestinal tract became apparent and almost as long before it was recognised that the protracted abuse of phenacetin could produce renal papillary necrosis; and several years before the association of phocomelia with thalidomide became obvious.

Withdrawals from the market as a result of spontaneous reporting

- Find examples of medicines known in MZ

After the “thalidomide tragedy” many countries have established drug monitoring systems for early detection and prevention of possible

drug-related morbidity and mortality. Their success depends on the cooperation of the medical profession in reporting suspected ADRs, especially to new drugs.

Some examples demonstrate how very astute, alert and observant medical doctors have been helped to prevent the development of drug morbidity and drug mortality by reporting on suspected ADRs which resulted in the withdrawal of dangerous drugs from the market or in restriction of their use.

How voluntary reporting on ADRs can influence labelling

There are many examples of the importance of ADRs reporting in the improvement of information in labelling of many effective pharmaceutical products (new possible ADRs, contraindications, dosage etc.).

Cyclophosphamide has been on the market for several years in many countries. In January 2001 there were some new reactions included in the labels: Stevens Johnson syndrome and toxic epidermal necrolysis; they were not included in the Physician Desk Reference (PDR) 1995.

For example:

EPIDERMAL NECROLYSIS
ERYTHEMA MULTIFORME
STEVENS JOHNSON SYNDROME

- *New example(2)*

Who should and to whom

The effectiveness of a national postmarketing surveillance programme is directly dependent on the active participation of health professionals. Health professionals are in the best position to report on suspected ADRs observed in their every day patient care.

All healthcare providers:

physicians,
pharmacists,
technicians,
nurses,
dentists
others

should report ADRs as part of their professional responsibility, even if they are doubtful about the precise relationship with the given medication. After filling the report form should be sent directly to CIMed or by the appropriate created facilities (see information flow pag...).

**You can reduce the suffering
and save thousands
of patients lives by doing
one thing:**

Report suspected adverse drug reactions.

How to recognize ADRs

Since ADRs may act through the same physiological and pathological pathways as different diseases, they are difficult and sometimes impossible to distinguish. However, the following step-wise approach may be helpful in assessing possible drug-related ADRs:

1. Ensure that the medicine ordered is the medicine received and actually taken by the patient at the dose advised;
2. Verify that the onset of the suspected ADR was after the drug was taken, not before and discuss carefully the observation made by the patient;
3. Determine the time interval between the beginning of drug treatment and the onset of the event;
4. Evaluate the suspected ADR after discontinuing the drugs or reducing the dose and monitor the patient's status. If appropriate, restart the drug treatment and monitor recurrence of any adverse events.
5. Analyse the alternative causes (other than the drug) that could

on their own have caused the reaction;

6. Use relevant up-to-date literature and personal experience as a health professional on drugs and their ADRs and verify if there are previous conclusive reports on this reaction. The CIMed is very important resources for obtaining information on ADR. The manufacturer/importers of the drug can also be a resource to consult;

7. Report any suspected ADR to the person nominated for ADR reporting in the hospital or directly to the CIMed.

What should be reported?

- . For “new” drugs (eg. SP-AQ, Art-Lum) - report all suspected events, including minor ones.
- . For established or well-known drugs - report all ADRs, including minor ones;
- . Report if an increased frequency of a given reaction is observed;
- . Report all suspected ADRs associated with drug-drug, drug-food or drug-food supplements (including herbal and complementary products) interactions;
- . Report ADRs in special fields of interest such as drug abuse and drug use in pregnancy and during lactation and inappropriate drug use;
- . Report when suspected ADRs are associated with drug withdrawals;
- . Report ADRs occurring from overdose or medication error;
- . Report when there is a lack of efficacy or when suspected pharmaceutical defects are observed.

Thus, report all suspected adverse reactions that you consider of clinical importance as soon as possible!

How to report ADRs?

Case Report Forms (CRF) should be obtained from the CIMed (see annex 1). After filling the report form should be sent directly to CIMed or by the appropriate created facilities (see information flow pag...).

How to complete the ADRs report form?

The case report form has seven sections which should be completed :

1. Health unit information:
 - Name
 - Unit
 - District (localidade)
2. Patient information:
 - Patient identifier (initials)
 - Age at time of event or date of birth
 - Gender
 - Weight
 - Height
 - Pregnancy?
3. Adverse event/reaction or product problem:
 - Description of event or problem
 - Date of event
 - Duration
4. Suspected medication(s):
 - name (INN and brand name)

- dose, frequency & route used
- therapy date
- diagnosis for use
- batch number
- expiration date
- concomitant medical products and therapy dates

5. Result

- event abated after use stopped or dose reduced
- event reappeared after reintroduction of the treatment
- Outcome attributed to adverse event

6. Comments

- relevant tests/laboratory data (if available)
- Other relevant patient information/history

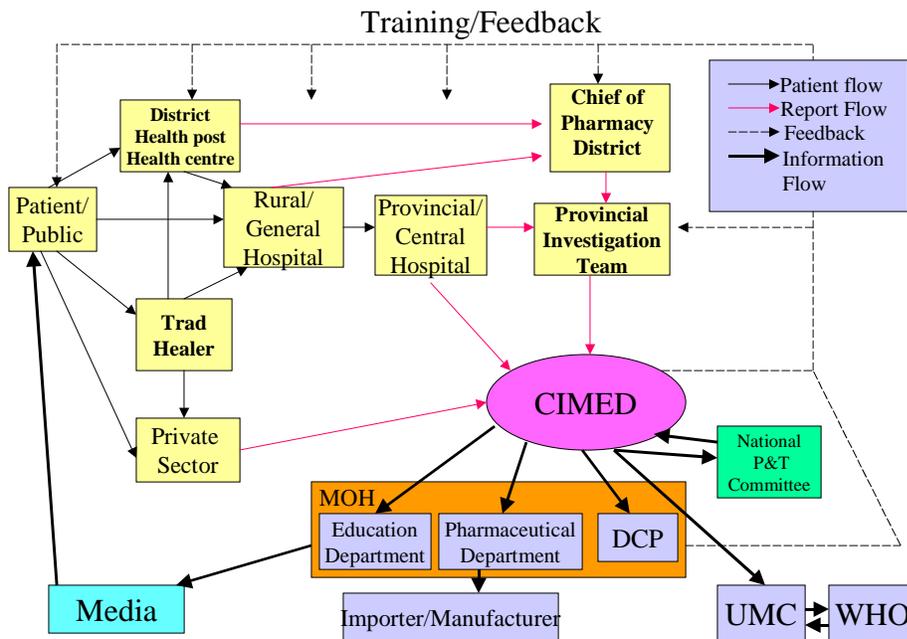
7. Reporter:

- name, address and telephone number
- speciality and occupation
- notification date

- Include one completed form

The completed Case Report Form should be sent to CIMed (see flow information).

Pharmacovigilance Infrastructure: Mozambique



Role and Responsibilities

Patient:

- Presents at health facility when experiencing adverse event
- Takes medicines as directed

Traditional healers:

- Detect/Diagnose suspected adverse events
- Refer patients to the health facilities when experiencing adverse event
- Educate patients on ADRs and how to take their medicine

District Health facilities staff (physicians, pharmacists, technicians, nurses, dentists, others) :

- Detect/Diagnose suspected adverse events
- Complete ADR report forms
- Send ADR form to Chief District Pharmacist
- Educate patients on ADRs and what to do in case of ADR

Chief District Pharmacist :

- Promote/encourage reporting by District health facilities staff.
- Remind health staff to report
- Provide forms to health facilities
- Collect completed ADR forms
- Send report to the Provincial Investigation Team
- Assist Provincial Investigation Team in investigations
- Provide feedback received from national office where necessary

Chief Provincial Pharmacist :

- Send ADR and Investigation reports to CIMed
- Facilitate Investigation of signal events on instruction of CIMed
- Encourage reporting by provincial and district staff
- educate the public, health staff
- Give feedback to the Chief District Pharmacist (and reporters and patients where necessary)

Provincial Investigation Team :

(Members:provincial hospital physician, head nurse of provincial directorate, member of Disease Control Programme (where necessary), Chief Provincial Pharmacist)

- Investigate signal events as directed by CIMED
- Report findings of investigation to CIMED via Chief Provincial Pharmacist
- Promote ADR reporting by provincial health staff

CIMed/Pharmacovigilance Unit :

- Training and supervision of provincial and district level health staff
- Collect and storage all suspected ADRs in national database
- Assess causality and clinical importance of the ADRs
- Recommend and coordinate investigations
- Assist and advise during investigations
- Provide feedback to reporters
- Secretarial support to National P&T Committee
- Communicate findings, analyses and recommendations of National Pharmacy and Therapeutics Committee (CTTF) to MOH, Pharmaceutical Department, relevant disease control Programme and public.
- Publish drug safety alerts in Drug Information Bulletin
- Train and educate media in medical journalism
- Submit reports to UMC

Expert safety review panel (CTTF) :

(CIMed member,pharmacologist, pharmacist, physician, specialists, member of MCP)

- Assess ADRs for causality and need for action
- Make recommendations of actions to be taken by MOH (Pharmaceutical Department, Disease control programme or other) or CIMed.
- Assist CIMed in encouraging reporting

- Advise MOH in times of crisis related to drug safety.
 - Assist investigation team where required.
- Pharmaceutical Department :
- Take and enforce regulatory actions where recommended by CTTF
 - Report these actions to the manufacturers/importers
 - Mandate manufacturers/importers to submit safety information to CIMed.
- Disease Control Programme :
- Disseminate information on proper medicine use to public and health providers
 - Assist in assessment of risk-benefit of suspect drug
 - Update treatment guidelines
 - Assist in investigations
 - Training health facilities staff to report and use medicines correctly
 - Assist PIT and MOH in Crises
- Media :
- Develop skills in writing on medical information
 - Pass correct information to the public
 - Assist MOH and CIMED in distributing important safety alerts
- International support (WHO/UMC0 :
- Support CIMed with database
 - Provide technical guidance
 - Assist with training and training materials
 - Facilitate communication and collaboration with other national centres

What happens to my ADR report

All ADRs sent to CIMed will be evaluated and assessed for causality by CIMed staff. Further investigations will be done by PIT or CTTF if needed. Feedback information will be provided to the reporters.

If is necessary to take any decision (change label, suspend the use of the drug, withdrawl the drug) the MOH will be informed and this information will be provide to the reporters.

Training and supervision of provincial and district level health staff

Collect and storage all suspected ADRs in national database

Assess causality and clinical importance of the ADRs

Recommend and coordinate investigations

Assist and advise during investigations

Provide feedback to reporters

Secretarial support to National P&T Committee

Communicate findings, analyses and recommendations of National Pharmacy and Therapeutics Committee (CTTF) to MOH, Pharmaceutical Department, relevant disease control Programme and public.

Publish drug safety alerts in Drug Information Bulletin

Train and educate media in medical journalism

Submit reports to UMC

Expert safety

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Useful Websites

WHO

www.who.int/medicines/

Section: Quality Assurance and Safety: Medicines

WHO Collaborating Centre for International Drug Monitoring (Uppsala Monitoring Centre)

www.who-umc.org

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Pharmacovigilance Infrastructure: Mozambique

Training/Feedback

