MINISTRY OF HEALTH AND SOCIAL SERVICES

National Guidelines for Medicine Safety Surveillance

Know YOUR medicines

Therapeutics Information and Pharmacovigilance Center, TIPC

FORWARD

The need for the provision of unbiased medicine information and the monitoring of adverse events related to the use of medicines are well recognized by the Ministry of Health and Social Services in our policy and legal documents. The National Medicines Policy (NMP) of 1998 prescribes for the establishment of drug information center(s). Also the Namibia National Pharmaceutical Master Plan produced in 2000 following the adoption of the NMP recommended for the establishment of a National Medicines Information Center. With regards to adverse reactions, Regulation 17 of the Regulations relating to medicines and related substances control Act, No. 13 of 2003stipulates clearly the duties of holders of certificate of registration of a medicine and health professionals in informing Council of adverse reactions which occur during the use of a medicine and of substandard medicines.

It was in an effort to advance the actualization of these goals set out in the National Medicine Policy and the Act 13 of 2003 that the Ministry of Health and Social Services, MoHSS set up the Therapeutics Information and Pharmacovigilance Centre Implementing Working Group (TIPC-IWG). Subsequently, the Therapeutics Information and Pharmacovigilance Centre (TIPC) was established in 2006 with the dual function that integrates therapeutics information and pharmacovigilance activities in a unified services so as to take advantage of the potential synergies between the two services. The mandate of TIPC is to improve the rational and safer use of medicines in Namibia. It is the MoHSS official centre for the provision of unbiased therapeutics information and pharmacovigilance services to health care professionals and the general public. Medicines safety information is collected using adverse reaction reporting forms and analyzed at the center to detect medicines safety problems. The information obtained from this safety monitoring system is used to prevent harm to patients, waste of resources and the repetition of avoidable harm and ultimately improves the patient care and safety.

Since coming into existence, the TIPC has achieved several milestones one of which is the admission of Namibia as the 90th full member country and collaborating centre of the WHO international drug monitoring program. The WHO international drug monitoring program recommends national centres to develop guidelines to harmonize the medicine safety monitoring. In Namibia, it is our intention to use such a guideline as a roadmap for the monitoring of safety and effectiveness of all health products including orthodox medicines, traditional medicines, vaccines, blood products, complementary and alternative medicines, and other health technologies. This new document — *National Guidelines for Medicine Safety Surveillance* fulfils that intention. These guidelines will direct health workers and consumers on how to monitor safety of all health products and also how to monitor for counterfeit and other product quality problems, medication errors and how to improve patient safety. The *National Guidelines for Medicine Safety Surveillance* covers all aspects of monitoring for both old and new essential medicines. The

guideline will help to entrench a culture of spontaneous reporting of all suspected adverse events that occurs in the use of a health product to the TIPC. The guidelines also provide basic information to all stakeholders with regards to the conduct of active surveillance and other post-license safety studies in Namibia.

The TIPC has chosen "Know your Medicines" as it's motor. I wish to most sincerely call on all Namibians to 'Know your Medicines." This means knowing why your doctor or healthcare provider has recommended that medicine, know how to take the medicine and the need for adherence, know what not to combine with your medicine, know what to expect from your medicine, and know to report adverse events suspected to be related to that medicine. When we know our medicines, we will be good partners with our health providers and we can work collaboratively with them to address all our healthcare needs.

Finally, the launch of this *National Guidelines for Medicine Safety Surveillance* is evidence that MoHSS commitment to the health of Namibians goes beyond ensuring availability of essential medicines. The MoHSS is equally committed to ensure the safety and effectiveness of all medicines used in Namibia. I therefore encourage all, patients and their family, healthcare workers, and the public to put this document — *National Guidelines for Medicine Safety Surveillance* in good use, to know your medicines, and to become more diligent in monitoring the safety and effectiveness of all medicines in use in Namibia.

Hon. Dr. Richard Nchabi Kamwi

Minister of Health and Social Services

PREFACE

The TIPC was established in 2006 and officially launched in May 2008. Since then, the centre is providing therapeutic information and pharmacovigilance services to the health care professional and the public at large.

As passive surveillance is the major safety monitoring system to identify rare but serious adverse reaction, health professionals have to be vigilant and report any suspected reaction to the TIPC within reasonable time. In order to achieve good reporting of ADRs, it is important that all health care workers be aware of the existing system for reporting unexpected harm to patients. Beyond rare events, the MoHSS is equally interested in characterizing known, but clinically significant, adverse drug reactions so as to understand their incidence and severity in our population. This necessitates the need for the *National Guidelines for Medicine Safety Surveillance* to address in a more comprehensive way all aspects of medicine safety monitoring including guidelines for the conduct of active surveillance studies, guidelines for the promotion and advertising of medicines, and guidelines for the provision of therapeutics information.

Realizing the wide spread lack of awareness of medicines safety surveillance and the role of the TIPC in ensuring medicines safety, the centre developed this comprehensive guidelines for monitoring safety of medicines. This first *National Guidelines for Medicine Safety Surveillance* was specifically prepared to address Namibia peculiar needs while adapting relevant parts of the WHO recommendations and pharmacovigilance guidelines from several other countries. Attempt has been made to make it as informative and comprehensive as possible. The *National Guidelines for Medicine Safety Surveillance* provides basic information on policy and legal framework for pharmacovigilance, the establishment of the TIPC, the notification system, the roles and responsibilities of various stakeholders, and the scope of pharmacovigilance and medicine safety surveillance activities in Namibia. The guidelines also discuss types of adverse drug reactions and how to recognize and prevent ADRs. It discusses methods used in medicine safety surveillance including both spontaneous reporting and active surveillance. The *National Guidelines for Medicine Safety Surveillance* describes how safety will continue to be monitored post-licensing through ongoing benefit-harm assessment, the provision of therapeutics information, and provides guidelines on the responsibilities of market authorization holder towards ensuring immediate communication of all serious safety alerts related to the product they have market authorization for in Namibia. The guidelines also recommend strategies for capacity building and training in the area of medicine safety surveillance and how the efforts of the TIPC will be monitored and evaluated. Several tools and scales that are used by the TIPC are annexed at the end of the guidelines. I will encourage healthcare workers to familiarize themselves with the tools contained

in the annexes. Healthcare workers should also spare time and review the glossary also provided in the annex and familiarize themselves with these terms to ensure common understanding.

The Ministry of Health and Social Services wishes to recognize the contributions of the Directorate of Tertiary Health Care Services, division pharmaceutical services, members of the implementing working group, Management Sciences for Health's Strengthening Pharmaceutical Systems, MSH/SPS project, and all healthcare workers and other stakeholders who have participated in the development of this *National Guidelines for Medicine Safety Surveillance*.

This *National Guidelines for Medicine Safety Surveillance* is now the official guide for the monitoring of safety and effectiveness of health products in Namibia and I therefore urge all healthcare workers and the public to use the guidelines and also take part in ensuring that we improve safety and effectiveness of health products used in Namibia.

Mr. Kahijoro S.M. Kahuure

Permanent Secretary, MoHSS

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ACRONYMS

ACTs	Artemisinin-based Combination Therapies
ADR	Adverse Drug Reactions
AE	Adverse Event
CC	Clinical Committee of NMRC
CHW	Community Health Workers
DSP	Directorate of Special Programs
DUR	Drug Utilization Review
EAC	Expert Advisory Committee
EMLC	Essential Medicine List Committee
ESRP	Expert Safety Review panel
ICSR	Individual Case Safety Report
I-TECH	International Training and Education Centre on HIV / AIDS
IWG	Implementing Working Group
MAHs	Market Authorization Holders
MDM	Medicos del Mundo
MIP	Medicines Information Pharmacist
MoHSS	Ministry of Health and Social Services
MRSCA	Medicines and related substances control Act, Act 13 of 2003
MSH / SPS	Management Science for Health / Strengthening Pharmaceutical Systems
NMRC	Namibia Medicines Regulatory Council
PC&I	Pharmaceutical Control and Inspection
PEM	Prescription event monitoring
PSUR	Periodic Safety Update Reports
PhV	Pharmacovigilance
SPC	Summary of Product Characteristics
STG	Standard Treatment Guidelines
TC	Therapeutic Committee
THC& CSS	Tertiary Health Care and Clinical Support Services
TI	Therapeutics information
TIPC	Therapeutics Information and Pharmacovigilance Centre
UMC	Uppsala Monitoring Centre
WHO	World Health Organization

1. INTRODUCTION

New medicines are tested for quality, safety, and efficacy before they are made available for use. These series of tests provide only limited information about how well the medicine works in real-life use in a large population of people. Therefore, when medicines are used in large populations for a long period of time more information can be obtained about their safety and effectiveness.

Recently many new essential medicines, particularly antiretroviral medicines, malaria and tuberculosis medicines, whose registration were fast-tracked to make life-saving medicines available to patients in need, are available to large population of patients globally. Public health programs are extending access to all in need of treatment including the young, elderly, pregnant women, malnourished, patients with co-morbid conditions and genetic predispositions different from those used in clinical trials.

With more patients being exposed to these new medicines for long periods of time, the chances of developing adverse reactions and interactions increase significantly. Such adverse reactions for medicines used in public health programs may erode the confidence of the patients on the safety of the medicines and consequently affect the whole program. Therefore, in a developing countries like Namibia where relatively new essential medicines are being used in large scale in the national public health programs like antiretroviral therapy (ART) program, tuberculosis (TB), and malaria control programs, monitoring of safety of medicines is of paramount importance.

Spontaneous reporting of an adverse drug reaction by health care professionals has shown to be effective in the detection of new adverse drug reactions. Consequently, it is being used in many countries to generate safety signal. However, individual report is not conclusive concerning causal association between an adverse drug reaction and medicine.

Recent experiences have shown that voluntary adverse reaction reports from health professionals has limitations as it can rarely validate some drug-induced disorders and may not provide full information about the safety of medicines. Comprehensive safety and effectiveness data can only be generated through routine medicine safety surveillance and targeted active surveillance studies. Thus an integrated system of medicines regulation and surveillance system and use of routinely collected data is believed to further medicines safety information. Pharmacoepidemiologic methods

involving the study of drug use in the population can be used to assess safety of medicines in real-life use.

Information obtained from such surveillance systems is entered to a medicines safety database and analyzed periodically so that appropriate action is taken whenever there is a safety concern. This may be regulatory action including dear health care professionals letter to provide information about the new safety concern, product recall or revision of information on the package insert and label.

The Namibia Medicines and Related Substances Control Act, (MRSCA)Act. No. 13 of 2003 requires every registration holder and health care professionals to inform the council of any adverse drug reaction, ADR which occurred during the use of any medicine.

Accordingly, the Ministry of Health and Social Services, MoHSS has set up and made operational a centre, the Therapeutic Information and Pharmacovigilance Center (TIPC), with dual functions of providing unbiased and up to date therapeutics information and monitoring of medicines safety with due emphasis on safety of medicines used in the public health programs.

2. NATIONAL MEDICINES POLICY AND LEGAL PROVISIONS FOR PHARMACOVIGILANCE AND ADVERTIZING OF MEDICINES

The Namibia national medicines policy clearly stated the need for the establishing a medicines information and adverse reaction monitoring services The policy documents envisaged that the unit that provides such services will be able to co-ordinate adverse reaction reporting and manage data collection, analysis and dissemination. The policy also indicates that the Namibia Medicines Regulatory Council, NMRC will co-operate closely with medicines information centres in the Southern African Region and the WHO Collaborating Centre for International Drug Monitoring in the monitoring and reporting of adverse drug reactions.

The Medicines and related substances control Act, 2003: regulations related to medicines and related substances, Regulation number 17 on Informing Council of adverse reactions which occur during the use of medicines and of substandard medicines makes provision that requires the holder of a certificate of registration to inform the Council of any adverse reaction which occurred during the use of a medicine for which he or she holds an application for registration or a certificate of registration. It must also inform the Council without delay of the steps which he or she intends to take with regard to an adverse reaction concerned.

The Market Authorization Holders (MAHs) therefore should ensure that they have an appropriate system of pharmacovigilance in place in order to assume responsibility for their products on the market and to ensure that appropriate action will be taken, when necessary. This includes the MAH having a system for the collection, preparation and submission of expedited adverse drug reactions (ADR) and periodic safety update reports, PSUR to NMRC.

Every Market Authorization Holders must inform the Council of any formulation, labeling or other error which has occurred with regard to a medicine for which he or she holds an application for registration or a certificate of registration and also inform the Council of steps taken by him or her to rectify the error immediately.

Although the regulation states that every authorised prescriber must inform the Council of any adverse reaction which occurred during the use of any medicine within a reasonable time, voluntary reporting by health care professional is believed to be effective enough for early detection of unknown adverse reaction and thus appropriate in our setting. A person can also report to the Council any medicine with quality problem which may render it unfit for use.

With regard to advertisement of Medicines the act states that medicines which do not contain a scheduled substance; or contain a Schedule 0 or a Schedule 1 substance, may be advertised to the public. Medicines which contain a Schedule 2, Schedule 3 or Schedule 4 substance may be advertised only to medical practitioners. An advertisement of a medicine must be approved by the Council before such advertisement is used to advertise medicine to the public.

Any advertisement of a medicine that contains a statement which deviates from; is in conflict with; or goes beyond, the evidence and particulars submitted in the application for registration of such medicine with regard to safety or efficacy constitutes an offence as contemplated in section 38(g) of the Act.

3. ESTABLISHMENT OF THE THERAPEUTICS INFORMATION AND PHARMACOVIGILANCE CENTER, TIPC

A working group drawn from the MoHSS Directorate of Special Programs (DSP), Tertiary Health Care and Clinical Support Services (THC& CSS) and various development partners including Management Science for Health (MSH), Medicos del Mundo (MDM) and the International Training and Education Centre on HIV / AIDS (I-TECH) was formed under the leadership of the Ministry of

Health and Social Services (MoHSS) in 2006. The working group was responsible to set up and monitor the proper functioning of the centre.

Subsequently TIPC established in 2007 with the dual functions of providing therapeutics information and monitoring safety of medicines which are already in the market. The centre serves as the Namibian Ministry of Health and Social Service's official Therapeutics Information and Pharmacovigilance centre for health care worker and the general public. The centre is currently located at the basement of Windhoek central hospital. The center is well equipped with all necessary infrastructures, databases, and electronic resources comparable to resources available in other such facilities globally.

TIPC was successfully launched in May 2008.

Major objective of TIPC

- To improve the rational use of medicines available in the country and to contribute to their safer use

Specific objectives

- To provide both proactive and query response therapeutics Information to health professionals and the general public in Namibia
- To become a reference unit on Pharmacovigilance by collecting and monitoring adverse reactions

4. NOTIFICATION SYSTEM

Patients / Family / Community health workers (CHW) verbally report any adverse event possibly associated with the use of medicines immediately to their health care provider or directly to TIPC using the simplified reporting form.

Healthcare worker, after doing appropriate investigation, immediately report any suspected adverse drug reactions, drug interaction and unusual effects to TIPC through the fax, email or post using the safety yellow form. A copy of the report is kept in the health facility for review by the TC.

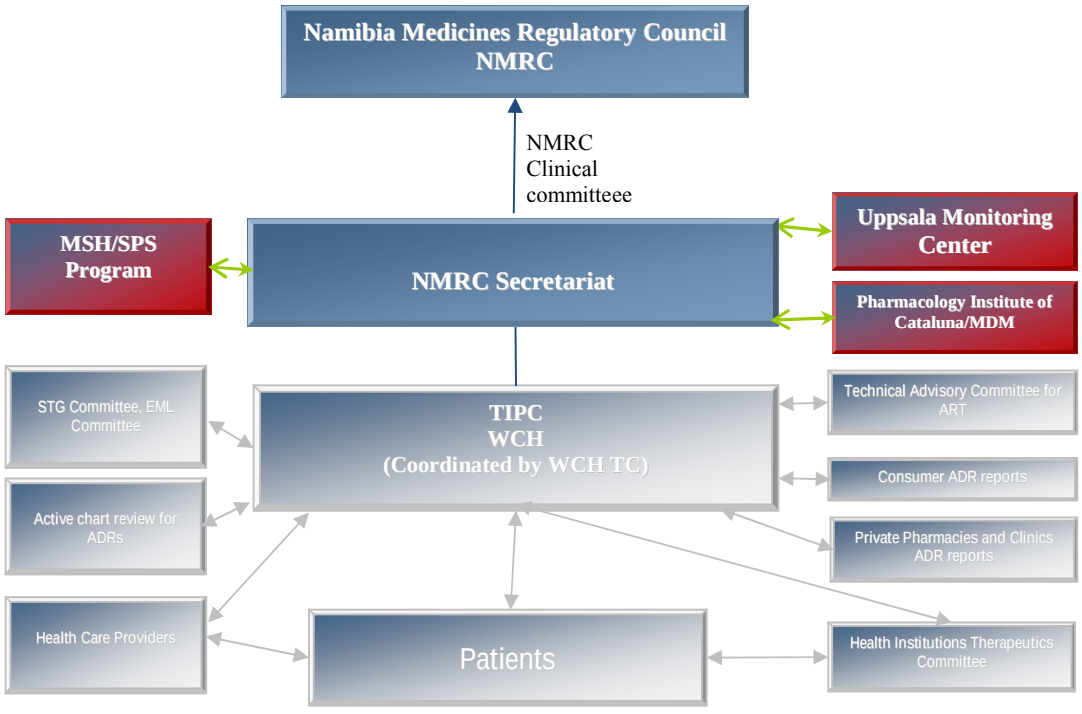
Each adverse drug reaction reported through Post, Fax, e mail or verbally through telephone will be reviewed by the MIP or the TC to sort new and follow up ADR report. New reports given a unique

Id number and follow up report linked to the 1st report. Receipt of report acknowledged. Illegible, missing or entry that is not understandable clarified with the reporter. The MIP or the TC enters data into Vigiflow within the following 48 hours. He/she look for additional information on the specific case report from product monograph and other literature and do causality assessment with the information obtained from the report and literature. The data entered in to the VIGIFLOW data base and saved. Those with all the necessary information committed to the WHO international DB (VIGIBASE).

The ADR case reports with additional information from literature are summarized and presented to Clinical Committee of the NMRC. After investigating the case further, the Clinical Committee of the NMRC recommends possible regulatory actions to be taken by NMRC.

Based on such recommendations from National Drug advisory committee (Clinical Committee of the NMRC), Namibia Medicine Regulatory Council takes regulatory decision and communicate the decision to the registration holder and all other relevant body.

Figure1. Medicine safety surveillance notification system



Keys

	Reporting lines		Technical assistance/ External collaboration		Service provision/ Internal collaboration

5. ROLES AND RESPONSIBILITIES

The success of any pharmacovigilance activity depends on the reporting of suspected adverse drug reactions which is collaborative effort from the public to the NMRC. Thus the roles and responsibilities of each actor have to be clearly defined to ensure effective pharmacovigilance activity.

Patients/ Family/ CHW

Report any adverse event possibly associated with the use of medicines immediately to their health care provider or directly to TIPC using the yellow card.

Healthcare worker/ Traditional practitioner (Herbalist)

Detection and appropriate management of adverse reactions to medicines

Documentation and immediate reporting of all serious and non serious suspected reactions, unknown or unexpected ADRs , unexpected therapeutic effects, all suspected drug interactions, product quality problem, treatment failure and medication error

Advice patients on possible adverse drug reactions and drug interactions

Prevent the occurrence of medication errors and other avoidable adverse events by using medicines rationally

Pharmacist/ pharmacist assistants

Ensure the availability of the reporting forms

Mail the ADR report to TIPC

Advice patients on possible adverse drug reactions and drug interactions

Report any suspected adverse drug reactions, drug interactions and unusual effects immediately.

Therapeutic committee (TC)

Retain the necessary documentation.

Ensure all ADR reports are kept confidential and identity of patients, reporters and trade names of the suspected drug not disclosed.

Review (analyse) reports and take corrective action to prevent adverse events

Revise the drug list of health institution

Promote rational use of drugs

Registration Holders

Inform the council of any adverse drug reaction arising from the use of the registered product within two weeks after receipt of such adverse reactions

Ensure that an appropriate pharmacovigilance system is in place in the company in order to accept responsibility and liability for its product on the market

Submit Periodic Safety Update Reports(PSUR), Company sponsored post registration study reports, etc to the council as per the registration guide

Respond promptly and fully to requests on risk-benefit information from the council

TIPC

Collect adverse reaction report

Provide feedback to reporter

Maintain ADR database

Analyze data in the database and detect genuine (generate) signals

Review adverse reaction reports and prepare case summary

Submit summary of adverse drug reaction case report to the National Drug advisory committee (Clinical Committee of the NMRC) for regulatory recommendations

Promote prevention of ADR and rational use of drugs

Collect current information on safety of medicines and disseminate to health professionals (alerting prescribers, manufacturers and the general public to new risk of adverse reactions)

Follow up the implementation of the regulatory decisions by the council

Share adverse reaction information with WHO programme for international drug monitoring

Participate in active surveillances and researches on adverse reaction

Advocacy, training and education

Communicate medicine safety information through Medicines Watch and NMRC web site

Respond to medicine safety enquiries

Public Health programes

Collaborate closely with TIPC and PC&I (NMRC)

Involve TIPC in the collection and processing of ADR report

Coordinate with the pharmacovigilance activity of the TIPC

Training of health workers in reporting adverse reactions

Clinical Committee of the NMRC

Serve as the National medicines advisory committee

Provide technical advice to the NMRC on safety and effectiveness of all medicines registered in Namibia

Advise Council in causality assessments, comparative effectiveness reviews

Provide technical advice to the Council in the post-registration evaluation of quality, safety, and effectiveness

Monitor compliance and implementation of the National Guidelines for Medicines Safety Surveillance

Advice NMRC on the implementation of post authorization safety studies, PASS

Provide advice on local PASS including observational epidemiological studies and clinical trials

Recommend national priorities concerning medicines safety studies

Serve as expert review body for the Namibia Medicine Watch and related therapeutics information publications

Provide technical advice on compliance to standards related to adverts and promotion of pharmaceuticals

Recommend interventions that will enhance the dissemination of unbiased therapeutics information and other activities to improve safety and rational use of medicines by healthcare workers and consumers

Provide technical advice to the the NMRC on all issues related to patient safety

Advice NMRC on all other issues related to medicines safety in Namibia.

Namibia Medicine Regulatory Council

Take regulatory decision based on the recommendation from the Clinical Committee of the NMRC

Communicate the regulatory decision taken by the council to the registration holder and all other relevant body using official letter and other means of communication.

After a significant ADR is detected and a decision on the course of action determined, the information must be communicated rapidly and systematically.

6. SCOPE OF PHARMACOVIGILANCE AND MEDICINE SAFETY SURVEILLANCE ACTIVITIES

The Pharmacovigilance (PV) which is "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug related problems" enables the monitoring of medicines safety and effectiveness after they are in the market. It also enables to detect use of in effective, substandard and counterfeit medicines minimizing the possibility of wastage of resources.

In developed countries where there are stringent medicine regulatory authorities, several medicines have been withdrawn from the market and several other products have received additional warnings and restrictions based on data from pharmacovigilance activities in the past.

But there is weak or no such pharmacovigilance activity (safety monitoring system) in most developing countries where patient genotype and phenotype markedly differ from developed countries. With the faster scaling up of public health programs such as HIV/AIDS and tuberculosis, several million people are taking medicines for chronic diseases. Making the situation even worse, relatively new medicines are reaching the public in greater numbers and more quickly due to availability of fund for the different programs.

The specific aims of Pharmacovigilance are:

Improve patient care and safety in relation to the use of medicines and all medical and paramedical interaction

Improve public health and safety in relation to the use of medicines

Detect problem related to the use of medicines and communicate the findings in a timely manner

Contribute to the assessment of benefit, harm, effectiveness and risk of medicines, leading to the prevention of harm and maximization of benefit

Encourage the safe, rational and more effective (including cost effective) use of medicines and

Promote understanding, education and clinical training in pharmacovigilance and its effective communication to the public

These can be achieved by:

Early detection of unknown adverse reactions and interactions and other drug induced problems

Detection of increase in frequency of previously known adverse reactions

Identification of predisposing factors and possible mechanisms underlying adverse reactions

Estimation of quantitative aspects of risk benefits analysis and dissemination of information needed to improve drug prescribing and regulation

Ultimate goal of pharmacovigilance is the safe and proper use of effective medicines.

Pharmacovigilance is concerned about the safety of medicines, medical devices, traditional and complimentary medicines, herbal medicines, vaccines, blood products and biological. It is also relevant in detection of substandard medicines, medication errors, lack of efficacy and off label use of medicines. Information on other issues like acute and chronic poisoning, drug related mortality, abuse and miss use of medicines, and interactions with other medicine and food can also be obtained from pharmacovigilance.

6.1 Types of Adverse Drug Reaction

AMR(ADR) is *noxious* and *unwanted* reaction to medicines / drugs that occurs at a *dose used in human* for diagnosis, treatment or prophylaxis. Many unwanted effects of medicines are medically trivial. It is therefore convenient to retain the term side- effects for minor effects, which are related to the pharmacological properties of the medicines.

There are two principal types:

1. Type A (Augmented) Related to the principal action of the medicine/ drug
   - Will occur in everyone
   - Dose related
   - Pharmacodynamic effects
   - Common
   - Skilled management reduce their incidence
2. Type B (Bizarre) - Not related to the principal action of the medicine/ drug
   - Will occur in some people
   - Not part of the normal pharmacology of medicine / drug

- Not dose related
- Unpredictable
- Include idiosyncrasy and drug allergy
- Account for most drug fatalities

Four subordinate types

3. Type C (continues)
   - Reaction due to long term use

4. Type D (delayed)
   - Effects like teratogenesis, carcinogenesis

5. Type E (ending of use)
   - Abrupt discontinuation e.g. rebound adrenocortical insufficiency

6. Type F (failure of therapy)
   - Treatment failure

6.2 How to recognize ADRs

Distinguishing between natural progression of a disease and medicine induced deterioration is challenging. When an unexpected event, for which there is no obvious cause, occurs in a patient already taking a drug, the possibility that it is caused by the drug must always be considered.

Describe the reaction clearly

Take proper history, try to exclude all possible cause that can explain the event like co morbid conditions, foods and other medicines concomitantly used that possibly interact

Note the time relationship between the event and use of the medicine. Some reactions immediately follow use of medicine, while others take time to develop.

Examine the patient thoroughly and do relevant laboratory investigation. Some laboratory tests are useful for early detection of sub clinical reactions, others are used to measure severity and or to monitor patient management.

Dechallenge and rechallenge

Positive dechallenge is improvement of the reaction after discontinuation of the medicine. It is a strong indicator of possible association of the medicine and the adverse event.

Rarely there may be no alternative medicine for the one suspected to have caused the reaction. In such cases when the benefit of using the medicine outweighs the risk of the reaction, it is justifiable to try to treat the patient with the same medicine with extra precautions. This is called rechallenge. Positive rechallenge is recurrence of the reaction which has subsided with prior dechallenge.

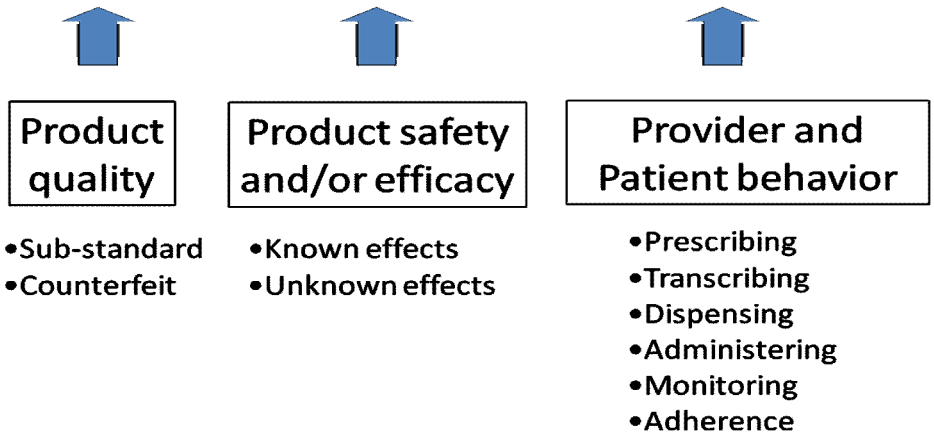
Check the pharmacology of the medicine

Check if the reaction is known and documented on the package insert or product monograph submitted during registration.

Adverse drug reaction should be considered when there is no other sufficient explanation

6.3 Sources of medical products-related adverse events

Picture and Halas



6.4 Preventing adverse events

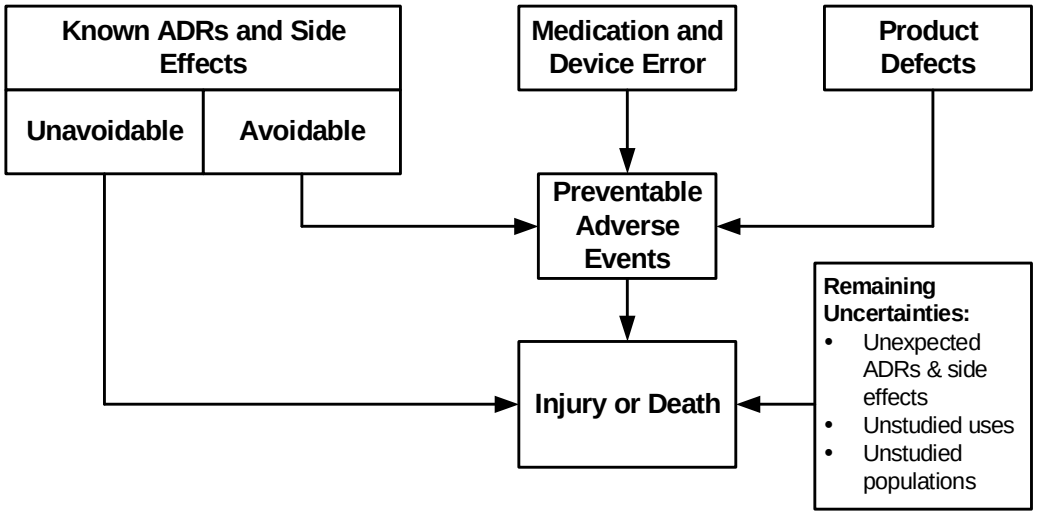
Adverse Drug Events are any unintended and undesirable response or injury caused by a drug *irrespective* of dose. Adverse drug event includes medication errors. Medication errors are errors in which the patient actually receives the erroneous prescription or erroneous dispensing, or the erroneous preparation (mixing) / administration of the medicine.

Medication errors are common to all health systems and players in the medication use process. It is common to all health professionals. But It is most often associated with prescribers, with nursing, with pharmacists, and with pharmaceutical manufacturers and regulatory agencies

The most frequent reasons for errors include:

- High staff workload and fatigue
- Inexperienced and inadequately trained staff
- Poor communications among healthcare workers including poor handwriting and verbal orders
- Environmental factors e.g. poor lighting, much noise, frequent interruptions
- Increased number or quantity of drugs per patient
- Frequency and complexity of calculations needed to prescribe, dispense, or administer
- Large number of formulary drugs and dosage forms??
- Confusing drug nomenclature, packing, or labeling
- Lack of effective drug policies and procedures

Figure 2: Schematic of Preventable and Unavoidable Adverse Events



6.5 Factors predisposing to adverse effects

It is well known that different patients often respond differently to a given treatment regimen. Therefore, in addition to the pharmaceutical properties of the drug, there are characteristics of the patient which predispose to ADRs.

The very old and the very young are more susceptible to ADRs. Drugs which commonly cause problems in the elderly include hypnotics, diuretics, non-steroidal antiinflammatory drugs, antihypertensives, psychotropics and digoxin.

All children, and particularly neonates, differ from adults in the way they respond to drugs. Some drugs are likely to cause problems in neonates, but are generally tolerated in children.

Besides the condition being treated the patient may also suffers from another disease, such as kidney, liver or heart disease. Special precautions are necessary to prevent ADRs when ptients have such intercurent illness.

Medicines interactions are among the commonest causes of adverse effects. When two drugs are administered to a patient, they may either act independently of each other, or interact with each other. Interaction may increase or decrease the effects of the drugs concerned and may cause unexpected toxicity. As newer and more potent drugs become available, the number of serious drug interactions is likely to increase. Interactions may also involve non-prescription medicines, non-medicinal chemical agents, social drugs such as alcohol, traditional remedies, as well as certain types of food.

Interactions may occur between medicines when

- the medicines compete for the same receptor or act on the same physiological system.
- one drug alters the absorption, distribution or elimination of another drug, such that the amount which reaches the site of action is increased or decreased.
- or indirectly when a medicines-induced disease or a change in fluid or electrolyte balance (physiologic change) alters the response to another medicine.

Genetics

It is well known that the genetic make-up of individual patient may predispose to ADRs.

Use of other traditional medicines

Patients who have been or are taking traditional herbal remedies may develop ADRs. It is not always easy to identify the responsible plant or plant constituent.

7. METHODS FOR MEDICINE SAFETY SURVEILLANCE

7.1 Spontaneous reporting

When an adverse reaction to medicine is suspected, one has to complete the reporting form (Annex I) and send it to the TIPC address by mail or fax. Adverse reactions can also be reported electronically using electronic reporting form which is available NMRC website at www.nmrc.com.na/tipc/adr report form or can simply be reported by calling TIPC.

TIPC (Medicines Information Pharmacist) ensures that the ADR forms are readily available at all treatment facilities and conduct quarterly *survey to* review availability of the ADR forms at treatment facilities. Electronic reporting form will also be available which can either be downloaded or completed directly and submitted at the NMRC website.

All reports submitted to TIPC will be kept confidential.

What to report

Report all suspected reaction to modern medicines, traditional / complimentary medicines, herbal medicines, vaccines, blood products and biological, dental and medical supplies, contrast media and cosmetics.

Product quality problems such as colour change, separating of composition, caking, change of odour, questionable stability, suspected contamination, poor packaging and labelling, miss labelling, incomplete pack, defective and expired product can also be reported.

When to report

Any suspected ADR should be reported to the TIPC as soon as possible. Reporting while the patient is still in the health institution will give the reporter the chance to clear any ambiguity by re-questioning or examining the patient.

7.1.1 Completing the ADR reporting form

General

The ADR reporting form (Annex I) comprise basic information about the patient, the drug, the adverse reaction, the action taken and the outcome

- The age, sex, description of the adverse reaction, information on suspected drug, and outcome are all considered essential and should be completed.
- The form should be completed by: Physicians, Medical Officers, Dentist, pharmacists, Nurses
- Complete the form to the best of your ability
- Avoid non-standard abbreviations.
- Use a separate form for each patient.
- Write legibly.

Specific

The patient's identity

Information about the patient's age, sex, weight, ethnicity and use of substance of abuse should be provided. The passport (card) number have to be stated as it is useful to get additional information when needed.

Information on the suspected drug

This information includes the name of the medicine, source, the dose, route of administration and the impact of withdrawal and re-administration of the suspected medicine upon the adverse reaction.

Use brand name of suspected drug(s). If generic name is used, specify the manufacturer of the drug. Avoid non-standard abbreviations such as PPF, CAF, MTC, TTC, etc. List any other prescription, non- prescription drugs and/or traditional medicine used concurrently with the suspected drug with all description i.e. brand name, route, dosage form, strength, frequency, indication, date started and date stopped.

The dosage form such as tablet, capsule, syrup, suspension, elixir, emulsion, injection, eye drop/ointment, topical crème/ ointment, otic drop, nasal drop, suppositories rectal/ vaginal etc. should be stated. The strength must also be expressed in metric system. e.g. 500mg tab, 250mg/5ml syrup,1gm rectal suppository etc. Sometimes strength can be expressed in % e.g. 2% hydrocortisone ointment.

Frequency of drug administration should be clearly notified using standard abbreviations. e.g. 3 times a day as tid or 8 hrly , 2 times a day as bid or 12hrly, 4 times a day as qid or 6 hrly etc. Route of administration expressed using standard abbreviation (Annex II). E.g. Per os as PO, Intra-muscular as IM, Intra-vascular as IV, Per-rectal as PR, Topical as TO etc.

The date the drug was started and discontinued (if applicable) is an important data to assess the cause and effect relationship of the drug and adverse reaction. Therefore it has to be stated clearly on the report form as date/ month/ year. If the drug has not been discontinued at the time of reporting, write continuing.

Write the reason why the drug was used or the diagnosis for which the drug prescribed for both suspected drug and other drugs concurrently used.

Information on the adverse reaction

Clear and brief description about the nature of adverse reaction, the date of onset, duration, time course and laboratory test results including "negative" and normal results of any relevant test performed should be reported. The severity of the reaction i.e. weather it has necessitated prolonged hospitalization or not, discontinuation of the drug or not, etc. and the outcome of dechallenge and rechallenge with the suspected medicines have to be reported.

Additional information

Any reaction the patient may have experienced previously, particularly similar to the current adverse event, either caused by the same or different medicine has to be reported. Other relevant medical history, such as allergy, chronic disease, pregnancy and other factors, which may contribute i.e. herbal products, foods and chemicals, should be included under this heading. You may also add here why you think the adverse effect is due to the particular medicine.

Follow-up report for an ADR that has already been reported

Any follow-up information for an ADR that has already been reported can be sent on another ADR form, or it can be communicated by telephone, fax or e-mail to TIPC indicating that it is follow up information, the date of the original report and the report case number so that the follow up information can be matched with the original report. It is very important that follow-up reports are identified and linked to the original report.

In case where the health care professional has concurrently reported ADRs to the manufacturer, he/she should indicate on the TIPC report that the case has also been reported to manufacturer.

TIPC Patient Medicine Safety Alert Card

Patient who experienced serious adverse drug reaction shall be given TIPC Patient *Medicine Safety* Alert Card by the health care provider who diagnosed and managed the reaction.

The TIPC Patient Medicine Safety Alert Card (Annex III) alerts all healthcare workers that the bearer of the card had experienced serious intolerance (typically hypersensitivity reactions) or had experienced a serious adverse reaction to a particular medicine.

The card will be carried by the patient at all times and be presented to healthcare worker at the time of consultation. This will help the healthcare worker identify the patient's medicines-related co-morbidity and prevent similar drug reactions.

7.1.2 Expedited reporting requirements

All serious reactions occurring in Namibia must be reported on an expedited basis. Expedited reports should be submitted immediately and not later than 15 calendar days from receipt of the minimum information required for an adverse reaction report by any personnel of the manufacturer.

A second company who entered into relationships with manufacturer for the marketing of the suspected product should submit adverse reaction reports as soon as any personnel of the sponsor receive the minimum information. The time frame for regulatory submission should be no longer than 15 days from first receipt of the minimum information by the second company.

Serious suspected adverse reactions occurring in all post-registration studies of which the manufacturer is aware should be reported to the NMRC on an expedited basis.

Lack of efficacy of medicines used for the treatment of life-threatening diseases, vaccines and contraceptives should be considered as requiring expedited reports.

When additional medically relevant information is received for a previously reported case, the reporting time is considered to begin again for submission of the follow-up report. In addition, a case initially classified as a non-expedited report, would qualify for expedited reporting upon receipt of follow-up information that indicates the case should be re-classified (e.g., from non serious to serious).

7.1.3 Reporting product quality and medication errors

Medicines quality concerns include a number of hazards, which may be due to improper formulation, packaging, or labelling. Some product quality defects may occasionally pose a threat. Problem of quality defect that occur during the manufacturing, shipping, or storage of prescription or over-the-counter products shall be reported to the Marketing Authorisation Holder or direct to TIPC using the safety yellow form. On receipt of report of medicine quality defect that are associated with serious adverse reactions, Marketing Authorisation Holder should assess the situation and take immediate action within reasonable time. Simultaneously, Marketing Authorisation Holder should report such product quality defects and measure taken to NMRC in writing.

"A medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use."

Reporting of Medication Errors

Medication errors can occur when prescribing, repacking, dispensing, or administering a product. Common causes of medication errors include poor communication, patient misunderstanding, and ambiguities in product names or directions for use.

Medication Errors Reporting by health care professionals

Errors, near-errors or hazardous conditions including administering the wrong drug, strength, or dose of medications; confusion over look-alike/sound-alike drugs; incorrect route of administration; calculation or preparation errors; misuse of medical equipment; and errors in prescribing, transcribing, dispensing, and monitoring of medications may be reported to TIPC using the safety yellow form. You will have the option of including or not including your identity and location on the yellow safety form. Medication Errors reporters are encouraged to submit associated materials such as product photographs, containers, labels, prescription order scans, etc, that help support the information being submitted. TIPC guarantees confidentiality of information received and respects reporters' wishes as to the level of detail included in publications.

Case studies can be published on the Namibian Medicines Watch and NMRC website about recommendations to prevent errors to alert healthcare professionals and others. Reporter's identity, affiliation, and location are not revealed in these reports.

When reporting errors, please include the following:

- Describe the error or preventable adverse drug reaction. What went wrong?
- Was this an actual medication error (reached the patient) or are you expressing concern about a potential error or writing about an error that was discovered before it reached the patient?
- Patient outcome.
- Type of practice site (hospital, private office, retail pharmacy, drug company, long-term care facility, etc).
- The generic name (INN or official name) of all products involved.
- The brand name of all products involved.
- The dosage form, concentration or strength, etc.
- How was the error discovered/intercepted?

- State your recommendations for error prevention.

NB. Do not submit any patient identifiable information when reporting medication errors

Medication Errors Reporting by Marketing Authorisation Holder

The Marketing Authorisation Holder should report cases of medication errors that are associated with serious adverse reactions on an expedited basis. Cases not associated with adverse reactions and near misses should only be reported in PSUR. Cumulative information on medication errors, resulting in adverse reaction or not, should be discussed in the section of the Periodic Safety Update Report on the overall safety evaluation. The potential for medication errors and their prevention should be addressed in the Risk Management Plan.

7.1.4 Reporting suspected adverse events to herbal medicines and other complementary products

Health professionals who are provider of herbal medicines, patients / consumer and manufacturers should report any suspected adverse reactions to herbal medicines. Details of the suspected herbal product species name and / or brand name or ingredients name(s), country of origin, batch number, expiry date and provider should be provided. The precise Latin binomial botanical name (genus, species, author as well as name of family) of the medicinal plants concerned should be used whenever possible together with the plant parts used and extraction and preparation methods employed. Suspected adverse reaction to herbal medicines in the prescription medicines categories, in the non-prescription medicines categories and other herbal products intended for use in health care should be reported to TIPC using yellow reporting form.

Herbal products targeted for safety monitoring

According to their regulatory status

- Herbal medicines in the prescription medicines category
- Herbal medicines in the non-prescription medicines category
- Other herbal products intended for use in health care

According to their registration / marketing status

- Herbal medicines undergoing the new drug development process: in clinical trials prior to national drug regulatory approval.
- Herbal medicines undergoing the new drug development process: under post marketing safety surveillance.

- Herbal medicine undergoing re-evaluation under the current protocol: in clinical trials
- Herbal medicine undergoing re-evaluation under the current protocol:
- Herbal medicines on the market:under post-marketing safety surveillance.
- Other herbal products marketed for health care, such as dietary supplements.

How to report suspected adverse events to herbal medicines

A single adverse reaction reporting form is used covering all medicines, including herbal medicines. Report can also be made through telephone, letter or e-mail. If possible, a sample of herbal product and its packaging should be submitted with the report.

If the finished herbal product concerned or its raw material were imported from other countries, the drug regulatory authority of the exporting country may be able to provide helpful information.

The precise Latin binomial botanical name (genus, species, author; as well as name of family) of the medicinal plant concerned should be used whenever possible, together with information about the plant parts used and the extraction and preparation methods employed. This information allows accurate comparison with other reports. A common vernacular name may be used in order not to delay or cancel submission of a report. The TIPC will collaborate with the relevant departments of universities regarding taxonomic (botanical and chemical) identification and botanical and vernacular nomenclature.

Assessment of case reports

Assessment of reports on adverse reactions to herbal medicines will be undertaken by TIPC in the same way as for other medicines. The assessment is based on:

- The association in time between administration of the herbal product and the event
- The outcome of dechallenge and rechallenge.
- Known pharmacology (including current knowledge of the nature and frequency of adverse reactions).
- Medical or pharmacological plausibility (the sequence of symptoms,signs and laboratory tests and also pathological findings and knowledge of mechanisms).
- Likelihood of other causes or their exclusion
- Testing for adulterants or contaminants that could be the source of adverse events

Each data element in the report should be considered and a causality assessment made using a standard approach.

Inappropriate use

Misdiagnosis and use outside an established tradition by poorly trained providers and practitioners can be unsafe and may lead to overdose and adverse reactions. A change in the procurement sources of herbal materials, misidentification of the medicinal plant (s) and /or herbal material(s) used, or a change in the mode of preparation should be taken into account when assessing individual cases that may lead to entirely preventable and sometime serious adverse reactions. It is therefore important to determine whether a reaction is caused by the way a herbal medicine has been used or prepared.

7.1.5 Patients and Consumer reporting

Simplified reporting form (yellow card) will be used to collect information on adverse experience from patients. See annex VI. The reports coming from patients will be entered in to a separate database. Further information on the report can be sought from the health care provider for serious and /or unknown reaction reported directly from patients.

7.1.6 Processing ADR report

Identifying and documenting ADR report

ADR report can be received through phone calls or completed forms returned through Fax and Post or through an e-mail. In the case of ADR report received through phone calls, TIPC staff receiving the call enters available data in to ADR form as provided by the caller.

All reports that are coming in will be reviewed for completeness and whether the report is a new ADR report or follow up report. New reports will be given new unique Id number and follow up report will be matched with the unique Id number which was given to the 1st report. Reporter will be contacted through phone calls, e-mails or fax and acknowledged for sending ADR report. At the same time missing data or illegible entries will be clarified and the reporter will be informed of the unique Id number given to his report.

TIPC staffs will enter data from the report forms into the Vigiflow within the following 48 hours and archive copies of received forms

Entering data into the Vigiflow

Technical staffs trained on the use of the Vigiflow will enter all required data into Vigiflow and save it. Missing data in required fields will be clarified again by contacting the reporter and further information will be sought from product monograph and other literature. All case report will be

assessed for causality with the information available on the report. The information entered in to the data base (VIGIFLOW) shall be updated and saved whenever there is new information. Those reaction case reports with all the necessary information will be committed to the international DB (VIGIBASE).

Evaluation of the ADR report

The team of experts at the Therapeutics Information and Pharmacovigilance Centre evaluates each report for the temporal relationship between the reaction and the drug, result for dechallenge and rechallenge, the seriousness of the reaction, the current labelling lists the reaction and whether the reaction is reported on medical literature. ADR report will be classified as Certain, Probable/Likely, Possible, Unlikely, Inaccessible/unclassified, and conditional/unclassified according to the WHO causality assessment criteria (See annex II). Reaction to new medical entities and unexpected or serious reactions receive priority. Additional information may be requested from manufacturer or reporter if needed.

Documenting ADR reports

TIPC will run statistics on the Vigiflow data base and produce summary of reported ADRs and conduct literature scan for ADRs in relevant publications like *reactions* and other publications at least once weekly (Preferably on Fridays)

It document PSUR, ICSR, and other medicines safety reports from across the world particularly those related to medicines in the Namibia medicines register by liaising with NMRC to confirm if such reports were submitted

The centre also prepares summary of the case and present to the Expert Advisory Committee(EAC)/ Clinical Committee of NMRC)

Communicating ADR reports

Signals generated by running query on Vigiflow's will be communicated to health care professionals and actively monitored. The drug advisory committee evaluates monitored ADR using available medical literature, and reactions to medicines within the same pharmacologic class and availability of additional databases for further investigation.

The committee will finally recommend action to be taken by the regulatory body on the particular medicine with serious adverse drug reaction. The possible measures are: withdrawal of the drug

from the market, change on the product labelling and alert prescriber and consumer to the potential hazards.

Results from the literature scan and the statistics and regulatory measures taken will be communicated to health care professionals by using next issue of the *Medicines Watch* and all other available means after approval from the EAC / Clinical Committee of NMRC.

7.1.7 Promoting Spontaneous adverse event reporting

In countries where there is an organized ADR monitoring, the number of ADR reported remained extremely low within the medical profession. Most physicians considered ADR to be unexpected or harmful reactions; in fact half of them exclude well-established side effects as ADRs.

Though almost all physicians would take some action (i.e. withdrawing the drug or reducing the dose) when ADR occurred or suspected, only few would actually notify or seek advice. The most common explanation for the non-compliance in reporting ADRs was that unusual or serious reactions were infrequent and the assumption those common and trivial ones did not warrant reporting. The other factors were indifference, fear of personal consequence and uncertainty about what to report.

For the above reasons adverse drug reactions will remain largely outside the reach of monitoring agency. Therefore diverse understanding of the concept of ADR remains critical issue in the non-compliance of physicians in reporting ADRs. The pharmacy unit and pharmacy and therapeutic committee should exert effort to raise the interest of health professionals to report ADR and not to overlook the possibility of ADR.

It has to be known that data received by the national center will only be used for prevention of ADR and promotion of rational and safe drug use. It will not be made available to support any legal, administrative or other actions to the detriment of the reporting health care professional, the patient or the coordinator. In this regard all the collected report will be kept confidential and identity of patients and reporter will not be disclosed. Publications will not disclose trade names unless regulatory actions have been taken.

7.1.8 Data collection, investigation, management and reporting in Public health programs

Expert from TIPC will be the secretary for the expert safety review panel to be appointed in each public health programme. Health worker from primary health care centre with the district health officer or program manager, the tertiary health care hospital and expert from TIPC form the unit responsible for the reporting, detection, investigation and managing reported ADRs. The district program manager coordinates adverse reaction monitoring activity. Send all suspected case reports without delay to the TIPC for entry in to the data base which can later be presented to the safety review panel.

7.2 Active surveillance

Although spontaneous ADR reporting system is a powerful generator of signal , it has limitation of difficulty to differentiate possible ADR from disease progression or coincidental problems. It has also a problem of under and over reporting. It is an excellent method for generating signal. However, it cannot be used to calculate the true rate at which ADR is occurring in a population in question. In contrast to passive surveillance, active surveillance obtains comprehensive data on individual adverse reports and also seeks to ascertain the ratio/ number of ADRs via a continuous pre-organized process. Therefore, there is a need for an active surveillance which is more structured, systematic, comprehensive, and proactive way to follow the evolving drug experience in large population.

7.2.1 Cohort Event Monitoring

Cohort Event Monitoring is prospective, inceptional (each patient is monitored from the beginning of treatment), dynamic (new patients are added as the programme proceeds) and longitudinal (effects are studied over time). It has the advantages to get complete adverse event and/or adverse reaction profile and it is possible to produce rates. Events can be disaggregated by age, sex, duration to onset- can be used to examine safety issues in special populations (the elderly, children, patients with co-morbid conditions, pregnant women)

The two basic requirements for the collection of data for cohort event monitoring are establishing a cohort of patients for each medicine and/or medicine combination and recording adverse events for patients in the cohort(s) for a defined period.

7.2.2 Prescription event monitoring (Drug event monitoring)

Prescription event monitoring (PEM) is a non-interventional cohort technique in which patients are identified from dispensed prescriptions,

Questionnaires requesting detailed information including suspected ADRs since the first prescription for the study drug posted to the prescribing doctor. Outcome data obtained from the information on returned forms. It is used to generate hypothesis. It is applicable mostly for new medicines intended for long term widespread use. It can be used by the TIPC to examine the safety of new medicines intended for widespread use in primary care.

7.2.3 Case-control studies

Case-control studies are used to validate signals and to identify risk factors for adverse events (establishing association between drug and one specific rare adverse event. It compares two groups: those with a condition (event) under study (cases) and a similar group who do not have the condition (controls) by looking backwards in time (retrospectively) to measure the exposure status of the two groups (to the medicine) and compare to estimate the relative risk of developing the condition in the two groups. Compares two groups: those with a condition (event) under study (cases) and a similar group who do not have the condition (controls) by looking backwards in time (retrospectively)

7.2.4 Registries

Disease registries (e.g. congenital malformations) can help collect data on drug exposure and other factors associated with a clinical condition. It is a list of patients presenting with the same characteristics.-e.g. a disease (disease registry) or a specific exposure (drug) registry

Some exposure registries can address drug exposures in specific populations, such as pregnant women-pregnancy exposure registry. Pregnancy exposure registry is a prospective observational study that collects information on medicinal product exposure during pregnancy and the associated outcomes.

7.2.5 Drug Utilization Review studies

Drug Utilization Review (DUR) studies describe how a drug is marketed, prescribed, and used in a population, and how these factors influence outcomes, including clinical, social, and economic outcomes. It can be used to determine rates. It can also be used to describe the effect of regulatory actions and media attention on the use of drugs, as well as to develop estimates of the economic burden of the cost of drugs. Compare recommended and actual clinical practice

7.2.6 Guidelines for conducting active surveillance studies

Post-authorisation safety studies may be conducted for the purpose of identifying previously unrecognised safety concerns (hypothesis-generation), investigating potential and identified risks (hypothesis-testing in order to substantiate a causal association), or confirming the known safety

profile of a medicinal product under normal conditions of use. They may also be conducted to quantify established adverse reactions and to identify risk factors.

Post-marketing safety studies would be appropriate in situations where there is uncertainty as to the clinical relevance of a toxic effect in animals; where there is uncertainty as to the safety profile; where there is a need to better quantify adverse events identified in clinical trials and elucidate risk factors; where there is a need to confirm or refute safety concerns suggested by other sources (e.g. spontaneous reporting); where there is a concern regarding the use of the medicinal product (e.g. to quantify the off-label use); and when there is a need to evaluate the effectiveness of a risk minimisation measure.

The research priorities should be set by the NMRC. All proposals for the conduct of pharmacoepidemiology studies should be submitted to the NMRC. Protocol should be approved by the ethical Committee formed to ensure adherence to the good pharmacoepidemiology practices, GPP[1]. The Committee will also ensure that the objective of the study is relevant to Namibia and the responsibilities and plans to ensure compliance to international ethical standards clearly stated.

A variety of designs may be appropriate including observational cohort studies, case-control studies or registries. Clinical trials involving systematic allocation of treatment (e.g. randomisation) may also be used to evaluate the safety of authorised products. The design to be used will depend on the objectives of the study, which must be clearly defined in the study protocol. Any specific safety concerns to be investigated should be identified in the protocol and explicitly addressed by the proposed methods. A reference to the Risk Management Plan should be made in the protocol when such a plan exists.

Responsibilities for the conduct of Post-Authorisation Safety Studies

The Marketing Authorisation Holder who initiates, manages and/or finances the study is responsible for its conduct and should meet the pharmacovigilance obligations concerning PASS. The study should be supervised by a designated monitor(s) or monitoring organisation and the names of the monitors should be recorded in the study documents. In case the Marketing Authorisation Holder does not directly conduct the study, detailed and clear contractual agreements for meeting pharmacovigilance obligations should be documented.

[1] International Society for Pharmacoepidemiology, ISPE. Guidelines for Good Pharmacoepidemiology Practices, GPP. PDS 2008; 17: 200–208

Studies requested by the council

Meetings will be organised between NMRC and the Marketing Authorisation Holder in order to agree upon a protocol and a timetable. A member of the NMRC with relevant skills in the type of study under consideration will serve as a co-investigator for the study. When the Marketing Authorisation Holder considers that the protocol requires a major amendment, this should be reported to NMRC. Refinements of exposure and/or case definitions will normally not require notification.

Studies performed at Marketing Authorisation Holder's initiative

When the study has commenced, the Marketing Authorisation Holder should inform the NMRC. Any major amendment to the protocol should be reported accompanied by a justification for it. Refinements of exposure and/or case definitions will normally not require notification.

Reporting of Adverse Reactions

Reports of all serious adverse reactions arising from such studies should be reported on an expedited basis (i.e. within 15 days), to the NMRC. These reports should also be included in the PSURs. Reports on non-serious adverse reactions should be reported on PSURs.

Marketing Authorisation Holders should ensure that they are notified by the investigator of serious adverse reactions and, if specified in the study protocol, of events (those not suspected by the investigator or the Marketing Authorisation Holder to be adverse reactions).

All adverse reactions/events including those which are considered non-serious, should be summarised in the final study report.

In certain study designs, such as case-control or retrospective cohort studies in which it is not feasible or appropriate to make an assessment of causality between medical events recorded and the medicinal products at individual case level, expedited reporting of Individual Case Safety Reports (ICSRs) is not required.

Progress and Final Study Reports

a) Studies requested by the council

Marketing Authorisation Holders should provide a study progress report annually, or more frequently as requested by NMRC (e.g. according to the Risk Management Plan milestones) or on

their own initiative. If the study is discontinued, a final report should also be submitted, which will include the reasons for stopping the study.

The content of the progress report should follow a logical sequence and should include all the available data which is judged relevant for the progress of the study; e.g. number of patients who have entered the study according to their status (exposure, outcome, etc.), problems encountered and deviations from the expected plan. After review of the report, the council may request additional information.

A final study report should be submitted according to an agreed timetable (e.g. Risk Management Plan milestones). The findings of the study should be made public, preferably through scientific journals.

b) Studies performed at the Marketing Authorisation Holder's initiative

Progress and final reports should be included or updated in the corresponding PSUR and/or Risk Management Plan. When a safety concern is raised, a report should be submitted immediately to the council. The findings of the study should be made public, preferably through scientific journals.

Post-authorisation studies should not be planned or conducted for the purposes of promoting the use of medicinal products. Company sales and marketing representatives should not be involved in studies in such a way that it could be seen as a promotional exercise, such as in the recruitment of patients and physicians.

Participation of Healthcare Professionals

Subject to the Healthcare Professional's terms of service, payment should be restricted to compensation of the Healthcare Professional for any additional time and expenses incurred. No additional payment or inducement for a Healthcare Professional to participate in a post-authorisation safety study should be offered or given.

Ethical Issues

For non-interventional post-authorisation safety studies, the Marketing Authorisation Holders and investigators should follow relevant national legislation in addition to the guidance given here.

The highest possible standards of professional conduct and confidentiality must always be maintained and legislation on data protection followed. The Patient's right to confidentiality is

paramount. The Patient's personal identifiers should be replaced by a code in the study documents, and only authorised persons should have access to identifiable personal details if data verification procedures demand inspection of such details. Responsibility for the retrieval of information from personal medical records lies with the Healthcare Professional(s) responsible for the Patient's care. Such information from medical records should be provided to the Marketing Authorisation Holder, who is thereafter responsible for the handling of such information.

It is recommended that non-interventional post-authorisation safety studies are referred to an Ethics Committee. Studies conducted entirely using records not containing any personal identifiers (e.g. anonymised records) may not require an ethical review of individual study protocols.

Procedure for Complaints

Concern on post-authorisation safety study, its objective, design or conduct (e.g. using the study as a promotional activity), should be referred to the council.

8. ONGOING BENEFIT-HARM ASSESSMENT

One of the key responsibilities of Marketing Authorisation Holders is to immediately notify the NMRC of any change in the balance of risks and benefits of their products. Any failure to do so may pose a significant threat to public health. Any evidence of failure to notify such changes will result in consideration of enforcement action by the Council.

Overall risk-benefit assessment should take into account and balance all the benefits and risks. Risk-benefit assessment should be conducted separately in the context of each indication and population, which may impact on the conclusions and actions.

Assessment of Benefits

When a new or changing risk is identified, it is important to re-evaluate the benefit of the medicinal product using all available data. The benefit of a medicinal product can be seen as the decrease in disease burden associated with its use. Benefit is composed of many parameters including: the extent to which the medicinal product cures or improves the underlying condition or relieves the symptoms; the response rate and duration and quality of life. In the case of prophylactic medicinal products, the benefit may be considered as the reduction of the expected severity or incidence of the disease. With diagnostics, the benefit will be defined in terms of sensitivity and specificity or, in other words, false negative and false positive rates. Any available information on misuse of the product and on the level of compliance in clinical practice, which may have an impact on the evaluation of its benefits, should also be considered. The quality and degree of the evidence of benefit should be taken into account. Benefit should, as far as possible, be expressed in quantitative terms in a

way that makes it comparable to the risks.

Assessment of Risks

Assessment of risk involves a stepwise process requiring identification, confirmation, characterization (including identification of risk factors), and quantification of the risk in the exposed population. Overall assessment of risk should consider all available sources of information, including:

- Spontaneous adverse reaction reports;
- Adverse reaction data from studies which may or may not be company-sponsored;
- In vitro and in vivo laboratory experiments;
- Epidemiological data
- Registries, for example of congenital anomaly/birth defects;
- Data published in the worldwide scientific literature or presented as abstracts, posters or
- Communications
- Investigations on pharmaceutical quality, and
- Data on sales and product usage.

Important issues, which should be addressed in the assessment of adverse reactions, include evidence of causal association, seriousness, absolute and relative frequency and presence of risk factors, which may allow preventive measures. The quality and degree of evidence of risk should be taken into account. In the assessment of risks and consideration of regulatory action, it is important to note that rarely even a single case report may establish a causal association with the suspected medicinal product and impact on the risk-benefit balance. Risk assessment should also take account of the potential for overdose, misuse, abuse, off-label use and medication errors.

When new safety concerns are identified, which, could have an impact on the overall risk-benefit balance of a medicinal product, the Marketing Authorisation Holder should propose appropriate studies to further investigate the nature and frequency of the adverse reactions. A new or updated Risk Management Plan should be proposed accordingly. The studies should comply with GPP.

Risk-Benefit Assessment

Whenever possible, both benefits and risks should be considered in absolute terms and in comparison to alternative treatments. The magnitude of risk that may be considered acceptable is dependent on the seriousness of disease being treated and on the efficacy of the medicinal product. The populations being treated must also be taken into account.

Improving the Risk-Benefit Balance

The Marketing Authorisation Holder should aim to optimize the safe use and the risk-benefit balance of an individual product and ensure that the adverse effects of a medicinal product do not exceed the benefits within

the population treated. The risk-benefit balance of a medicinal product cannot be considered in isolation but should be compared with those of other treatments for the same disease.

The risk-benefit balance may be improved either by increasing the benefits (e.g. by restricting use to identified responders), or by reducing the risks by risk minimising measures (e.g. by contraindicating the use in patients particularly at risk, reducing dosage, introducing precautions of use and warnings and, if appropriate, pre-treatment tests to identify patients at risk, monitoring during treatment for early diagnosis of adverse reactions. When proposing measures to improve the risk-benefit balance of a product, their feasibility in normal conditions of use should be taken into account. If dose reduction is considered as a method of risk minimization, the impact of dose reduction on efficacy should be carefully evaluated.

The following types of action may be necessary and may be initiated by the Marketing Authorisation Holder or by the Council:

- Variation of marketing authorization(s) in respect of the indication, dosing recommendations, contraindications, warnings and precautions for use or information about adverse reactions or other sections of the SPC and the Package Leaflet (PL);
- Direct provision of important safety information to Healthcare Professionals and Patients/the public (e.g. through letters and/or bulletins or via electronic media)

If there are important new safety concerns requiring urgent action, the Marketing Authorisation Holder, should initiate an urgent safety restriction (USR). These measures should be immediately communicated to the council. If no objections are raised within 24 hours after receipt of an application, the USR may be introduced and the corresponding application for the variation should be submitted without delay to council.

Withdrawal of a medical product from the market

Market withdrawals are a manufacturer's removal or correction of a distributed product which involves a minor violation that would not be subject to legal action by the NMRC, or which involves no violation. In the event that the overall risk-benefit balance is considered to be unfavourable and proposed risk minimization measures are considered inadequate to redress the balance, the medicinal product should be withdrawn from the market and Healthcare Professionals and Patients/the public should be informed as appropriate. Such action may be taken voluntarily by Marketing Authorization Holders. It is recommended that any such intended measure be discussed at an early stage with the council. The council should be informed immediately of any definite action.

Recalls are a firm's removal or correction of a marketed product that the NMRC considers to be in violation of the laws it administers and against which the agency would initiate legal action, e.g.,

seizure. Recalls may be conducted on a manufacturer's own initiative, by request from NMRC, or by NMRC order under statutory authority.

9. THERAPEUTICS INFORMATION IN MEDICINE SAFETY SURVEILLANCE

Different printed and electronic reference materials such as journals (clinical pharmacy and therapeutics, pharmacology, infectious disease, public health, AIDS and other fields of medicine) text books, safety update report, WHO publications, electronic data base(micromedex, chchrane Library), medicines interaction and toxicology references are available at the TIPC. It assists the search for current information and provide access to latest references to health care providers, EMLC, STG committees and the general public.

9.1 Literature review and comparative effectiveness

The goal of TIPC in review of Guidelines and Comparative Effectiveness Search is to utilize information from notable guidelines and evidence-based publications and abridge and adapt their recommendations to local relevance in Namibia. The centre routinely search the following databases

1. Clinical practice guidelines and consensus statements- Notable international guidelines databases; Guideline International Network (GIN), National Guidelines Clearinghouse (NGC)

   Search on key individual guidelines databases like NICE, SIGN,

2. Systematic reviews and meta-analysis

   Cochrane Library of systematic reviews

   Other large systemic reviews of randomized controlled studies and observational studies not included in the Cochrane libraryComparative effectiveness / Health technology assessment reviews

3. Comparative effectiveness review conducted by Agency for Healthcare Research and Quality (AHRQ), Canadian Coordinating Office for Health Technology Assessment

4. Drug information bulletins

WHO Drug Information, member bulletins of the International Society of Drug Bulletin (ISDB) including Prescrire International, Regulatory information newsletters including FDA drug safety newsletter, MHRA Drug safety update, and WHO Pharmaceutical newsletter

Conclusions and recommendations from these databases will be helpful for decision making by health managers, clinicians, healthcare workers. TIPC produces summary of comparative effectiveness and communicate it to the health care professionals and relevant players using TIPC publications.

9.2 Publication of Namibia Medicine Watch, IEC materials and communication activities

The center produces *Medicines Watch* and other printed IEC materials to promote rational and safe use of medicines. It provides information that improves regulation, prescribing, dispensing and use of medicines. The *Medicines Watch* provides therapeutics information that can guide treatment decisions, support essential medicines management system and guide regulatory and guidelines decisions.

The target audience for the *Medicines Watch* include all health care workers particularly doctors, nurses, pharmacists, community health care workers, other health care workers, and consumers in Namibia. The publication will work closely with local opinion leaders and local associations like the Namibia Medical Association, the Pharmaceutical Society of Namibia, Namibia Nurses Association, the Interim Health Professions Councils of Namibia, and other professional associations.

10. GUIDELINES FOR ETHICAL PROMOTION OF HEALTH PRODUCTS

Samples of informational and promotional materials must be submitted to NMRC for approval prior to any promotional activity. One shall not therefore carryout promotional activity unless approved by the NMRC.

The information on promotional material must be consistent with the information in the product monograph. The Information shall be based on scientific evidence, capable of substantiation, must clearly and accurately set out and must be sufficiently comprehensive to enable the recipient to make an independent assessment of the therapeutic usefulness of the preparation

All promotional claims concerning medicines should be reliable, accurate truthful, informative, balanced, up-to-date and capable of substantiation. All promotional claims should not contain

misleading, unverifiable statements, omissions, exaggerated and should not contain disparaging comparisons.

Any medicine, medicinal products, active ingredient or substance shall not be advertised for purposes that cause danger to life or health of the public. The information shall not contain misleading or unverifiable statements or omissions likely to induce medically unjustifiable drug use or to give rise to undue risks.

New information, other than those submitted at the time of registration, must be submitted to the council for approval before being disseminated to health professionals.

'Medical representative' (Med rep) is a representative of a manufacturing firm licensed by the council to carry out promotional activities and provide information on the medicines manufactured by the firm.

Medical representatives should have an appropriate educational background. They should be adequately trained. They should possess sufficient medical and technical knowledge and integrity to present information on products and carry out other promotional activities in an accurate and responsible manner.

Employers should be responsible for the statements and activities of their medical representatives. Medical representatives should not offer inducements to prescribers and dispensers. Prescribers and dispensers should not solicit such inducements.

Mode of advertisement

Unless approved by the council on special condition, medicines shall not be advertised by mass media.

Advertisements should contain full product information, as defined by the approved scientific data sheet or similar document. Advertisements that make a promotional claim should at least contain summary scientific information.

Advertisements should usually contain

- the name(s) of the active ingredient(s) using either international nonproprietary names (INN) or the approved generic name of the drug;
- the brand name;
- content of active ingredient(s) per dosage form or regimen;

- name of other ingredients known to cause problems;
- approved therapeutic uses;
- dosage form or regimen;
- side-effects and major adverse drug reactions;
- precautions, contra-indications and warnings;
- major interactions;
- name and address of manufacturer or distributor;
- reference to scientific literature as appropriate.

Advertisements are permitted without claims (reminder advertisements), they ought to include at least the brand name, the international nonproprietary name or approved generic name, the name of each active ingredient, and the name and address of the manufacturer or distributor for the purpose of receiving further information.

FREE MEDICAL SAMPLE

Free samples of legally available prescription drugs may be provided in modest quantities to prescribers, generally on request. The information on the label of free medical samples shall be consistent with the information approved by the council and shall not be distributed through postal address , at medical or pharmaceutical congresses, symposia and exhibitions . Free medical samples shall not be sold.

The value of promotional items given during promotion shall not be high

11. POST-LICENSE RESPONSIBILITIES OF MEDICINAL PRODUCT MARKET AUTHORIZATION HOLDER

Registration holders of new chemical entities should report any adverse event that they received to the NMRC within 15 days of the receipt. If the adverse event is serious, it should be reported within 5 working days of the receipt of such reports. They are also obliged to submit a "Null" report six monthly for the first two years and annually for three years if there is no ADR report submitted to them.

NMRC (TIPC) should be informed of any significant safety issue or action taken by foreign agency, including the basis for such action, within three days of first knowledge by the registration holders. Information on withdrawal of the registration status in any country must be notified to the NMRC within 24 hours of first knowledge by the Registration holders. Whenever requested by the NMRC,

the registration holder is obliged to submit report on adverse drug reaction occurring outside Namibia.

Registration holders should also collaborate with the NMRC towards the conduct of post-authorization safety studies when deemed necessary.

11.1. Case reports from worldwide literature

The manufacturer is expected to screen the worldwide scientific literature and report cases of suspected serious adverse reactions associated with the use of the active substance(s) of its products within 15 calendar days. A copy of the relevant published article should be provided in English or summary or translation in English. The NMRC should be notified in writing where difficulty is experienced in meeting the 15-calendar day requirement.

11.2. Risk minimization strategies

The NMRC may require manufacturers or product sponsor to submit a REMS plan when a drug first comes on the market or later if NMRC becomes aware of new safety concern. REMS is a strategy to manage a known or potential serious risk associated with a medicines or biological product. It can include a medication guide, patient package insert, communication plan, provider training and patient monitoring. It must include a timetable for assessment of the REMS.

12. REQUIREMENTS FOR RISK MANAGEMENT SYSTEMS

A medicinal product is authorized on the basis that in the specified indication(s), at the time of authorization, the risk-benefit is judged positive for the target population. However, not all actual or potential risks will have been identified when an initial authorization is sought. In addition, there may be subsets of patients for whom the risk is greater than that for the target population as a whole.

Planning of pharmacovigilance activities will be improved if it were more closely based on product specific issues identified from pre- or post-authorization data and from pharmacological principles. Such planning will also guide the use of electronic data, which are routinely collected within health services to provide rapid investigation of predicted or emerging safety concerns.

The management of a single risk can be considered as having four steps, risk detection, risk assessment, risk minimization and risk communication. However, a typical individual medicinal product will have multiple risks attached to it and individual risks will vary in terms of severity, and individual patient and public health impact. Therefore, the concept of risk management should also consider the combination of information on

multiple risks with the aim of ensuring that the benefits exceed the risks by the greatest possible margin both for the individual patient and at the population level.

The detailed description of a risk management system should be provided in the form of Risk Management Plan (RMP) in the situations requiring an RMP. It is strongly recommended that discussions with the Council on the need for, and content of, an RMP should take place in advance of submission. The description of the risk management system should be submitted when appropriate.

Description of the Risk Management System

A risk management system is a set of pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to medicinal products, including the assessment of the effectiveness of those interventions. The aim of a risk management system is to ensure that the benefits of a particular medicine (or a series of medicines) exceed the risks by the greatest achievable margin for the individual patient and for the target population as a whole.

Risk Management Plan (RMP)

The description of a risk management system should be submitted in the form of RMP.

The RMP contains two parts:

Part I:

- A Safety specification,
- A Pharmacovigilance Plan; and

Part II:

- An evaluation of the need for risk minimization activities; and if there is a need for additional (i.e. non-routine) risk minimization activities
- A risk minimization plan.

Situations requiring an RMP

An RMP may need to be submitted at any time of a product's life-cycle – i.e. during both the pre-authorization and post-authorization phases. In particular an RMP should be submitted with the application for a new marketing authorization for:

- any product containing a new active substance;
- a similar biological medicinal product;
- a generic/hybrid medicinal product where a safety concern requiring additional risk minimization

activities has been identified with the reference medicinal product.

- with an application involving a significant change in a marketing authorization (e.g. new dosage form, new route of administration, new manufacturing process of a biotechnologically derived product, significant change in indication) unless it has been agreed with the Council that submission is not required;
- on request from the Council (both pre-and post-authorization);
- on the initiative of an Applicant/Marketing Authorization Holder when they identify a safety concern with a medicinal product at any stage of its life cycle.

In some circumstances, products which are not in the above categories which are seeking a new authorization may require an RMP:

- Known active substances
- Hybrid medicinal products where the changes compared with the reference medicinal product suggest different risks
- Fixed combination applications.

For situations where the submission of an EU-RMP is not mandatory, the need for it should be discussed with the Competent Authority well in advance of the submission.

Safety Specification

The Safety Specification should be a summary of the important identified risks of a medicinal product, important potential risks, and important missing information. It should also address the populations potentially at risk (where the product is likely to be used), and outstanding safety questions which warrant further investigation to refine understanding of the risk-benefit profile during the post-authorization period. The Safety Specification is intended to help industry and the council identify any need for specific data collection and also to facilitate the construction of the Pharmacovigilance Plan. In the RMP the Safety Specification will also form the basis of the evaluation of the need for risk minimization activities and, where appropriate, the risk minimization plan.

It is recommended that Applicants/Marketing Authorisation Holders follow the structure of elements provided below when compiling the Safety Specification. The elements of the Safety Specification that are included are only a guide. It can include additional elements, depending on the nature of the product and its development programme.

At the end of the Safety Specification a summary should be provided of the:

- Important identified risks;

- Important potential risks; and
- Important missing information.

Based on this summary the Applicant/Marketing Authorization Holder should provide a Pharmacovigilance Plan and an evaluation of the need for risk minimization activities.

Pharmacovigilance Plan

The Pharmacovigilance Plan should be based on the Safety Specification and propose actions to address the safety concerns identified. Early discussions between Council and the Applicant or Marketing Authorisation Holder are recommended to identify whether, and which, additional pharmacovigilance activities are needed. It is important to note that only a proportion of risks are likely to be foreseeable and the Pharmacovigilance Plan will not replace but rather complement the procedures currently used to detect safety signals.

Routine Pharmacovigilance

For medicinal products where no special concerns have arisen, routine pharmacovigilance should be sufficient for post-authorization safety monitoring, without the need for additional actions (e.g. safety studies).

Additional Pharmacovigilance Activities and Action Plans

For medicinal products with important identified risks, important potential risks, or important missing information, additional activities designed to address these safety concerns should be considered.

Applicants/Marketing Authorization Holders should also consider the situations when routine pharmacovigilance is likely to be inadequate. The objective(s) of additional pharmacovigilance activities will normally differ according to the safety concern to be addressed. For important identified and potential risks, objectives may be to measure the incidence rate in a larger or a different population, to measure the rate ratio or rate difference in comparison to a reference medicinal product, to examine how the risk varies with different doses and durations of exposure, to identify risk factors or to assess a causal association. For important missing information, the objective may simply be to investigate the possibility of a risk or to provide reassurance about the absence of a risk.

The threshold for investigating a safety concern further will depend upon the indication, the target population, and the likely impact on public health. Additional pharmacovigilance activities included in the Pharmacovigilance Plan should be designed and conducted according to the recommendations in the Guidelines for Good Pharmacoepidemiology Practices (GPP).

Action Plan for Safety Concerns

Within the Pharmacovigilance Plan the action plan for each safety concern should be presented and justified according to the following structure

- Safety concern
- Objective of proposed action(s)
- Action(s) proposed
- Rationale for proposed action(s)
- Monitoring by the Applicant/Marketing Authorization Holder for safety concern and proposed action(s)
- Milestones for evaluation and reporting.

Protocols (draft or otherwise) for any formal studies should be provided. Details of the monitoring for the safety concern in a clinical trial could include: stopping rules, information on the drug safety monitoring board and when interim analyses will be carried out.

Although not explicitly included in this structure, it is also necessary in the EU-RMP to explain the decision making processes which will depend on the outcomes of the proposed actions. The possible consequences of the study outcomes should be discussed.

Evaluation of the Need for Risk Minimization Activities

On the basis of the Safety Specification, the Applicant/Marketing Authorization Holder should provide an evaluation of the need for risk minimization activities.

For each safety concern, the Applicant/Marketing Authorization Holder should assess whether any risk minimization activities are needed. Some safety concerns may be adequately addressed by the proposed actions in the Pharmacovigilance Plan, but for others the risk may be of a particular nature and seriousness that risk minimization activities are needed. It is possible that the risk minimization activities may be limited to ensuring that suitable warnings are included in the product information or by the careful use of labelling and packaging, i.e. routine risk minimization activities. If an Applicant/Marketing Authorization Holder is of the opinion that no additional risk minimization activities beyond these are warranted, this should be discussed and, where appropriate, supporting evidence provided. However, for some risks, routine risk minimization activities will not be sufficient and additional risk minimization activities will be necessary. If these are required, they should be described in the risk minimization plan which should be included in Part II of the RMP.

Within the evaluation of the need for risk minimization activities, the Applicant/Marketing Authorization Holder should also address the potential for medication errors and state how this has been reduced in the final design of the pharmaceutical form, product information, packaging and, where appropriate, device.

As a rule, Applicants/Marketing Authorization Holders should always consider the need for risk minimization activities whenever the Safety Specification is updated in the light of new safety information on the medicinal product. In some circumstances, it may be appropriate to suggest that an additional risk minimization activity be stopped because experience with the medicinal product suggests that it is no longer necessary for the safe and effective use.

13. TOOLS FOR MEDICINE SAFETY SURVEILLANCE ACTIVITIES

Several tools have been developed or adopted for activities of the TIPC that standardize medicine safety surveillance in Namibia. These tools will also harmonize the medicines safety practice with the international practice for better information sharing and collaboration.

Some of the tools that are critical for the functioning of such activities include the safety yellow form, patient report form, therapeutics information request form, WHO causality assessment tool, adverse event severity and avoidability tools?, medication error assessment tool?, Vigiflow, TI database and others.

Definitions and Terminologies

To harmonize medicine safety surveillance activities of the TIPC with the WHO international drug monitoring programme, pharmacovigilance terms and definitions has been adopted from the international programme. these terms and definitions are provided as Annex I

WHO causality assessment criteria

TIPC will use the WHO causality assessment criteria to assess the causal association of suspected product and an adverse event. The criterion is classified as Certain, Probable/Likely, Possible, Unlikely, Inaccessible/unclassified, and conditional/unclassified. The WHO causality assessment criteria is attached as Annex II.

Patient Medicine Safety Alert Card

Patient who experienced serious adverse drug reaction shall be given TIPC Patient *Medicine Safety* Alert Card by the health care provider who diagnosed and managed the reaction.

The TIPC Patient Medicine Safety Alert Card (Annex III) alerts all healthcare workers that the bearer of the card had experienced serious intolerance (typically hypersensitivity reactions) or had experienced a serious adverse reaction to a particular medicine. The card should be carried by the patient at all times and presented to healthcare worker at the time of consultation.

Safety Yellow Form

The adverse event Notification Form (Annex IV) is the tool for reporting all suspected adverse reactions by health care professionals. Effort have been made to make it simple and user friendly. An electronic version will also be available on the NMRC website. It can be used to report any suspected ADR ,product problem, error and therapeutic ineffectiveness for all medicines including conventional, biological, complementary and alternative medicines, traditional / herbal medicines, and cosmetics, nutritional, dietary supplements and medical devices.

Patient Adverse Reaction Reporting Form/ Safety Yellow Card/

Patient Adverse Reaction Reporting Form / Safety Yellow Card / is a simplified Adverse Reaction Reporting Form (Annex V) for reporting suspected adverse reactions by patients or non health care professionals. It can be used to report any suspected ADR ,product problem, error and therapeutic ineffectiveness for all medicines including conventional, biological, complementary and alternative medicines, traditional / herbal medicines, and cosmetics, nutritional, dietary supplements and medical devices.

Vigiflow

VigiFlow developed by the UMC in collaboration with the Swiss medicines agency (Swissmedic) to improve ADR reporting and managment. It is a web based tool that has improved communication of drug adverse reaction reports between all involved in the reporting process; reporting and prescribing physicians, pharmaceutical companies, regional and national pharmacovigilance centres and WHO.

TIPC uses Vigiflow to manage its ADR database. All data are stored on a database server in Uppsala, Sweden.

Therapeutics Information Request Form

The therapeutics information request form (Annex 2) is the tool to make a therapeutic information enquiry to the TIPC related to health products and therapeutics. Requesting can be made through phone calls and email.

TI data base

An access based DB has been developed to enter the therapeutic enquiries and the answer provided from the centre. All enquiries will be entered to the database. Proactive information will be given based on the frequently asked question. The questions and answer will be made available on line. Response provided, reference used and time of response will be captured on the same database.

Medicines watch

Medicines watch is a quarterly publication of the TIPC. Safety updates, comparative effectiveness, new development in the field of medicines, regulatory affairs and local rational medicines use activities will be made available using the medicines watch.

NMRC Web site

All NMRC legislations, guidelines and other publications will be available on this website. The NMRC Web site is also used to communicate medicine information. It will also used for online reporting of ADRs.

Other printed materials (Brochures , Posters, Stickers)

Various printed materials will be used tool to pass information on medicines safety and efficacy to the general public.

Adverse event severity grading scale

There is no universally accepted scale for describing or measuring the severity of an adverse drug reaction. Assessment is largely subjective. Reactions can be described as mild, moderate, severe, or lethal.

Reactions usually described as mild and of minor significance include digestive disturbances, headaches, fatigue, vague muscle aches, malaise (a general feeling of illness or discomfort), and changes in sleep patterns. However, such reactions can be very distressing to people who experience them. As a result, people may be less willing to take their drug as instructed, and the goals of treatment may not be achieved.

Reactions that are usually described as mild are considered moderate if the person experiencing them considers them distinctly annoying, distressing, or intolerable. Other moderate reactions include skin rashes (especially if they are extensive and persistent), visual disturbances (especially in people who wear corrective lenses), muscle tremor, difficulty with urination (a common effect of many drugs in older men), any perceptible change in mood or mental function, and certain changes in blood components, such as a temporary, reversible decrease in the white blood cell count or in blood levels of some substances, such as glucose.

Mild or moderate adverse drug reactions do not necessarily mean that a drug must be discontinued, especially if no suitable alternative is available. However, doctors are likely to reevaluate the dose, frequency of use (number of doses a day), and timing of doses (for example, before or after meals; in the morning or at bedtime). Other drugs may be used to control the adverse drug reaction (for example, a stool softener to relieve constipation).

Severe reactions include those that may be life threatening (such as liver failure, abnormal heart rhythms, certain types of allergic reactions), that result in persistent or significant disability or hospitalization, and that cause a birth defect. Severe reactions are relatively rare. People who develop a severe reaction usually must stop using the drug and must be treated. However, doctors must sometimes continue giving high-risk drugs (for example, chemotherapy to patients with cancer or immunosuppressants to patients undergoing organ transplantation). Doctors use every possible means to control a severe adverse drug reaction.

The WHO Toxicity Grading Scale for determining the severity of adverse events will be used as the tool for the grading of severity of adverse events. The tool is attached as Annex.

Adverse event avoidability

Several studies have shown that most adverse events are preventable. TIPC will work closely with healthcare workers to identify preventable adverse events and develop strategies for mitigating them. This guideline has therefore identified the adverse event avoidability scale from Halas[2] as the official tool for the documentation of preventability of adverse events that occur in the Namibia health system. The Halas adverse event avoidability scale is attached as Annex.

Medication error assessment tool

Medication errors will be assessed and classified according to NCC MERP (National Coordinating Council for Medication Error Reporting and Prevention) Index for Categorizing Medication Errors. Annex

14. CAPACITY BUILDING

Under reporting is a common problem in spontaneous reporting system. One of the reasons for not reporting is luck awareness about the need for monitoring of safety of medicine or the existing system among health care professionals. An on job training is therefore required for those professionals who are already working in the health facilities so that they will consider ADR as one possible cause of their patients suffering.

Training modules for on pharmacovigilance will be prepared for on job training of health care professionals. Pharmacovigilance shall also be incorporated in all trainings concerning medicines use to improve the diagnosis, management and reporting skills of all health care professionals.

[2] Hallas, J; Harvald, B; Gram, LF, et al. Drug related hospital admissions: the role of definitions and intensity of data collection, and the possibility of prevention. *J Intern Med*

The center will be involved in the organizing and conducting refresher courses and CME on current development in the area of medicines safety and efficacy which are required to keep up with the changing field of medicine.

New graduate prescribing and dispensing professionals need to have the skill to make evidence based decision on patient safety. Therefore, the center will work closely with medicine and pharmacy professional training institutes in Namibia to incorporate medicines safety monitoring in to their under graduate curriculum.

15. MONITORING AND EVALUATION

Performance indicators for monitoring and reporting of the centre's medicine safety activities to the IWG and the NMRC include:

- Number ADR reports received per year
- Percent increase in ADR reporting rate
- Number of medication errors detected
- Number of treatment failure detected
- Number of product quality problem detected
- Number of safety summary reports presented to the clinical committee
- Number of products withdrawn from the market
- Percent ADR reports entered in database within stipulated time
- Percent incomplete ADR reports followed up for missing data
- Percent planned medicines advisory committee/subcommittee meetings held
- Time between identification of safety signal (serious ADR) or medicines safety issue and communication to HCW and public
- Number of Dear Doctor letters and other safety alerts developed and distributed
- Percent availability of ADR forms in sample of health facilities
- Percent health facilities from where ADR report has ever been submitted
- Percent HCW with demonstrated knowledge of the ADR reporting procedure (what to report, where, follow-up, etc)
- Percent HCW sampled who have ever submitted an ADR report
- Percent HCW trained/yr in PhV and medicines safety
- Number of safety update publications (bulletins and newsletters)per year
- Number of regulatory decisions taken by NMRC based on ADR monitoring activities
- Percent planned public enlightenment and education activities carried out

- Number of active surveillance activities (sentinel surveillance, registries, cohort event monitoring, PEM, case control studies, DUS, etc)

Indicators for public health programs

Public health programs routinely monitor safety of the products used in their programs. The EAC of each programme ensures the incorporation of medicines safety and monitor its functions by monitoring and routinely reporting the following indicators to TIPC.

- Percent of patients modifying treatment due to toxicity
- Percentage of patients experiencing "New unknown AE"
- Number of mortality attributed to specific drugs
- Number of morbidity attributed to specific drugs

ANNEX 1. DEFINITIONS AND TERMINOLOGIES

Adverse Medicine Reaction(AMR)/ Adverse Drug Reaction(ADR)

A response to a medicine which is noxious and unintended, and which occurs at a dose normally used in human for prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function.

The term adverse drug reaction should be considered for harmful or seriously unpleasant effects occurring at doses intended for therapeutic, prophylactic or diagnostic effect and which calls for reduction of dose or withdrawal of the drug and / or forecast hazard from future administration.

Adverse Event /adverse experience

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

Medicine/ Drug

A pharmaceutical product, used in or on human body for the prevention(prophylaxis, Mitigation diagnosis and / or treatment of disease, or for the modification of physiological function.

Medicine safety surveillance

The processes involved in the collection, collation, analysis, and dissemination of data and other activities carried out in relations to safeguarding the safety and effectiveness of pharmaceuticals and related products

Medicine safety system

All organisations, institutions and resources that contribute to efforts, whether in personal health care, public health services or through intersectoral initiatives, whose primary purpose is to protect the public from harm related to the use of medicines.

PSUR

A Periodic Safety Update Report is an update of the world-wide safety experience of a product obtained at defined times post registration.

Pharmacovigilance

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems. Recently, its concerns have been widened to include herbals, traditional and complementary medicines, blood products, biologicals, medical devices and vaccines.

Serious adverse event

Serious adverse event is any untoward occurrence which:

a. is life-threatening or fatal
b. cause or prolong hospital admission
c. cause persistent incapacity or disability
d. concern misuse or dependence
e. congenital anomaly / birth defect

Signal

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.

Side effect

Any unintended effect of a pharmaceutical product occurring at doses normally used in man, which is related to the pharmacological proprieties of the drug

Spontaneous reporting

A system whereby case reports of adverse drug events are voluntarily submitted by health professionals and pharmaceutical manufacturers to the national regulatory authority / pharmacovigillance centre

Toxicity

Toxicity implies cell damage from a direct action of the drug, often at a high dose, e.g. liver damage from paracetamol overdose.

Unexpected adverse reaction

An adverse reaction, the nature or severity of which is not consistent with domestic labeling or market authorization, or expected from the characteristics of the drug.

ANNEX II. WHO CAUSALITY ASSESSMENT CRITERIA

Causality term	Assessment criteria
Certain	• Event or laboratory test abnormality, with plausible time • relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, • pathologically) • Event definitive pharmacologically or phenomenologically • (i.e. an objective and specific medical disorder or a • recognized pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/ Likely	• Event or laboratory test abnormality, with reasonable time • relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time • relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug • intake that makes a relationship improbable (but not • impossible) • Disease or other drugs provide plausible explanations
Conditional/ Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable / Unclassified	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or • contradictory • Data cannot be supplemented or verified

Republic of Namibia

Ministry of Health and Social Services

ANNEX III. PATIENT MEDICINES SAFETY ALERT CARD

NAMIBIA MEDICINE REGULATORY COUNCIL Therapeutics Information and Pharmacovigilance Centre Windhoek Central Hospital, P.O. BOX – TEL: (061) 203 2312 Fax: (061)-226631 e mail: info@tipc.com.na PATIENT MEDICINES SAFETY ALERT CARD		
PATIENT NAME:		
AGE:	GENDER: ☐ MALE ☐ FEMALE	DATE ISSUED: …… /……../……..
ADDRESS:		
SUSPECTED DRUG(S):		
DESCRIPTION OF REACTION:		
Other comments (if any):		

Please pay attention! The bearer of this card experienced SERIOUS adverse reaction.

Back Side

Please carry this card with you at all times and remember to produce it to your health care professional at each time of consultation

CRITERIA FOR ISSUE OF A PATIENT ALERT CARD

The criteria for issue of the Patient Alert Card is as follows:
The alert card is given to:

- Patients who are hypersensitive / allergic / intolerant
- Patients who developed a serious reaction
- Patients who had a drug-induced morbidity
- Patients who had hospital admission due to an ADR
- Patients who developed an ADR which caused increase in the health care expenditure

Republic of Namibia

Ministry of Health and Social Services
Safety Reporting Form
For reporting Adverse Drug Reactions (ADRs) and medicine use /product problems

Reporters are not culpable for the adverse events and their reports are confidential.

A. PATIENT INFORMATION

Patient initials / Hospital Reg. No.)		Date of birth / Age	(……../……../……) / ( )	Gender	☐ Male ☐ Female
Pregnancy	☐ Yes ☐ No ☐ Don't know	Weight (Kg)		Height (cm)	

B. ADVERSE EVENT INFORMATION

Type of Event: Adverse event ☐ Product problem ☐ Medication error ☐

Description of Event(s):

Relevant tests / Laboratory results:

Date the event started…… /……../……..	Date of reporting…… /……../……..	Date the event stopped…… /……../……..
Treatment of adverse event? ☐ Yes ☐ No	If yes, please specify:	

Reaction subsided after stopping / reducing the dose of the suspected product ☐ Yes ☐ No ☐ Not applicable

Reaction reappeared after reintroducing / increasing the suspected product ☐ Yes ☐ No ☐ Not applicable

Seriousness of the adverse event		Outcomes attributed to the adverse event
☐ Hospitalization ☐ Prolonged hospitalization ☐ Disability or permanent damage ☐ Other important medical condition	☐ Congenital anomaly / birth defect ☐ Death ☐ Life-threatening ☐ Toxicity related treatment switch	☐ Recovered without consequences / relapse ☐ Recovered with consequences / relapse ☐ Recovering ☐ Not yet recovered Death: Date of death …… /……../……..

Other relevant history, including pre-existing medical conditions (allergies, pregnancy, smoking, alcohol use, liver, kidney problems, race etc):

C. PRODUCT INFORMATION

Suspected Product	Generic name		Indication the product was used for	
	Brand name		Daily dose / route of administration	
	Manufacturer		strength	
From where did the patient obtain the product?			Expiry date	…… /……../……..
Date product started	…… /……../……..	Date product stopped	…… /……../……..	Lot / Batch No

D. Other products used in the last three months

	Product 1	Product 2	Product 3	Product 4
Brand Name of Product				
Indication				
Expiry date				
Lot / Batch No				
Daily dose				
Route of administration				
Date product was started				
Date product was stopped				

E. REPORTER INFORMATION

Name (last, first)		Telephone / Fax	
Profession		Postal address	
Health Facility		Email	
Region		Date	

Republic of Namibia

Ministry of Health and Social Services
Safety Reporting Form
For reporting Adverse Drug Reactions (ADRs) and medicine use /product problems

What to report

- All suspected reactions to new drugs
- Unknown or unexpected ADRs
- Serious adverse drug reactions
- Unexpected therapeutic effects
- All suspected drug interactions
- Product Quality Problem
- Treatment failure
- Medication error

Report any suspected adverse events to

- Prescribed medicines
- Over the counter medicines
- Vaccines
- Herbal medicines
- Biological including blood and blood related products e g serum, plasma etc.

Fill in the Adverse Drug Reaction reporting form as completely as possible and send it to the Therapeutics Information and Pharmacovigilance Centre by e-mail, fax or post:

Republic of Namibia

Ministry of Health and Social Services

Therapeutics Information & Pharmacovigilance Centre (TIPC)

Windhoek Central Hospital,
Room 21, Basement Area
Private Bag 13198
Windhoek, Namibia
Tel: 061 203 2312
Fax: 061 22 66 31
E-mail: info@tipc.com.na

For TIPC Use Only		Unique TIPC ID No._____	
Reporter acknowledged Yes ☐ NO ☐	Report entered to the data base (Vigiflow) Yes ☐ NO ☐	Case evaluation done Yes ☐ NO ☐	Is the reaction known / listed in SPC Yes ☐ NO ☐
Causality Assessment: Certain ☐ Probable ☐ Possible ☐ Unlikely ☐ Conditional ☐ Unclassifiable ☐			
Case summary presented to advisory committee Yes ☐ No need ☐ Not yet ☐	Date case summary presented to advisory committee …… /……../……..	Report submitted to UMC Yes ☐ NO ☐	Date Report submitted to UMC …… /……../……..
Summary of recommendation by the advisory committee			
Processed by	Date …… /……../……..	Signature	

ANNEX VI: YELLOW CARD

Republic of Namibia

Ministry of Health and Social Services

Adverse Drug Reaction Patients' Reporting Form

For reporting Adverse Drug Reactions (ADRs) and medicine use /product problems by Non Health Professionals

Person Reporting

Patient ☐ Community health worker ☐ Mother ☐ Relative ☐

Other ☐ Specify _____

Name of the health facility the medicine is obtained from

Health facility record number if any

Age of the patient

Gender: Male ☐ Female ☐

Brief description of the event

Seriousness of the adverse reactions

Doesn't require hospital admission ☐ Required hospital admission ☐

Life threatening ☐ Caused death: Date of death

Date the reaction observed

Date reported

Date the reaction stopped

Please give details of Medicines or products the patient was taking where the adverse reaction occurred

Name of Medicine	Dose Taken	Number of Times/day	Mode of administration	Date medicine started	Date medicine stopped

Description of any herbal medicine the patient was taking

Source of the medicine

Hospital pharmacy ☐ Private pharmacy ☐ Family/ Neighbour ☐ Super market ☐

Open market ☐ Other source ☐ Specify _____

Reporter name and contact address

Name (Optional)

Contact address

Telephone number

Therapeutics Information and Pharmacovigilance Centre: Room 21, Basement Area, Windhoek Central Hospital;
Tel: 061 203 2312 Fax: 061 22 66 31 E- mail: info@tipc.com.na

Republic of Namibia

Ministry of Health and Social Services

Therapeutics Information Request Form

PART 1- To be completed by the Enquirer			
A. Details of Enquirer			
Last Name		Phone	
First Name		Fax	
Health Facility		Email	
Region		Profession	
City/town			
B. Information requested			
Enquiry:			
Relevant background information: *(Patient demographic profile, clinical condition, concurrent diseases, medication history)*			
C. Time and required mode of response			
Date and time of request:		Date and time response is required:	
Required mode of response:			
PART 2: For official use			
Response to query: *(Attach an extra sheet of paper if required)*			
References:			
Respondents Names and Signature		Time taken to answer query (minutes, hours, days)	
Enquiry category:		Date and time response is provided:	

Send/ Fax to the Therapeutics Information and Pharmacovigilance Centre: Room 21, Basement Area, Windhoek Central Hospital; Tel 061 203 2312 Fax 061 226631

Severity Grading Definitions

1) General definition for estimating symptom severity grade (use specific definition if available): For abnormalities NOT found in the Toxicity Tables use the scale below to estimate grade of severity:

GRADE 1: Mild -Transient or mild discomfort (< 48 hours); no medical intervention/therapy required
GRADE 2: Moderate - Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required
GRADE 3: Severe - Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible
GRADE 4: Life-threatening - Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required hospitalization or hospice care probable

2) Specific Definitions

(abbreviations: sx= symptoms, tx = treatment, IV = intravenous fluids, BP = blood pressure)

Clinical Effect	mild grade 1	moderate grade 2	severe grade 3	life threatening grade 4
General				
Fever	37.7- 38.6 C	38.7- 39.3 C	39.4- 40.5 C	>40.5 C
Weight (± from baseline)	NA	5-9% change	10-19% change	>= 20% change
Infection (other than HIV)	No antibiotic, minor sx	Antibiotic OR moderate sx	Antibiotic AND severe sx	Life threatening (e.g. septic shock)
Allergic Reaction	localized rash, no tx	localized rash WITH tx or mild angioedema	generalized rash OR angioedema with tx OR mild bronchspasm	Anaphylaxis OR severe bronchospasm laryngeal edema
GI				
Diarrhea	intermittent unformed stools OR ↑ of 1-3 /day > baseline	Persistent unformed-watery stools OR ↑ of 4-6/ day > baseline	Bloody diarrhea OR ↑ >6 stools/ day > base-line OR IV fluid tx	Life threatening consequences eg shock
Constipation	NA	tx daily laxative/ diet	tx manual evacuation	bowel obstruction
Nausea	< 24 h or intermittent	↓ oral intake 24-48 h	↓ intake >48 h or tx IV	eg shock
Vomiting	transient, oral intake OK	frequent, no dehydration	persistent, ↓ BP or tx IV	eg shock
Neuropsych/ Neuromuscular				
Altered mental status	minimal interference	lethargy, somnolence; some impaired function	confusion, memory impairment; can't function normally	delirium OR obtundation OR coma
Mood (depression/ anxiety)	minimal interference	some impaired function	can't function normally	suicidal, homicidal; OR can't care for self
Seizures (new or pre-existing)	NA	1 acute or ↑ frequency	2-4 acute or change in seizure character	prolonged, repetitive and/or refractory to tx
Neuromuscular weakness	minimal ↓ strength	weakness impairs function	weakness prevents normal function	impaired ventilation or disabling weakness
Respiratory				
Bronchospasm *	FEV1 ↓ to 70-80%	FEV1 ↓ to 50-69%	FEV1 ↓ to 25-49%	cyanosis; FEV1<25%
SOB/ dyspnea	on exertion	on exertion, impairs function	at rest; prevents normal function	requires ventilator support
Skin/ Fat				
Rash/ hives *	localized rash	diffuse rash	diffuse rash and vesicles/ bullae/ ulcerations	Stevens-Johnson or extensive bullae/ ulceration of mucosa
Lipodystrophy/ Lipoatrophy	detectable by patient	detectable on physical exam (healthcare prof)	disfiguring or obvious on casual visual inspection	NA

* not an allergic reaction

Adverse event Avoidability Scale[3]

1. *Definitely avoidable:*

- Drug event was due to a drug treatment procedure inconsistent with present day knowledge of good medical practice
- Drug treatment procedure was clearly unrealistic, taking the known circumstances into account

2. *Possibly avoidable:*

- Prescription was not erroneous, but the drug event could have been avoided
- Avoidance requires an effort exceeding the obligatory demands

3. *Not avoidable:*

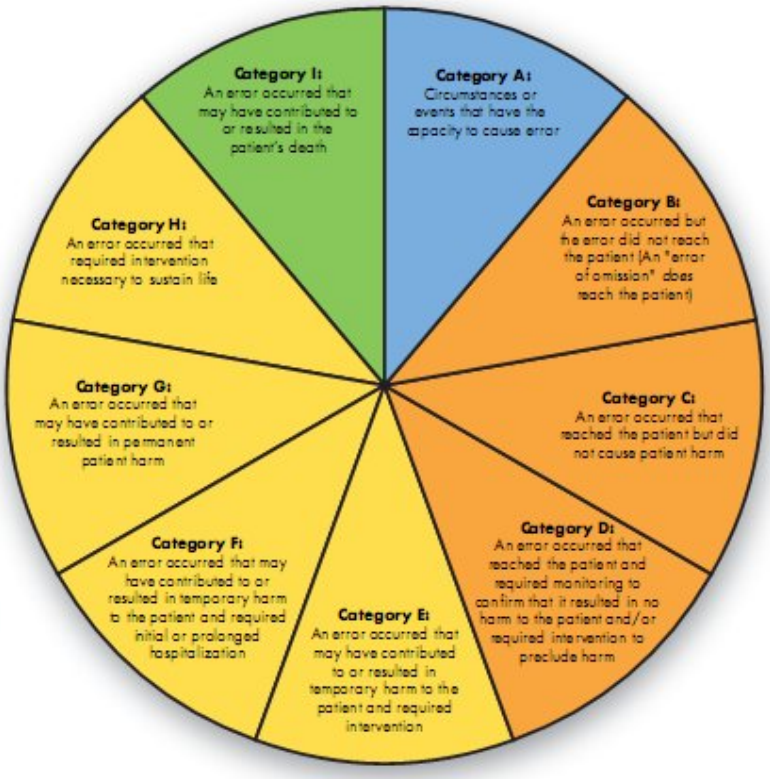
- Drug event could not have been avoided by any reasonable means
- Drug event was unpredictable event in the course of a treatment fully in accordance with good medical practice

4. *Unevaluable:*

- Data for rating could not be obtained
- Evidence was conflicting

[3] Hallas J, Harvald B, Gram LF, Grodum E, Prosen K, Haghfelt T, et al. Drug related hospital admissions: the role of definitions and intensity of data collection, and the possibility of prevention. *J Intern Med* 1990;228: 83-90.

NCC MERP Index for Categorizing Medication Errors



No Error
Error, No Harm
Error, Harm
Error, Death

Definitions

Harm
Impairment of the physical, emotional, or psychological function or structure of the body and/or pain resulting therefrom.

Monitoring
To observe or record relevant physiological or psychological signs.

Intervention
May include change in therapy or active medical/surgical treatment.

Intervention Necessary to Sustain Life
Includes cardiovascular and respiratory support (e.g., CPR, defibrillation, intubation, etc.)

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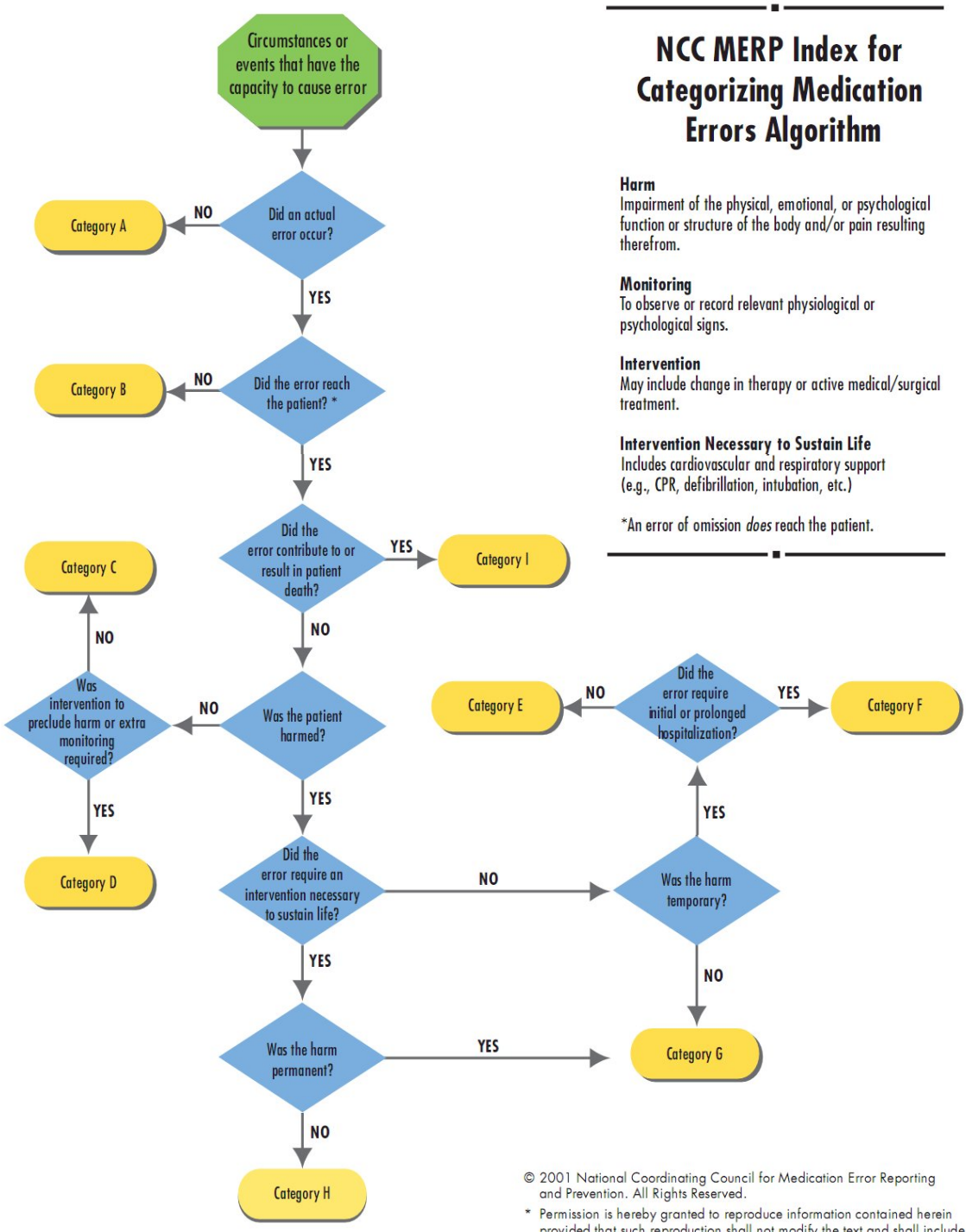

MINISTRY OF HEALTH AND SOCIAL SERVICES

National Guidelines for Medicine Safety Surveillance

Therapeutics Information and Pharmacovigilance Center, TIPC

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MÉDICOS DEL MUNDO