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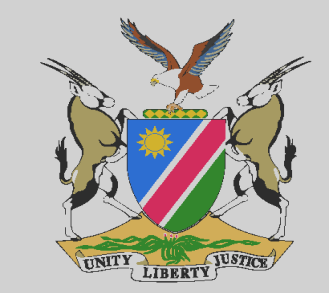

Ministry of Health and Social Services

Namibia Medicines Regulatory Council

National Guidelines for Medicine Safety Surveillance

Therapeutics Information and Pharmacovigilance Centre | **TIPC**

October 2011

NATIONAL GUIDELINES FOR MEDICINES SAFETY SURVEILLANCE OCTOBER 2011

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FOREWARD

The need for unbiased medicine information and the monitoring of adverse events (AEs) related to the use of medicines is well recognized by the Ministry of Health and Social Services (MoHSS) in our medicines policy and related legislation. The National Medicines Policy (NMP) of 1998 provides for the establishment of medicine information center(s). Also the Namibia National Pharmaceutical Master Plan of 2000 recommended the establishment of a National Medicines Information Centre. With regard to adverse reactions, Regulation 17 of the Medicines and Related Substances Control Act (Act 13 of 2003) clearly stipulates the duties of holders of certificates of registration for medicines and health professionals to inform the Namibia Medicines Regulatory Council (NMRC) of adverse reactions.

To advance these goals, the MoHSS set up the Therapeutics Information and Pharmacovigilance Centre Implementing Working Group (TIPC-IWG). Subsequently, the TIPC was established in 2007 with the dual function of providing therapeutics information to the public and health care professionals and coordinating pharmacovigilance (PhV) activities in one unified service to take advantage of the potential synergies between these two closely related activities. The mandate of TIPC is to improve the rational and safe use of medicines in Namibia. Medicines safety information is collected on adverse reaction reporting forms and analyzed at the centre to detect safety problems. The information is used to prevent medicine-induced harm in patients, minimize waste of resources, and stop the repetition of avoidable iatrogenic patient harm. Ultimately, this improves the quality of 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 in the WHO's international medicine monitoring programme. This programme recommends that national centres develop guidelines to harmonize medicine safety monitoring. The *National Guidelines for Medicine Safety Surveillance* is therefore drafted to direct health workers and consumers on how to monitor safety of all health products; how to monitor and avoid medication errors and implement related strategies to improve patient safety.

The TIPC has chosen "Know your Medicines" as its motto. I wish to most sincerely call on all health care providers to take this motto to heart. When we know our medicines, we will be able to use them safely and effectively by providing the right medicine to the right patient and prevent all avoidable harm to our patients.

Finally, the launch of this *National Guidelines for Medicine Safety Surveillance* is evidence that the MoHSS's commitment to the health of Namibians goes beyond ensuring the availability of essential medicines. The MoHSS is equally committed to ensuring the safety and effectiveness of all medicines used in Namibia.

Hon. Dr. Richard Nchabi Kamwi
Minister of Health and Social Services

PREFACE

The Therapeutics Information and Pharmacovigilance Centre (TIPC) was established in 2007 and officially launched in May 2008. Since then, TIPC has provided therapeutic information and Pharmacovigilance services to health care professionals and the public at large.

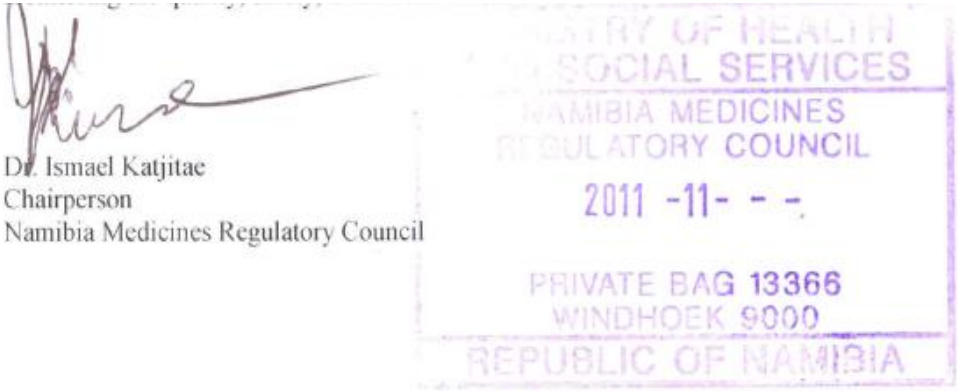
Because passive surveillance is the main safety monitoring system used worldwide to identify rare, but serious, adverse reactions to medicines, health professionals have to be vigilant and report any suspected reaction to the TIPC within a reasonable time. To achieve good reporting of adverse medicine reactions (AMRs), 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, AMRs to understand their incidence, prevalence, and severity in our population. This necessitates that the *National Guidelines for Medicine Safety Surveillance* address, in a more comprehensive way, all aspects of medicine safety monitoring including guidelines for the conduct of active surveillance studies.

Realising the widespread lack of awareness about safety surveillance and the role TIPC plays in ensuring medicines safety, TIPC developed this comprehensive document on monitoring the safety of medicines and has made it as informative as possible. This first *National Guidelines for Medicine Safety Surveillance* was specifically prepared to address Namibia's particular needs by adapting relevant parts of the WHO recommendations as well as PhV guidelines from several other countries.

MoHSS wishes to recognise the contributions of the Directorate of Tertiary Health Care and Clinical Support Services, the Division of Pharmaceutical Services, members of the Therapeutics Information and Pharmacovigilance Centre Implementing Working Group (TIPC-IWG), Management Sciences for Health's Strengthening Pharmaceutical Systems programme, Clinical Committee of the Namibia Medicines Regulatory Council (NMRC) and all health care workers and other

stakeholders who have participated in the development of these guidelines.

The *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 encourage all health care workers to put the *National Guidelines for Medicine Safety Surveillance* to good use, to know your medicines, and to become more vigilant in monitoring the quality, safety, and effectiveness of all medicines in Namibia.



Dr. Ismael Katjitae
Chairperson
Namibia Medicines Regulatory Council

ACKNOWLEDGMENTS

The content of these guidelines has been written after extensive review of national pharmacovigilance guidelines from several countries and international pharmacovigilance guidelines which are listed as reference at the end of the document. Several individuals and institutions have been involved in the review of the draft document at various stage of the drafting process.

We owe the Division Pharmaceutical Services of the Ministry of Health and Social Services a special acknowledgement for reviewing and providing guidance in the drafting of these guidelines.

This work would not have been completed without the financial and technical support from our development partner, USAID through Management Sciences for Health (MSH), Strengthening Pharmaceutical Systems Project and the personal commitment and encouragement of Mr. J. Nwokike, Dr. D. Mabirizi and Mr. E. Sagwa.

We are also equally grateful to Ms. Kirti Narsai, Head: Scientific and Regulatory Affairs Pharmaceutical Industry Association of South Africa (PIASA) and the entire PIASA team, for reviewing the draft document and providing us with valuable input. Last but not least our thanks go to the admin staff of MSH Namibia who facilitated the printing of the final document.

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Abbreviations and Acronyms

AMR	Adverse Medicine Reaction
AE	Adverse Event
ESRP	Expert Safety Review Panel
GPP	Good Pharmacoepidemiology Practices
IEC	Information, Education, and Communication
IWG	Implementing Working Group
HCR	Holder of Certificate of Registration
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
PASS	Post-authorization Safety Studies
PSUR	Periodic Safety Update Report
PhV	Pharmacovigilance
REMS	Risk Evaluation and Minimization Strategies
RMP	Risk Management Plan
TIPC	Therapeutic Information and Pharmacovigilance Centre
UMC	Uppsala Monitoring Centre
WHO	World Health Organization

1. Introduction

New medicines are tested for pharmaceutical quality, safety and efficacy in highly controlled trials involving relatively small, carefully chosen populations before they are made available for wider use by the general public. These series of tests provide only limited information about how well the medicine works in real life in a large population of people of diverse demographic, genetic, geographic, disease, socioeconomic, and cultural characteristics. 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 life-saving antiretroviral, malaria, and tuberculosis medicines, have undergone fast-tracked registration to make them available on a global scale to a large population of patients in need. National public health programmes are expanding availability and access of these new medicines to cover all categories of patients including the young, elderly, pregnant women, malnourished, those with co-morbid conditions, and those with genetic predispositions. This heterogeneous group of patients is clearly different from the neatly homogeneous group that participates in clinical trials.

With more patients being exposed to these new medicines for long periods of time, sometimes for a life time, the chances of developing adverse reactions and interactions increase significantly. Occurrence of intolerable adverse medicine reactions (AMRs) may erode patients' confidence in the safety of the medicines and consequently negatively affect the credibility and success of the whole public health programme. Therefore, in developing countries like Namibia, where relatively new essential medicines are being used on a large scale in the national public health disease control programmes, such as antiretroviral therapy, tuberculosis, and malaria control programmes, monitoring medicine safety is of paramount importance.

Spontaneous reporting of individual cases of AMRs by health care professionals has shown to be effective in the detection of new, hitherto unknown problems. It is being widely used by many countries to generate medicines-related safety signals. However, spontaneous reporting is not sufficient to confirm a causal association between an adverse reaction and a medicine. Experience has shown that data obtained from voluntary adverse reaction reports has limitations; some medicine-induced disorders are rarely validated, and the data may not provide full information about the safety profile of medicines. Comprehensive safety and effectiveness data can only be generated through routine medicine surveillance and targeted active surveillance studies. Thus, an integrated system of medicines regulation and post-marketing surveillance of quality and safety, combined with routinely collected medicine usage data, is believed to strengthen medicines safety information. Pharmaco-epidemiologic methods involving the study of medicine use in the population can be used to assess the safety of medicines in real life use.

Data gathered through such surveillance systems is entered into a medicines safety database and analyzed periodically. Based on this information, appropriate action is taken whenever there is a safety concern. This action may take the form of an educational intervention such as "Dear health care professional" letters about new safety concerns or a regulatory action including a product recall or revision of information on the package insert and label. In some circumstances the Holder of Certificate of Registration (HCR) may voluntarily recall or withdraw a product from the market.

The Namibia Medicines and Related Substances Control Act (Act 13 of 2003) requires that every Holder of Certificate of Registration (HCR) of a medicine and every health care professional informs the Namibia Medicines Regulatory Council (NMRC) of any AMR that occurred during the use of any medicine.

Accordingly, the Ministry of Health and Social Services (MoHSS) has set up and made operational the Therapeutic Information and Pharmacovigilance Centre (TIPC), with dual functions of providing

unbiased and up to date therapeutic information and monitoring the safety of medicines with due emphasis on medicines used in the public health programmes.

2. National Medicines Policy and Legal Provisions for Pharmacovigilance

The Namibia national medicines policy of August 1998 clearly stated the need for establishing medicines information and adverse reaction monitoring services for the country. The policy envisaged that a unit will be able to coordinate adverse reaction reporting and manage data collection, analysis, and dissemination. The policy also encouraged the NMRC to cooperate closely with medicines information centers in the Southern African Region and the WHO Collaborating Centre for International Drug Monitoring.

Regulation 17 of Medicines and Related Substances Control Act, Act 13 of 2003 (MRSCA) requires the holders of certificates of registration (HCR) and those who have applied to register medicines to inform the Council of any adverse reaction that occurred during the use of a medicine. The HCR must also inform the Council, without delay, of the steps the applicant or holder intends to take with regard to mitigating the risk of the concerned adverse reaction.

Therefore, HCRs should ensure that they have an appropriate system of pharmacovigilance (PhV) in place to assume responsibility for their products on the Namibian market and to ensure that appropriate action will be taken if necessary; this includes the HCR having a system for collection, preparation, and submission of expedited AMR reports and Periodic Safety Update Reports (PSUR) to the NMRC.

Every HCR must also inform the Council of any formulation, labelling, or other error that has occurred and also inform the Council of steps taken to rectify the error immediately.

Although the regulation states that every authorized prescriber must inform the Council of any adverse reaction within a reasonable time, voluntary reporting by health care professionals is believed to be

effective enough for early detection of unknown problems and thus appropriate in our setting. A person can also report to the Council any medicine having quality problems which may render the medicine unfit for human use.

3. Establishment of the Therapeutics Information and Pharmacovigilance Center

A working group drawn from the MoHSS Directorates of Tertiary Health Care and Clinical Support Services, Special Programmes, and various development partners, including Management Science for Health (MSH), Medicos del Mundo, and the International Training and Education Centre for Health (I-TECH), was formed under the leadership of MoHSS in 2006. The working group was mandated to set up and ensure the proper functioning of the TIPC.

Subsequently, the Therapeutics Information and Pharmacovigilance Center (TIPC) was established in 2007 with the dual functions of providing therapeutics information and monitoring safety of medicines that are already on the market. TIPC serves as MoHSS's official provider of therapeutics information and pharmacovigilance services for health care workers and the general public; it is equipped with all necessary infrastructures, databases, and electronic resources comparable to those available in other such facilities around the world.

TIPC was successfully launched in May 2008 "to improve rational use of medicines available in the country and to contribute to their safe use". The specific objectives are to—

- Provide both proactive and query response therapeutics information to health professionals and the general public in Namibia
- Become a reference unit on PhV by collecting and monitoring AMRs

4. Notification System

Patients, families and community health workers are encouraged to immediately report any adverse event (AE) possibly associated with the use of medicines to their health care provider or directly to the TIPC using the simplified reporting form. Health care workers, after conducting investigations, are required to immediately report any suspected AMRs, medicine interactions, and unusual effects to the TIPC by fax, email, or post on the safety yellow form. A copy of the report can be kept at the health facility for review by the therapeutic committee or equivalent body in private health facilities.

Each reported AMR will be reviewed by the medicines information pharmacist to sort new and follow-up AMR reports. New reports are given a unique identification number and follow-up reports are linked to the first report. Receipt of all reports are acknowledged. Illegible, missing or incomprehensible entries are clarified with the reporter. The medicines information pharmacist enters the data into the Vigiflow® database within 48 hours of receipt, looks for additional information on the specific case reports from the product monograph and other literature, and does a causality assessment with the information. The data is entered into Vigiflow® and saved for analysis. Those reports with all the necessary information are subsequently committed to the WHO international database called Vigibase®.

The AMR case reports, with additional information from the literature, are summarized and presented to the Clinical Committee of the NMRC, which advises on matters of medicine safety, among other things. After further investigation, the Clinical Committee may recommend regulatory actions. Based on such recommendations, the NMRC makes a regulatory decision and communicates it to the HCR and all other relevant bodies and stakeholders.

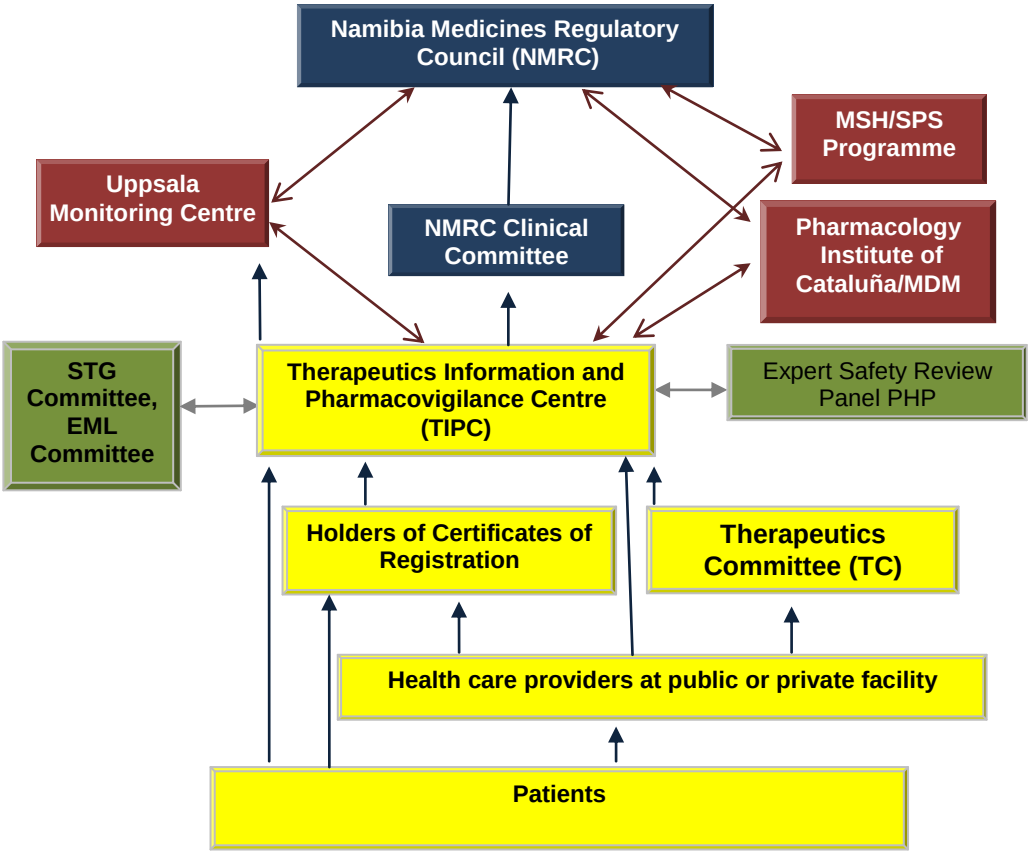

Figure 1: Medicine safety surveillance notification system

5. Roles and Responsibilities

The success of any PhV activity depends on the reporting of suspected AMRs, which is a collaborative effort from the public, health care workers, HCR, and the NMRC. Thus, the roles and responsibilities of each actor have to be clearly defined to ensure effective PhV activity.

Patients, Families, and Community Health Workers

- Immediately report any AE possibly associated with the use of medicines to the health care provider or directly to the TIPC using the yellow card.

Prescribers

- Detect and appropriately manage adverse reactions to medicines
- Document and immediately report all serious suspected reactions, unknown or unexpected AMRs, unexpected therapeutic effects (off-label use), all suspected medicine interactions, treatment failures, medication errors and suspected product quality problem
- Submit copy of report to TC
- Advise patients on possible AMRs and medicine interactions
- Prevent the occurrence of medication errors and other avoidable AEs by using medicines rationally

Dispensers

- Ensure the constant availability of the reporting forms
- Advise patients on possible AMRs and medicine interactions
- Immediately report any suspected AMRs, medicine interactions, medication error, unusual effects (off-label use) and suspected product quality problem
- Send AMR reports to TIPC
- Present copy of AMR reports to TC

Traditional Practitioners (Herbalists)

- Report all suspected reactions and suspected interactions to herbal medicines
- Advise patients on possible adverse reactions and interactions

Health Facility Therapeutics Committee

- Promote rational and safer use of medicines
- Revise the medicines list of the health institutions, based on safety and other considerations
- Review (analyse) reports and take corrective action to prevent AEs, including medication errors
- Ensure all AMR reports are kept confidential and the identities of patients, reporters, and trade names of the suspected medicine are not disclosed
- Retain the necessary documentation

Holders of Certificates of Registration

- Ensure that an appropriate PhV system is in place in the company in order to accept responsibility and liability for safety and effectiveness of its product(s) on the market
- Inform the Council of any AMR arising from the use of the company's registered product(s) within two weeks (14 days) after receipt of reports of such adverse reactions
- Submit PSURs, company sponsored post-registration study reports, etc. to the Council per the registration guide
- Respond promptly and fully to requests on risk–benefit information from the Council

TIPC

- Collect, receive, and process adverse reaction, medication error, and suspected product quality reports
- Review adverse reaction reports and prepare case summary of each case report
- Acknowledge the receipt of report and provide feedback to reporter
- Maintain AMR and other AE databases
- Analyse information in the database and detect potential medicine safety signals
- Submit summary of AMR case report to the clinical committee of the NMRC for review and regulatory recommendations
- Promote prevention of AMRs and medication errors through provision of therapeutics information
- Co-ordinate AMR reporting and pharmacovigilance with all public health programmes
- Promote safe and rational use of medicines through provision of medicine information
- Collect current local and international information on safety of medicines and disseminate to health professionals
- Alerting prescribers, manufacturers, and the general public to new risks of adverse reactions
- Follow up on the implementation of the medicine safety regulatory decisions by the Council
- Share adverse reaction information with the WHO Programme for international medicine monitoring
- Organise and coordinate in active surveillances and research on adverse reactions and medication errors
- Conduct advocacy, training, and education on medicine safety
- Communicate medicine safety information through Medicines Watch, NMRC web site and e-mails
- Respond to medicine safety enquiries in a timely manner

Public Health Programmes

- Appoint Expert Safety Review Panel
- Form district investigation team when required
- Collaborate closely with TIPC in the collection and processing of AMR reports
- Conduct investigation of safety signal of public health importance in collaboration with the TIPC
- Train health workers in reporting adverse reactions and preventing medicines-related AEs

Clinical Committee of the NMRC

- Serve as the national medicines safety advisory committee
- Provide technical advice to the NMRC on safety and effectiveness of all medicines registered in Namibia
- Advise the Council on causality assessments and risk benefit reviews
- Provide technical advice to the Council in the post-registration evaluation of quality, safety, and effectiveness of medicines
- Monitor compliance and implementation of the *National Guidelines for Medicines Safety Surveillance*
- Advise NMRC on the implementation of post-authorisation safety studies (PASS)
- Provide advice on local PASS, including observational epidemiological studies and clinical trials
- Recommend national priorities concerning medicine safety studies
- Recommend interventions that will enhance the dissemination of unbiased therapeutics information and other activities to improve safety and rational use of medicines by health care workers and consumers
- Provide technical advice to the NMRC on all issues related to patient safety

- Advise the NMRC on all other issues related to medicines safety in Namibia

NMRC

- Take regulatory decisions based on the recommendations of the Clinical Committee
- Communicate the regulatory decisions taken to the HCRs and all other relevant bodies by using official letters and other means of communication

6. Scope of Pharmacovigilance and Medicine Safety Surveillance Activities

PhV is concerned with the safety of medicines, medical devices, complementary medicines (which includes traditional and herbal medicines), vaccines, blood products, and other biologicals. It is also relevant in the detection of substandard medicines, medication errors, lack of efficacy, and off-label use of medicines. Information on other issues, such as acute and chronic poisoning, medicine related mortality, abuse and misuse of medicines, and interactions with other medicine and food, can also be obtained from PhV activities.

6.1. Types of AMRs

An AMR is a noxious and unwanted reaction that occurs at a dose used in humans for diagnosis, treatment or prophylaxis of diseases or medical conditions. Many unwanted effects (side effects) 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 of AMRs—

1) Type A (augmented) is related to the principal action of the medicine

- Will occur in everyone
- Dose related

- Pharmacodynamic effects
- Common
- Skilled management reduces their incidence

2) Type B (bizarre) is not related to the principal action of the medicine

- Will occur in some people
- Not part of the normal pharmacology of the medicine
- Not dose related
- Unpredictable
- Includes idiosyncratic and medicine allergies
- Accounts for most medicine fatalities

There are four subordinate types of AMRs—

3) Type C (continues) is a reaction due to long term use.

4) Type D (delayed) causes teratogenesis and carcinogenesis.

5) Type E (ending of use) is abrupt discontinuation, which can cause problems like rebound adrenocortical insufficiency.

6) Type F (failure of therapy) which is treatment failure.

6.2. How to Recognize AMRs

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

Describe the Reaction Clearly—

- Take a proper history, trying to exclude all possible causes that can explain the event like co-morbid conditions, foods, and other medicines concomitantly used that could possibly interact

- Note the time relationship between the occurrence of the event and use of the medicine; some reactions occur immediately following use of a medicine, whereas others take time to develop
- Examine the patient thoroughly and do relevant laboratory investigations; some laboratory tests are useful for early detection of subclinical reactions and others are used to measure severity and/or to monitor patient management

Check the Pharmacology of the Medicine

Check if the reaction is known and documented on the package insert, product monograph submitted during registration, or any other authoritative reference. AMR should be considered when there is no other sufficient explanation.

De-challenge and Re-challenge

Positive de-challenge is improvement of the reaction after discontinuation of the medicine. It is a strong indicator of possible association of the medicine and the AE. Rarely, there may be no alternative [substitute] medicine to the one suspected of causing 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 re-challenge. Positive re-challenge is recurrence of the reaction that had subsided with prior de-challenge.

Factors Predisposing to AMR

It is well known that different patients often respond differently to a given treatment regimen. In addition to the pharmaceutical and pharmacologic properties of a medicine, there are other factors that predispose the patient to develop AMRs.

The *very old and the very young* are more susceptible to AMRs. Medicines which commonly cause problems in the elderly include

hypnotics, diuretics, nonsteroidal anti-inflammatory medicines, antihypertensives, psychotropics and digoxin.

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

Besides the condition being treated, the patient may also suffer from another disease, such as renal, hepatic or cardiac disease. Special precautions are necessary to prevent AMRs when patients have such concurrent illness.

Medicine interactions are among the commonest causes of AMRs. When two medicines are administered to a patient, they may act independently of each other or interact with each other. Interaction may increase or decrease the effects of one or more medicines concerned and may cause unexpected toxicity. As newer and more potent medicines become available, the number of serious medicine 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 medicine alters the absorption, distribution or elimination of another medicine, such that the amount which reaches the site of action is increased or decreased
- Indirectly, a medicine-induced disease or a change in fluid or electrolyte balance (physiologic change) alters the response to another medicine

AMRs are any unintended and undesirable response or injury caused by a medicine irrespective of dose and includes medication errors. *Medication errors* occur when the patient actually receives the wrong prescription, there is a dispensing or preparation (mixing) error, or the medicine is administered incorrectly.

Medication errors are common to all health systems and all health professionals.

The most frequent reasons for medication errors include—

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

Genetics

It is well known that the genetic make-up of individual patients may predispose them to AMRs.

Use of Traditional Medicines

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

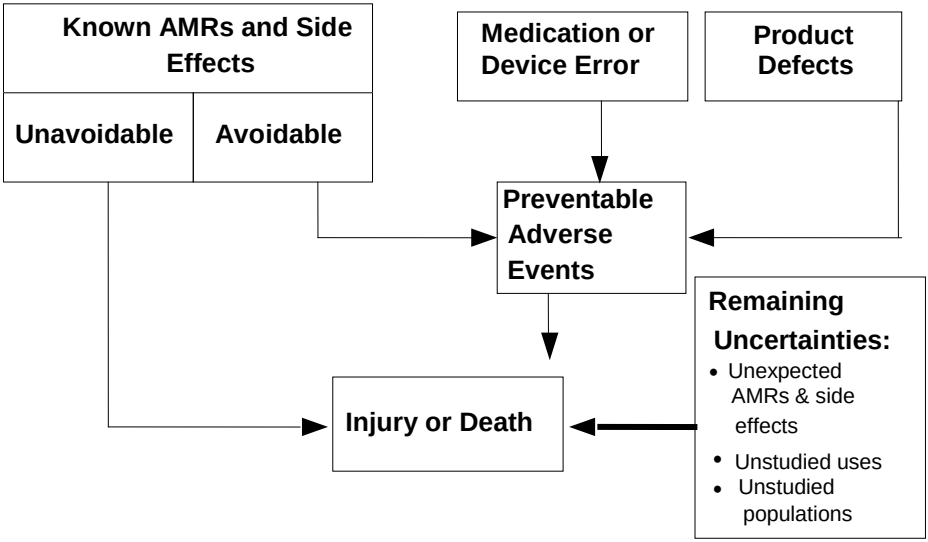

Figure 2: Schematic presentation of preventable and unavoidable AEs

7. Methods for Medicine Safety Surveillance

7.1. Spontaneous Reporting

When an adverse reaction to a medicine is suspected, the Adverse Medicine Reaction reporting form (annex 2) must be completed and sent to the TIPC by fax or post. Adverse reactions can also be reported electronically by using the reporting form available on the NMRC website (www.nmrc.com.na/tipc/adr_report_form) or by calling the TIPC.

At the TIPC, the medicines information pharmacist ensures that the AMR forms are readily available at all health facilities; the pharmacist conducts a quarterly survey to review the availability of the forms at health facilities. The electronic reporting form can either be downloaded from the NMRC website or completed online and submitted via the NMRC website.

Confidentiality

The TIPC will use the information collected through this voluntary reporting system to prevent AMRs and promote rational and safe use of medicines. The AMR report will not be made available to support any legal, administrative or other action detrimental to the reporting health care professional, the patient or the PhV coordinator. In this regard, *all the collected reports will be kept confidential* and the identities of patients, reporters and suspected products will not be disclosed. The proprietary name of a product will only be used when there is a need to notify regulatory action taken by the Council on the specific product.

What to Report

Report all suspected reactions to modern medicines, complementary medicines (traditional and herbal medicines), vaccines, blood products, other biologicals, dental and medical supplies, contrast media and cosmetics. Product quality problems such as color change, separation of composition, caking, change of odor, questionable

stability, suspected contamination, poor packaging and labelling, mislabelling, incomplete pack and defective and expired products shall also be reported.

When to Report

Any suspected AMR 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 questioning or examining the patient.

Completing the AMR Reporting Form

The AMR reporting form (annex 2) requires basic information about the patient, the medicine, the adverse reaction, the action taken, and the outcome. In general—

- The age and sex of the patient, a description of the adverse reaction, information on the suspected medicine and outcome are all considered essential and should be completed
- The form should be completed by physicians, medical officers, dentists, pharmacists, nurses or any other health care professionals
- The form should be completed to the best of the reporter's ability
- Avoid non-standard abbreviations
- Use a separate form for each patient
- Write legibly

The Patient's Identity

Information about the patient's age, sex, weight, ethnicity and use of substances of abuse should be provided.

Information on the Suspected Medicine

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

Use brand names of suspected medicine(s). If the generic name is used, specify the manufacturer. Avoid nonstandard abbreviations. List any other prescription, non-prescription, and/or traditional medicines used concurrently with the suspected medicine; include all descriptions, i.e. brand name, route of administration, dosage form, strength, frequency, indication, date started and date stopped.

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

The frequency of medicine administration should be clearly noted by using standard abbreviations, e.g. 3 times a day as tid or 8hrly, 2 times a day as bid or 12hrly, 4 times a day as qid or 6 hrly, etc. The route of administration should be expressed by using standard abbreviations, e.g. per os as PO, intramuscular as IM, intravascular as IV, per rectal as PR, etc.

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

Write the reason the medicine was used or the diagnosis for which the medicine was prescribed for both the suspected medicine and other medicines concurrently used.

Information on the Adverse Reaction

A clear and brief description about the nature of the adverse reaction, the date of onset, duration, time course and laboratory test results, including negative, abnormal and normal results of any relevant test performed, should be reported. The severity of the reaction, i.e. whether it leads to hospitalization or necessitated prolonged hospitalization, discontinuation of the medicine, and the outcome of the de-challenge and re-challenge tests of the suspected medicines, have to be reported.

Additional Information

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

Follow-Up Report for an AMR That Has Already Been Reported

Any follow-up information for an AMR that has already been reported can be sent on another AMR form, or it can be communicated by telephone, fax or e-mail to the TIPC, indicating that it is follow-up information; the date of the original report and the unique AMR report identification number from the acknowledgment letter must be included 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.

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

TIPC Patient Medicine Safety Alert Card

Patients who experienced a serious adverse medicine reaction shall be given TIPC patient medicine safety alert cards by the health care provider who diagnosed and managed the reaction. The card (annex 3) alerts all health care workers that the bearer of the card has experienced a serious intolerance (typically hypersensitivity reactions) or has experienced a serious adverse reaction to a particular medicine. The card shall be carried by the patient at all times and shall be presented to health care workers at the time of consultation so that the health care workers will be able to identify the patient's medicine-related morbidity and prevent similar medicine reactions.

Expedited Reporting Requirements by HCRs

All serious reactions must be reported on an expedited basis and not later than 15 calendar days from receipt of the minimum information required by any personnel of the HCR. For new chemical entities, HCRs should expedite the report of any AE; all serious AE reports for new chemical entities should be reported to TIPC within 5 working days of the receipt of such reports by the HCR.

A second company that entered into relationships with the manufacturer for the marketing of the suspected product should submit adverse reaction reports as soon as any personnel of the sponsor receives 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 from 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 reclassified from non-serious to serious.

Reporting Product Quality

Medicine quality concerns include a number of hazards, which may be due to improper formulation, packaging or labeling. Some product quality defects may occasionally pose a threat. Problems of quality defect that occur during manufacturing, shipping or storage of prescription or over-the-counter products shall be reported to the marketing authorization holder or to the inspectorate of the NMRC on the pharmaceutical product quality problem reporting form (Annex 4). Any Adverse Events in association with product quality shall be reported directly to the TIPC using the safety yellow form. Upon receipt of the medicine quality defect report, the marketing authorization holder should assess the situation and take immediate action within a reasonable time. Simultaneously, the marketing authorization holder should report such product quality defects and measures taken to the NMRC in writing.

Reporting Medication Errors

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

Medication Errors Reporting by Health Care Professionals

Errors, near errors or hazardous conditions including administering the wrong medicine, strength or dose; confusion over look-alike and sound-alike medicines; 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 the TIPC on the medication error reporting form (Annex 5). Including the reporter's identity and address on the medication error reporting form is optional. Reporters are encouraged

to submit associated materials such as product photographs, containers, labels and prescription order scans that would support the information being submitted. TIPC guarantees confidentiality of information received and respects reporters' wishes as to the level of detail included in the report.

To alert healthcare professionals and others, case studies with recommendations on how to prevent errors will be published in the Namibian Medicines Watch and on the NMRC website. The reporter's identity, affiliation and location are not revealed in these reports.

When reporting errors, please include the following—

- Describe the error or preventable AMR; 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 consulting rooms, retail pharmacy, pharmaceutical 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
- How was the error discovered/intercepted?
- State your recommendations for error prevention, if possible

NB. Do not submit any information that identifies the patient when reporting medication errors.

Medication Errors Reporting by HCRs

The HCR should report cases of medication errors associated with serious adverse reactions on an expedited basis. Cases not associated with adverse reactions and near misses should only be reported in PSURs. Cumulative information on medication errors, resulting in adverse reactions or not, should be discussed in the overall safety evaluation section of the PSUR. The potential for medication errors and their prevention should be addressed in the risk management plan.

Reporting Suspected AEs of Complementary Medicine

Health professionals, patients, consumers and manufacturers should report all serious adverse reactions suspected to be due to complementary medicines. Complementary medicine is a group of diverse medical and health care system, practices and products that are not generally considered to be part of conventional medicine. It includes use of a variety of herbal medicines and other natural products. Complementary medicine is used **together with** conventional medicine, and alternative medicine is used **in place of** conventional medicine.

Details of the suspected complementary product species name, brand name or ingredients name(s); country of origin; batch number; expiry date and provider (dispenser) should be reported. The precise Latin binomial botanical name (genus, species, and author, as well as name of family) of the medicinal plants concerned should be used whenever possible; the plant parts and extraction and preparation methods used should also be given. This information allows accurate comparison with other reports. A common vernacular name may be used so as 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. Reports should be made to the TIPC using the official safety yellow 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 medicines development process

    - In clinical trials prior to national medicines regulatory approval
    - Under post-marketing safety surveillance
- Herbal medicines undergoing re-evaluation under the current protocol in clinical trials
- 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 AEs of Herbal Medicines

The safety yellow form is used for reporting of suspected adverse reactions of herbal medicine. Reports can also be made by telephone, letter or e-mail. If possible, a sample of the herbal product and its packaging should be submitted with the report. If the finished herbal product or its raw material(s) were imported from other countries, the medicines regulatory authority of the exporting country may be contacted to provide helpful information.

Assessment of Case Reports

The TIPC will assess reports on adverse reactions to herbal medicines 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 de-challenge and re-challenge
- 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 AEs

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

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 the herbal medicine has been used or was prepared.

Patients and Consumer Reporting

A simplified reporting form (yellow card) will be used to collect information from patients on their adverse experiences with medicines (annex 6). Patients can report suspected adverse reactions directly to the TIPC or to the HCR. The HCR should submit patient reports to the TIPC within 15 days of receipt of the report to the TIPC. The reports coming from patients will be entered into a separate database. For serious and/or unknown adverse reactions reported directly from patients, further information will be sought from the health practitioner caring for the patient.

Processing AMR Reports Evaluation

A team of experts at the TIPC evaluates each report for the temporal relationship between the reaction and the medicine, the result of the de-challenge and re-challenge, the seriousness of the reaction, the current labeling information and whether the reaction is reported in medical literature. AMR reports will be classified as certain, probable/likely, possible, unlikely, in assessable/unclassified, and conditional/unclassified according to WHO causality assessment criteria (Annex 7). Adverse reactions to new medical entities and unexpected or serious reactions will receive priority. Additional information may be requested from the manufacturer or reporter, if needed.

Documenting AMR Reports

All reports that are coming in will be reviewed for completeness and then entered into the VigiFlow® within 48 hours from receipt of the report. New reports will be given a unique identifier (ID) number and follow-up reports will be matched with the first unique ID number issued. Reporters will be acknowledged for sending AMR reports.

Communicating AMR Reports

Results from the literature scan, statistical analyses and regulatory measures taken will be communicated to health care professionals through the Medicines Watch and all other available means after approval by the Clinical Committee of the NMRC.

Promoting Spontaneous AE Reporting

Because of under reporting, large proportion of AMRs will remain largely outside the reach of the TIPC. Therefore, diverse understanding of the concept of AMR monitoring remains a critical issue in the reporting compliance of health care professionals. The pharmacy unit and the therapeutics committees should exert effort to raise the awareness of health professionals to report and not to overlook the possibility of AMRs.

Monitoring Adverse Medicine Reactions in Public Health Programmes

Public Health Programmes shall appoint Expert Safety Review Panel (ESRP) at the launch of the programme. The panel shall consist of the Public Health programme manager, PhV coordinator (from TIPC), clinical pharmacologist (from UNAM), physician and disease expert (from DSP), pharmacist (from DSP), member of NMRC and other members with specific expertise as required (e.g. pediatrician, gynecologist and representatives of consumer organizations) may be included. The Chief Health Programme Administrator (CHPA) at

regional level and the Principal Medical Officers (PMO) at district level will coordinate the regional and district adverse reaction monitoring activity respectively. The standard reporting form, i.e. Safety Yellow Form, should always be made available at the primary health care sites, including health centres and clinics. If needed, a district AMR investigation team comprising of the the district PMO, medical officer from hospital, nurse responsible for special programme, and principal pharmacist shall be formed. The district investigation team will be responsible for following up adverse reactions reported from health facilities in the district. The district principal pharmacist will be responsible for reporting to the national PhV coordinator and communicating related medicine safety issues to the clinical staff and public. All reports of adverse reactions should be submitted to the national coordinator for inclusion in the national database. The ESRP will review reports referred by the PhV coordinator or the programme manager for seriousness, for the likely cause, and its impact on the programme and recommend further follow-up and appropriate action. The recommendation of the ESRP should be submitted to the district or regional programme manager, national programme director, TIPC and NMRC for their decision.

7.2. Active Surveillance

Although a spontaneous AMR reporting system is a powerful generator of medicine safety signals, it has limitations in terms of differentiating possible AMRs from disease progression or coincidental problems. Data obtained from spontaneous AMR reporting systems cannot be used to calculate the true rate at which AMRs occur in a population of interest because of the inherent problem of underreporting of some AMRs and over reporting of others. It is, however, an excellent method for generating medicine safety signals. On the other hand, active surveillance methods obtain comprehensive data on individual adverse reports and also enable determination of the rates of AMRs via a continuous pre-organized process. Therefore, surveillance methods are needed that are more structured, systematic, comprehensive and provide a proactive way of following up the evolving medicine experience in large populations.

7.2.1. Conducting of Active Surveillance Safety Studies

Active surveillance safety studies may be conducted for the purpose of identifying previously unrecognized safety concerns (hypothesis generation), investigating potential and identified risks (hypothesis testing 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.

Active surveillance safety studies would be appropriate in situations when there is —

- Uncertainty as to the clinical relevance of a toxic effect in animals
- Uncertainty as to the safety profile in routine use in human populations
- A need to better quantify AEs identified in clinical trials and elucidate risk factors
- A need to confirm or refute safety concerns suggested by other sources (e.g. spontaneous reporting)
- A concern regarding the use of the medicinal product (e.g. to quantify off-label use)
- A need to evaluate the effectiveness of a risk minimisation measure

The research priorities for investigating safety of medicines should be set by the NMRC. All proposals for the conduct of pharmacoepidemiology studies should be submitted to the Biomedical Research Ethics Committee of MoHSS. The research protocol should be approved by the Ethics Committee 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 that

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

the researcher's responsibilities and work plans are in compliance with international ethical standards.

A variety of research designs may be appropriate for investigating a medicine safety issue, including cross-sectional studies, observational cohort studies, case control studies or registries. Clinical trials involving systematic allocation of treatment (e.g. randomization) may also be used to evaluate the safety of authorized 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-Authorization Safety Studies (PASS)

The HCR who initiates, manages and/or finances a post-authorization safety study is responsible for its conduct and should meet the PhV obligations concerning the PASS. The study should be supervised by a designated monitor(s) or monitoring organization and the names of the monitors should be recorded in the study documents. In case the HCR does not directly conduct the study, detailed and clear contractual agreements that meet PhV obligations should be documented.

Studies Requested by the NMRC

NMRC may request HCR either at the time of authorisation or in the post-authorisation phase to conduct post-authorisation safety studies (PASS) in order to confirm, characterise and quantify safety concerns identified at an earlier stage of product development or during post-authorisation use as part of the Risk Management Plan. Meetings will be organized between NMRC and the HCR in order to agree upon a protocol and a timetable for conducting a medicine safety study. A member of the NMRC with relevant skills in the type of study under consideration will serve as a co-investigator. When the HCR believes that the protocol requires a major amendment, it should be reported to

the NMRC. Refinements of exposure and/or case definitions will not require notification.

Studies Initiated by the HCR

Before commencing a study, the HCR should inform the NMRC and submit a copy of the research protocol for review and advice. Any major amendment to the protocol should be reported and must be accompanied by a justification for it. Refinements of exposure and/or case definitions will normally not require notification.

7.2.2. Reporting of Adverse Reactions Observed in Studies

Reports of all serious adverse reactions arising from such studies should be reported on an expedited basis within 15 days to the NMRC. The HCR should ensure that they are notified of serious adverse reactions and events by the investigator(s) as specified in the study protocol. These reports should also be included in the PSURs. Reports on non-serious adverse reactions should be reported in the PSURs. All adverse reactions and events including those considered non-serious, should be summarized 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 is not required.

Progress and Final Study Reports
Studies Requested by the Council

The HCR 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 relevant for the progress of

the study, such as 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.

Studies Performed at the HCR'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-authorization 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 in PASS

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-authorization safety study should be offered or given.

Ethical Issues

For non interventional post-authorization safety studies, the HCR and investigators shall follow the Ministry of Health and Social Services Guidelines on Clinical Trials in Human Subjects in addition to the guidance given here.

The highest possible standards of professional conduct and confidentiality must always be maintained and the 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 authorized 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 HCR, who is thereafter responsible for the handling of such information. Non interventional post-authorization safety studies should also be referred to an ethics committee for ethical review of study protocol.

Procedure for Handling Complaints Regarding a PASS

Concerns on a post-authorization 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 the HCR 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 and 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 risks 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 risks 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 anomalies or birth defects
- Data published in the worldwide scientific literature or presented as abstracts, posters, or communications
- Investigations on pharmaceutical quality
- Data on sales and product usage

Important issues that 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 risks should be taken into account. In the assessment of risks and consideration of regulatory action, it is important to note that rarely does a single case report 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 that could have an impact on the overall risk–benefit balance of a medicinal product, the HCR 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 depends on the seriousness of the 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 HCR should aim to optimize the safe use and the risk–benefit balance of an individual product and ensure that the AEs 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 minimizing measures (e.g. by contraindicating use in patients particularly at risk, reducing dosage, introducing precautions of use and warnings, pretreatment tests (if appropriate) to identify patients at risk, and 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 on efficacy should be carefully evaluated.

The following types of actions may be necessary and may be initiated by the HCR or by the Council—

- Variation of marketing authorization(s) in respect of the indication, dosing recommendations, contra-indications, warnings, and precautions for use or information about adverse reactions or other sections of the summary of product characteristics (SPC) and the package leaflet
- Directly providing important safety information to healthcare professionals, patients, and the public (e.g. through letters and/or bulletins or via print and electronic media)

If there are important new safety concerns requiring urgent action, the Holder of Certificate of Registration, 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 unfavorable and proposed risk minimization measures are considered inadequate to redress the balance, the medicinal product should be withdrawn from the market and healthcare professionals, patients and the public should be informed as appropriate. Such action may be taken voluntarily by the HCR. 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's order under statutory authority.

9. Therapeutic Information in Medicine Safety Surveillance

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 reports, WHO publications, electronic databases (Micromedex, Cochrane Library), medicines interaction and toxicology references are available at TIPC. These resources enable TIPC to respond to medicine safety- related queries and to provide current information to health care providers, the Essential edicine List Committee, standard treatment guidelines committees and the general public.

9.1. Literature Review and Comparative Effectiveness

The goal of the TIPC in the review of treatment guidelines and in the comparative evaluation of the effectiveness of medicinal therapies is to utilize information from notable guidelines and evidence-based publications to abridge and adapt their recommendations to make them relevant to Namibia. In this regard, TIPC routinely searches the following databases—

- Clinical practice guidelines and consensus statements including notable international databases such as Guideline International Network and the National Guidelines Clearinghouse and key individual guidelines databases such as National Institute of Clinical Excellence and Safe Injection Global Network
- Systematic reviews and meta-analyses such as the Cochrane Library of systemic reviews and other large systemic reviews of randomized controlled studies and observational studies not included in the Cochrane Library's comparative effectiveness/health technology assessment reviews
- Comparative effectiveness reviews conducted by Agency for Healthcare Research and Quality, Canadian Coordinating Office for Health Technology Assessment, and other similar reputable organizations

- Medicine information bulletins, such as WHO Drug Information, member bulletins of the International Society of Drug Bulletins, including Prescrire International; regulatory information newsletters including FDA Drug Safety Newsletter, Medicines and Healthcare Products Regulatory Agency Drug Safety Update, and WHO Pharmaceuticals Newsletter

Conclusions and recommendations from these databases are helpful for decision making by health managers, clinicians and health care workers. TIPC produces a summary of comparative effectiveness evaluations and communicates this information to health care professionals and other relevant players by using TIPC publications, notably the *Namibia Medicines Watch*.

9.2. Publication of the Namibia Medicines Watch

TIPC produces The *Namibia Medicines Watch* and other printed information, education and communication (IEC) materials to promote rational and safe use of medicines. It provides information that improves regulation, prescribing, dispensing and use of medicines. The *Namibia Medicines Watch* provides therapeutics information that guides treatment decisions, supports the essential medicines management system and guides medicine regulatory and treatment guidelines decisions.

The target audience for the *Namibia Medicines Watch* includes all health care workers, particularly doctors, nurses, pharmacists, community and other health care workers and consumers in Namibia. The publication works closely with local opinion leaders and local associations like the Namibia Medical Association, the Pharmaceutical Society of Namibia, Namibia Nurses Association, the Health Professions Council of Namibia and other professional associations to promote awareness about key medicine safety, benefits and rational use issues.

10. Post-license Responsibilities of Holders of Certificates of Registration

HCR of a medicine should report any AE that occurs within Namibia to the NMRC within 15 days of being made aware of the AE. If the AE is serious, it should be reported within 5 working days of the receipt of such reports or being made aware of such information.

The NMRC should also be informed of any significant safety issue or action taken by a 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 given to the NMRC within 24 hours of first knowledge by the HCR.

10.1. 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 a summary or translation in English. The NMRC should be notified in writing when there is difficulty in meeting the 15 calendar day requirement.

10.2. Periodic Safety Update Reports

The HCR should submit to the NMRC the records of all suspected adverse reactions in the form of a periodic safety update report. This should be done immediately upon request by NMRC or periodically. The time period for PSUR shall be every six months for the first two years of initial marketing and annually for the subsequent three years. Thereafter, the periodic safety update reports shall be submitted at three-yearly intervals. Three-yearly interval shall be applicable to all medicinal products regardless of their date of authorization. The HCRs are therefore obliged to submit a ”null” report, if no AMR report is submitted to them in the specified period. Whenever requested by the NMRC, the HCR is obliged to submit a summary

report on AMRs occurring in and outside Namibia and collaborate with the NMRC in the conduct of PASS when deemed necessary. The HCR may request amendment of the periods referred to above either at the time of submission of the application for marketing authorization or following the granting of the marketing authorization.

10.3. Risk Evaluation and Minimization Strategies

The NMRC may require manufacturers or product sponsors to submit a risk evaluation and minimization strategies (REMS) plan when a medicine first comes on the market or later if NMRC becomes aware of new safety concerns. REMS are for managing known or potential serious risks associated with medicines or biological products. It can include a medication guide, patient package insert, communication plan, provider training, patient monitoring, and restrictions in distribution, prescribing or dispensing. A timetable for assessment of the REMS must be included.

Requirements for Risk Management Systems

A medicinal product is authorized when the risk–benefit is judged positive for the target population. However, not all actual or potential risks will have been identified when the initial authorization is sought and granted. In addition, there may be subsets of patients for whom the risk is greater than for the target population as a whole.

Management of risk has four steps — detection, assessment, minimization, and 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 the general population.

The detailed description of a risk management system should be provided in the form of a risk management plan (RMP). It is strongly recommended that discussions with the Council on the need for and

content of an RMP take place in advance of submitting the plan. 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 PhV 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 a Risk Minimization Plan (RMP). Part I of the RMP should contain a safety specification and a PhV plan. Part II should contain an evaluation of the need for routine and non-routine risk minimization activities and a risk minimization plan.

Situations Requiring an RMP

An RMP may need to be submitted at any time in a product's life cycle, i.e. during both the pre-marketing authorization and post-marketing 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 with a safety concern, requiring additional risk minimization activities, that has been identified with the reference medicinal product
- 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 the Council has agreed that submission is not required
- A request from the Council (both pre- and post-authorization)
- A request by the prospective or actual HCR when a safety concern has been identified at any stage of the product's life cycle

In some circumstances, products not in the above categories that are seeking a new authorization may require an RMP, such as —

- 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 RMP is not mandatory, the need for it should be discussed with the Council well in advance of the submission.

Safety Specification

The safety specification should be a summary of the serious identified and potential risks of a medicinal product 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 that warrant further investigation to refine the understanding of the risk–benefit profile during the post-authorization period. It can include additional elements, depending on the nature of the product and its development. The safety specification is intended to help industry and the Council identify any need for specific data collection and also to facilitate formulation of the PhV Plan. In the RMP, the safety specification will also form the basis of the need for risk minimization activities and, where appropriate, the RMP.

The prospective or actual HCR should provide a PhV plan and an evaluation of the need for risk minimization activities.

Pharmacovigilance Plan

The PhV plan should be based on the safety specification and should propose actions to address the identified safety concerns. Early discussions between the Council and the prospective or actual HCR are recommended to identify whether, and which, additional PhV activities are needed. It is important to note that only a proportion of risks are likely to be foreseeable. The PhV plan will not replace, but rather complement, the procedures currently used to detect safety signals.

Routine Pharmacovigilance

For medicinal products with no special safety concerns, routine PhV should be sufficient for post-authorization safety monitoring, without the need for additional safety studies.

Additional Pharmacovigilance Activities and Action Plans

Prospective and actual HCRs should also consider the situations in which routine PhV is likely to be inadequate. The objective(s) of additional PhV activities will normally differ according to the safety concern to be addressed. For important identified and potential risks, the 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 PhV activities included in the PhV plan should be designed and conducted according to the recommendations in the guidelines for GPP.

Action Plan for Safety Concerns

Within the PhV 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 prospective or actual HCR for safety concern(s) 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 medicine safety monitoring board and when interim analyses will be carried out.

Although not explicitly included in this structure, it is also necessary in the 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

For each safety concern, the prospective or actual HCR should assess whether any risk minimization activities are needed. Some safety concerns may be adequately addressed by the proposed actions in the PhV plan, but for others, the risk may be of a particular nature and seriousness that risk minimization activities are needed. Routine activities may be sufficient, for example, ensuring that suitable warnings are included in the product information or by the careful use of labelling and packaging. If a prospective or actual HCR 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 activities will not be sufficient and additional risk minimization activities will be necessary. If these are required, they should be described in part II of the RMP.

The prospective or actual HCR should also address the potential for medication errors and state how this has been reduced in the final design of the pharmaceutical dosage form, product information, packaging, and, where appropriate, device.

As a rule, prospective and actual HCRs should always consider the need for risk minimization activities whenever the safety specification is updated in the light of new 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 product suggests that it is no longer necessary.

11.Tools for Medicine Safety Surveillance Activities

Several tools have been developed or adopted by TIPC for PhV activities that standardize medicine safety surveillance in Namibia. These tools have harmonized Namibia's medicines safety practices with international practices 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 reporting form, therapeutics information request form, WHO causality assessment tool, AE severity grading, AE avoidability scale, algorithm for categorizing medication error, Vigiflow®, medicines or therapeutics information databases and others.

Safety Yellow Form

The AMR reporting form (annex 2), also called the safety yellow form, is the tool for reporting all suspected adverse reactions by health care professionals. Efforts have been made to make it simple and user friendly. An electronic version is available on the NMRC website. It can be used to report any suspected AMR and therapeutic ineffectiveness for all conventional, biological, complementary, i.e. alternative and traditional/herbal medicines, as well as cosmetics, nutritional and dietary supplements and medical devices.

Patient Adverse Reaction Reporting Form/Safety Yellow Card

The Patient Adverse Reaction Reporting Form, also called the Safety Yellow Card, is a simplified form (annex 6) that patients and those not in the health care profession can use to report any suspected AMR, medicinal product problem, medication error and therapeutic ineffectiveness for all medicines including conventional, biological, complementary, i.e. alternative and traditional/herbal medicines, as well as cosmetics, nutritional and dietary supplements and medical devices.

Patient Medicine Safety Alert Card

Patients who experience or have ever experienced serious AMRs will be given the TIPC patient medicine safety alert card by the health care provider who diagnosed and managed the reaction. The card (annex 3) alerts all health care workers that the bearer has experienced serious intolerance (typically hypersensitivity reactions) or has experienced a serious adverse reaction to a particular medicine. The card should be carried by the patient at all times and presented to health care workers at each consultation.

WHO Causality Assessment Criteria

TIPC will use the WHO causality assessment criteria (annex 7) to evaluate the causal association of suspected products and AEs. The categories of criteria are certain, probable/likely, possible, unlikely, inaccessible/unclassified and conditional/unclassified.

Vigiflow®

VigiFlow® was developed by the Uppsala Monitoring Centre in collaboration with the Swiss medicines agency (Swissmedic) to improve AMR reporting and management. It is a web-based tool that has improved communication of medicine adverse reaction reports between reporting and prescribing physicians, pharmaceutical companies, regional and national PhV centres and WHO. TIPC uses Vigiflow® to manage its AMR database. All data are stored on a database server in Uppsala, Sweden.

Therapeutics Information Request Form

The Therapeutics Information Request Form (annex 8) is used to make enquiries to TIPC on health products and medical treatment. Requests can also be made by phone call or e-mail.

Therapeutics Information Electronic Database

An Access database has been developed to document the therapeutics enquiries and answers provided by TIPC. Proactive information will be offered, which will be based on frequently asked questions. The questions and answers will be made available on line. Responses, references and the duration and times of responses will be captured on the same database.

The Namibia Medicines Watch

The *Namibia Medicines Watch* is a quarterly publication of TIPC. Safety updates, comparative effectiveness evaluations, new developments in the field of medicines, regulatory affairs and local rational medicines use activities will be published.

NMRC Web Site

The NMRC web site will make available all NMRC legislation, guidelines and other publications including the *Namibia Medicines Watch*. It will also be used to communicate medicine information as well as for online reporting of AMRs.

Other Printed Materials (Brochures, Posters, and Stickers)

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

AE Severity Grading Scale

There is no universally accepted scale for describing or measuring the severity of an AMR. Assessment is largely subjective. Reactions can be described as mild, moderate, severe or fatal (lethal). The WHO toxicity grading scale will be used as the tool for grading the severity of AEs (annex 9).

Reactions usually described as mild are 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 medicine 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 medicines 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 medicine reactions do not necessarily mean that a medicine must be discontinued, especially if no suitable alternative is available. However, doctors are likely to re-evaluate 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 medicines may be used to control the AMR (for example, a stool softener to relieve constipation).

Severe (or serious) reactions include those that may be life threatening (such as liver failure, abnormal heart rhythms and 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 medicine and must be treated. However, doctors may sometimes continue giving high-risk medicines (for example, chemotherapy to patients with cancer or immunosuppressants to patients undergoing organ transplantation). Doctors usually employ every possible means to control a severe AMR.

AE Avoidability

Several studies have shown that most AEs are preventable. TIPC will work closely with health care workers to identify preventable AEs and develop strategies for avoiding them.

Surely Namibia has adopted the Halas[2] AE avoidability scale as the tool for the documentation of preventability of AEs that occur in the Namibian health system (annex 10).

Medication Error Assessment Tool

Medication errors will be assessed and classified according to the Index for Categorizing Medication Errors adopted from the National Coordinating Council for Medication Error Reporting and Prevention in the United States (annex 11).

12. Capacity Building

Under reporting of suspected AMRs is a common problem in spontaneous reporting systems. Two reasons for not reporting are the lack of awareness among health care professionals about the need to monitor the safety of medicines and the existence of a system to do so. Therefore, on-the-job training is required for those professionals who are already working in health facilities so that they may consider AMRs as one possible cause of their patients' suffering.

Training modules for PhV has been prepared for on-the-job training of health care professionals. Effort will also be made to incorporate PhV in all trainings concerning medicines use to improve AMR diagnosis, management and reporting skills. TIPC will organize and conduct refresher courses and continuing professional development sessions on current developments in the area of medicines safety and efficacy.

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[2] Hallas, J.; Harvald, B.; Gram, L. F., et al. Drug related hospital admissions: the role of definitions and intensity of data collection, and the possibility of prevention. *J. Intern. Med. 1990 Aug; 228(2):83-90*

Newly graduated prescribing and dispensing professionals need to have the skills to make evidence-based decisions about patient safety. Therefore, TIPC will work closely with medicine, pharmacy and nursing training institutions in Namibia to incorporate medicines safety monitoring into their undergraduate and in-service course curricula.

13. Monitoring and Evaluation

Performance indicators for pharmacovigilance activities

- Number of AMR reports received per year
- Percentage increase in AMR reporting
- Number of medication errors detected
- Number of treatment failures detected
- Number of product quality problems detected
- Number of safety summary reports presented to the Clinical Committee
- Number of products withdrawn from the market because of AMR
- Percentage of AMR reports entered in the database within the stipulated time
- Percentage of incomplete AMR reports followed up for missing data
- Percentage of planned medicines advisory committee/subcommittee meetings held
- Time between identification of safety signal (serious AMR) or medicines safety issue and communication to health care workers and the public
- Number of Dear Healthcare Professional letters and other safety alerts developed and distributed
- Percentage of sampled health facilities in which AMR forms are available
- Percentage of health facilities from which AMR reports have ever been submitted
- Percentage of health care workers sampled who have ever submitted an AMR report

- Percentage of health care workers trained per year in PhV and medicines safety
- Number of safety update publications (bulletins and newsletters) per year
- Number of regulatory decisions taken by NMRC based on AMR monitoring activities
- Percentage of planned public enlightenment and education activities carried out
- Number of active surveillance activities (sentinel surveillance, registries, cohort event monitoring, prescription event monitoring, case control studies, drug use studies, etc.)

Indicators for Public Health Programmes

Public health programmes should routinely monitor safety of the products used in their programmes. The ESRP of each programme shall monitor functioning of its medicine safety surveillance by the following indicators.

- Percentage of patients treatment modified because of toxicity
- Percentage of patients experiencing “new unknown AE”

14. Bibliography

1. National Drug Policy for Namibia, Ministry of Health and Social Services, August 1998; www.healthnet.org.na/documents.html
2. Medicines and Related Substances Control Act, 2003 (Act 13 of 2003); Government Gazette of the Republic of Namibia, No. 3051; http://www.parliament.gov.na/acts_documents/44_act_13medssubstan.pdf
3. Medicines and Related Substances Control Act, 2003: Regulation 17 of Regulations relating to medicines and related substances
4. *Guidelines on Clinical Trials in Human Subjects*, MoHSS September 2003; http://www.healthnet.org.na/documents.html
5. WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre. Safety Monitoring of Medicinal Products: *Guidelines for Setting Up and Running a Pharmacovigilance Centre*; 2000; ISBN 91-630-9004-X
6. WHO, *Safety of Medicines: A Guide to Detecting and Reporting Adverse Drug Reactions*. WHO/EDM/QSM/2002.2
7. WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre. *The Importance of Pharmacovigilance: Safety Monitoring of Medicinal Products*; 2002; ISBN 92-4-159015-7
8. WHO Policy Perspectives on Medicines. Pharmacovigilance: ensuring the safe use of medicines. October 2004. WHO/EDM/2004.8
9. World Alliance for patient safety, WHO draft Guidelines for adverse event reporting and learning systems from information to action, 2005. WHO/EIP/SPO/QPS/05.3
10. Volume 9A of The Rules Governing Medicinal Products in the European Union–Guidelines on Pharmacovigilance for Medicinal Products for Human Use – September 2008;

http://ec.europa.eu/health/files/eudralex/vol-9/pdf/vol9a_09-2008_en.pdf

11. International Society for Pharmacoepidemiology. 2008. Guidelines for Good Pharmacoepidemiology Practices. *PDS* 17:200–208

12. *Australian Guidelines for Pharmacovigilance Responsibilities of Sponsors of Registered Medicines Regulated by Drug Safety and Evaluation Branch* (July 2003 Amended 31 May 2005); http://www.tga.gov.au/adr/pharmaco.pdf

13. Guidance for Industry on Providing Regulatory Information in Electronic Format in the Netherlands: Electronic submission of expedited Individual Case Safety Reports (ICSRs), Medicines Evaluation Board

14. Royal Decree 1344/2007, 11 October, regulating pharmacovigilance of medicinal products for human use. Agencia española de medicamentos y productos sanitarios, Minsterio De Sanidad Y consumo

15. Pharmacovigilance in Taiwan, National ADR Reporting Center http://recall.doh.gov.tw/

16. Guidelines for the National Pharmacovigilance system in Kenya, Pharmacy and Poisons Board, February 2009

http://www.pharmacyboardkenya.org/assets/files/national_pv_guidelines.pdf

17. *Safety of Medicines in Nigeria: A Guide for Detecting and Reporting ADRs*, National Pharmacovigilance Center; NAFDAC, Nigeria, 2004; http://www.nafdacnigeria.org/pharmacovigilance.html

18. Wood A.J.J., Stein C.M., Woosley R.. 1998. How Does FDA Conduct Post Marketing Surveillance and Risk Assessment? *New England Journal of Medicine* 339:1851–1854

19. Hartwig, Steven C., Jerry Siegel, and Philip J. Schneider. Sept. 1992. Preventability and Severity Assessment in Reporting Adverse Drug Reactions. *Am. J. Hosp. Pharm.* 49:2229–2232

20. Hallas, J., B. Harvald, L. F. Gram, et al. 1990. Drug Related Hospital Admissions: the Role of Definitions and Intensity of Data Collection, and the Possibility of Prevention. *J. Intern. Med.* 228:83–90.

21. Lyndon, Bill. 2003. Withdrawal of Useful Drugs from the Market. *Australian Prescriber.* 26:50–51

22. Chapter 4: The Assessment of Risk and Potential Benefit, Online Ethics Center for Engineering and Research

    http://www.onlineethics.org/CMS/2963/resref/nbacindex/mindex/mchapter4.aspx

23. Error! Hyperlink reference not valid.Handbook for good clinical research practice (GCP): Guidance for implementation WHO 2005; ISBN 92 4 159392

    http://apps.who.int/medicinedocs/index/assoc/s14084e/s14084e.pdf

24. Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. CPMP/ICH/377/95

25. http://www.fnclcc.fr/doc/pdf/lois/BPC-ICHE2A.pdf

15. Annexes

Annex 1. Definitions and Terminologies

Adverse medicine reaction (AMR): a noxious and unintended response to a medicine that occurs at a dose normally used in humans for prophylaxis, diagnosis, or therapy of disease or for the modification of physiological function; the term AMR should be reserved for harmful or seriously unpleasant effects that call for a reduction in the dosage, a withdrawal of the medicine, and/or a forecast of hazard from future administration

Adverse event/adverse experience (AE): 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: a pharmaceutical product, used in or on human body for the prevention, prophylaxis, mitigation, diagnosis, and treatment of disease, or for the modification of physiological function

Medication error: 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 labelling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use

Medicine safety surveillance: the processes involved in the collection, collation, analysis, and dissemination of data and other activities carried out in relation to safeguarding the safety and effectiveness of pharmaceuticals and related products

Medicine safety system: all organisations, institutions, resources, and processes that contribute to efforts in personal health care, public

health services, and intersectoral initiatives whose primary purpose is to protect the public from harm related to the use of medicines

New medicines: refers to the medicines with preparations of new chemical entities, compounding medications of new therapeutic activities, or new route of administration of old chemical entities; furthermore, the medical preparation, which is in the new dosage form, new dose, new dose per unit, or new route of administration that is still under the safety monitoring period, is monitored with an end date that is the same as the first preparation of the same component

New chemical entities (NCE) or **new molecular entity (NME):** according to the US Food and Drug Administration, a medicine that contains no active moiety that has been approved by FDA in any other application submitted

Periodic safety update report (PSUR): an update of the worldwide safety experience of a product obtained at defined times post registration

Pharmacovigilance (PhV): the science and activities relating to the detection, assessment, understanding, and prevention of AEs or any other possible medicine-related problems; recently, its concerns have been widened to include herbals, traditional and complementary medicines, blood products, biologicals, vaccines and medical devices
Serious AE: any untoward occurrence that is life threatening or fatal, causes or prolongs hospital admission, causes persistent incapacity or disability, causes misuse or dependence, and causes a congenital anomaly or birth defect.

Signal: refers to reported information on a possible causal relationship between an AE and a medicine, 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 medicine

Spontaneous reporting: a system whereby case reports of adverse medicine events are voluntarily submitted by health professionals, patients, and pharmaceutical manufacturers to the national medicine regulatory authority/PhV center

Toxicity: implies cell damage from a direct action of the medicine, 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 marketing authorization, or expected from the characteristics of the medicine

Republic of Namibia

Ministry of Health and Social Services

Annex 2. Adverse Medicine Reaction Reporting Form

A) PATIENT INFORMATION					
Patient initials or Hospital Reg. No.		DOB DD/MM/ YYYY Age……..	Gender: ☐ Male ☐ Female	Weight (Kg):	*Safety Yellow Form* *Confidential*
B) ADVERSE EVENT INFORMATION					
Type of report:	**Initial: ☐**	**Follow up: ☐**	**Write AMR ID number**		

DESCRIPTION OF ADVERSE EVENTS: Indicate provisional/final diagnosis of the adverse event	**Date the event started:**	**Date the event stopped:**	**Action taken:** (E.g. Medicine withdrawn/ substituted/Dose reduced /medical treatment etc...)

Seriousness	☐ Hospitalization	☐ Disability or permanent damage	☐ Congenital anomaly/ birth defect
	☐ Life-threatening	☐ Other serious medical event	☐ Non serious adverse event

Relevant Laboratory tests	**Test date**	**Result**
	DD /MM./ YYYY	

Patient Outcome	☐ Recovered ☐ Recovered with sequela ☐ Recovering ☐ Not recovered ☐ Unknown	**Died** ☐Due to reaction ☐ unrelated to reaction	☐ Reaction maybe contributory Date of death DD /MM./ YYYY

RELEVANT MEDICAL HISTORY: including pre-existing medical conditions (allergies, pregnancy, alcohol use, liver problems..)

C) INFORMATION ON MEDICINES: ***For vaccines please indicate the batch number***

LIST MEDICINES USED IN THE LAST 3 MONTHS TICK SUSPECTED MEDICINES ENTER FDC AS ONE EDICINE		**Strength**	**Frequency**	**Route of Admin.**	**Start date**	**Stop date or ongoing**	**Indic ation**
	☐						
	☐						
	☐						

D) REPORTER INFORMATION

Name (last, first)		Region		Email	
Profession		Telephone		Date	DD /MM./ YYYY
Health Facility Name		Fax			

Please tick if you need ☐ *AMR forms* ☐ *Additional information*

Please note that submission of a report does not constitute an admission that medical personnel or the medicine caused or contributed to the event

Send/ Fax/Email to TIPC: Therapeutics Information and Pharmacovigilance Centre
Room 21, Basement Area, Windhoek Central Hospital. Windhoek.
Tel: 061 203 2312 Fax: 061 22 66 31/ 088 618 776. Email: info@tipc.com.na

Back Side of AMR reporting form

What to report?

- All suspected reactions to new medicines
    - Unknown or unexpected AMRs
- Serious adverse medicine reactions
- Unexpected therapeutic effects
- All suspected medicines interactions
- Treatment failure

Complete the Adverse Medicine Reaction (AMR) reporting form as completely as possible and send it to address below

For TIPC Use Only	**Unique AMR ID No……**	**Vigiflow ID No……**
DATE RECEIVED:		Reporter acknowledged: Yes ☐ NO ☐
DATE ENTERED in VIGIFLOW:		Is the reaction known?: Yes ☐ NO ☐
Adverse Medicine Reaction Term:		
Suspected product:		Additional information provided? Yes ☐ No need ☐
Causality Assessment: Certain ☐ Probable ☐ Possible ☐ Unlikely ☐ Conditional ☐ Unclassifiable ☐		
Report committed to UMC Yes ☐ NO ☐ Date …… /……../…….. By……		Case summary presented to advisory committee: Yes ☐ No need ☐ Not yet ☐ Date if yes …… /……../……..
Summary of recommendation by the advisory committee:		
Processed by …… Date …… /……../…….. Signature		

Annex 3. Patient Medicines Safety Alert Card

Ministry of Health and Social Services
NAMIBIA MEDICINE REGULATORY COUNCIL
Therapeutic Information and Pharmacovigilance Centre
Windhoek Central Hospital, Private Bag 13198 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 MEDICINE(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 show to your health care provider at each consultation

CRITERIA FOR ISSUE OF A PATIENT ALERT CARD

The alert card is given to patients:

- Who are hypersensitive / allergic / intolerant
- Who developed a serious reaction
- Who had a medicine-induced morbidity
- Who had a hospital admission due to an Adverse Medicine Reaction (AMR)

Annex 4. Pharmaceutical Product Quality Reporting Form

Name of facility		Telephone	
Dispensing facility		Date of Report	DD/MM/YYYY
PRODUCT IDENTITY			
Brand name/ manufacturer		Batch / Lot Number	
Generic name		Date of manufacture	DD/MM/YYYY
Country of origin		Expiry date	DD/MM/YYYY
Supplier/ Distributor		Date of receipt	DD/MM/YYYY

PRODUCT FORMULATION (Tick appropriate box)	**QUALITY CONCERN (Tick appropriate box(es))**
□ Oral tablets/capsules □ Oral suspension/syrup □ Injection □ Diluent □ Powder for reconstitution of suspension □ Powder for reconstitution of injection □ Eye drops □ Ear drops □ Nebulizer solution □ Cream/Ointment/ Liniment □ other /specify	□ Colour change □ Separating of phases □ Powdering / Crumbling □ Moulding □ Change of odour □ Mislabelling □ Incomplete pack □ Other / specify

Describe quality concern in detail

……
……
……..

Storage conditions

Does the product require refrigeration?	□ Yes	□ No	(other details if any)
Was the product dispensed and returned by a patient?	□ Yes	□ No	
Was the product stored according to manufacturer recommendation?	□ Yes	□ No	

Comments (if any)

……
……

Name of person reporting		Contact number	
Job Title		Signature	

Once completed one copy of this form should be e-mailed or posted to:
Namibia Medicines Regulatory Council, Inspection and Licensing
P / Bag 13366 Windhoek
Fax: 061 225048 e-mail: inspect@nmrc.com.na

Ministry of Health and Social Services

Namibia Medicines Regulatory Council

To err is human! Notification without blame

Annex 5. Medication Error Notification Form

All medication errors should be notified. This information is strictly confidential.

B) Region:	**Health facility name: Optional** Hospital ☐ Health center ☐ Clinic ☐	**Name: Optional**
C) Date and time of the incident: **DD/MM/ YY YY Time 00:00**	**Patient Age:** _____ **Gender: ☐ Male ☐ Female**	**Was the medicine actually administered to the patient?** ☐Yes ☐ NO ☐ Unknown

D) **Place of Incident**: ☐ Main pharmacy ☐ ARV Pharmacy ☐Outpatient pharmacy ☐ Inpatient Ward ☐ Outpatient

E) Name of Medicine prescribed: *(Write exactly as the prescriber has written)*	*F)* **Name of the other medicine involved (prescribed/dispensed) in error.** (*If applicable):*

G) Type of incident:

☐ Incorrect medicine
☐ Incorrect route of administration
☐ Incorrect IV rate
☐ Incorrect IV/SC solution preparation
☐ Incorrect patient
☐ Incorrect duration of treatment
☐ Incorrect formulation
☐ Known allergic patient
☐ Expired medication
☐ Dose omitted
☐ Incorrect time
☐ Incorrect dose
○ Longer
○ Shorter
○High
○Lower
☐ Other:_____

H) At what stage did the incident occur?:

☐ Prescribing
☐ Transcribing
☐ Counseling
☐ Labeling
☐ Dispensing
☐ Administering
☐ Using/Taking
☐ Monitoring
☐ Other:_____

I) **Person that detected the incident:**

☐ Pharmacist
☐ Pharmacist assistant
☐ Pharmacist (intern)
☐ Doctor
☐ Doctor (intern)
☐ Nurse
☐ Patient
☐ Relative
☐ Other_____

J) Origin/source of the incident :

☐ Pharmacist
☐ Pharmacist assistant
☐ Pharmacist (intern)
☐ Doctor
☐ Doctor (intern)
☐ Nurse
☐ Patient
☐ Relative
☐ Other_____

K) Contributing factors:

☐ Unclear prescription
☐ Unclear patient identification
☐ "Sound-alike" medicine names
☐ look-alike packaging or pills
☐ Storage problems
☐ Inadequate knowledge
☐ Competing distractions
☐ Work load
☐ Other:_____

L) **Outcome** ***(tick only one outcome: the most appropriate one).*****The incident:**

☐ Did not reach the patient.
☐ Reached the patient but did not result in patient harm and there was no need for patient monitoring.
☐ Reached the patient but did not result in patient harm however there was need for patient monitoring.
☐ Resulted in ineffective treatment of the health problem.
☐ Resulted in adverse medicine reaction but there was no need for treatment with another medicine.
☐ Resulted in adverse medicine reaction that required treatment with another medicine.
☐ Resulted in permanent patient harm.
☐ Resulted in patient death.

M) **Description of the** incident(if needed):

N) **What do you recommend** to help prevent a similar incident from occurring again?

*If patient experienced any Adverse Medicine Reaction please also complete the Adverse Medicine Reaction form (Safety Yellow form)

Therapeutics Information and Pharmacovigilance Centre (TIPC)

Room 21, Basement Area, Windhoek Central Hospital. Windhoek.
Tel: 061 203 2312 Fax: 061 22 66 31/ 088 618 776. Email:
info@tipc.com.na

Ministry of Health and Social Services

Namibia Medicines Regulatory Council

Annex 6. Adverse Medicine Reaction Reporting Form for Public (Safety Yellow Card)

(Patients, Community Health Workers, Family, etc.)
Reporter
Patient □ Community Health Worker □ Mother □ Relative □
Other □ Specify _____

Hospital record number if any

Name of the hospital

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

Medicines or products the patient was taking

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

Description of herbal medicine

Source of the medicine
□ Hospital pharmacy □ Private pharmacy □ Family/Neighbour □ Supermarket □ Open market □ Other source □
Specify _____

Reporter name and contact address
Name (Optional)

Telephone Number

Therapeutics Information and Pharmacovigilance Centre (TIPC)

Room 21, Basement Area, Windhoek Central Hospital. Windhoek.
Tel: 061 203 2312 Fax: 061 22 66 31/ 088 618 776. Email:
info@tipc.com.na

Annex 7. WHO Causality Assessment Criteria

Causality term	Assessment criteria
Certain	• Event or laboratory test abnormality with plausible time relationship to medicine intake • Cannot be explained by disease or other medicines • 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 medicine intake • Unlikely to be attributed to disease or other medicines • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to medicine intake • Could also be explained by disease or other medicines • Information on medicine withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality with a time to medicine intake that makes a relationship improbable (but not impossible) • Disease or other medicines provide plausible explanations
Conditional/ unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, • Additional data under examination
Unassessable/ unclassified	• Report suggests an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

Ministry of Health and Social Services

Namibia Medicines Regulatory Council

Annex 8.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:	

Annex 9. Severity Greading 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 or therapy required

Grade 2: Moderate – mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention or therapy required

Grade 3: Severe – marked limitation in activity, some assistance usually required; medical intervention or therapy required, hospitalizations possible

Grade 4: Life threatening – extreme limitation in activity, significant assistance required; significant medical intervention or 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

Annex 10. Adverse Event Avoidability Scale

1. Definitely avoidable

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

2. Possibly avoidable

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

3. Not avoidable

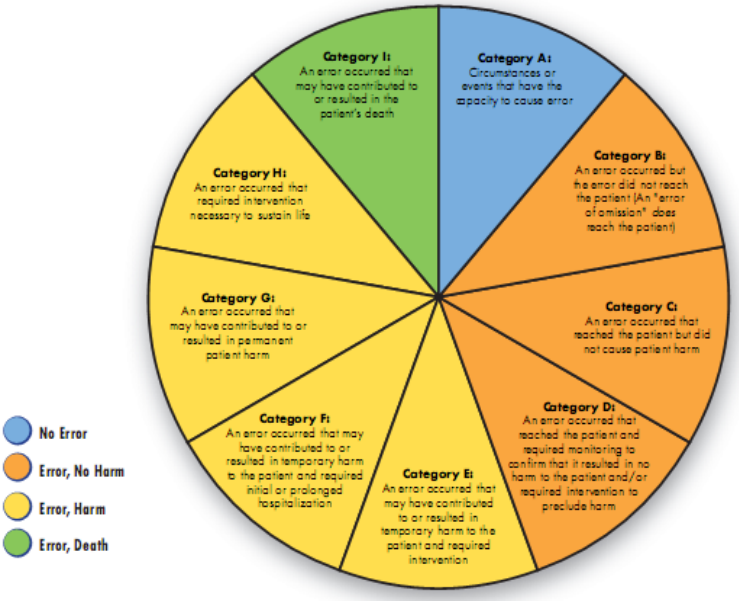
- Event could not have been avoided by any reasonable means
- Event was unpredictable event in the course of a treatment fully in accordance with good medical practice

4. Unevaluable

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

Annex 11. Medication Errors Categorization

NCC MERP Index for Categorizing Medication Errors



Definitions

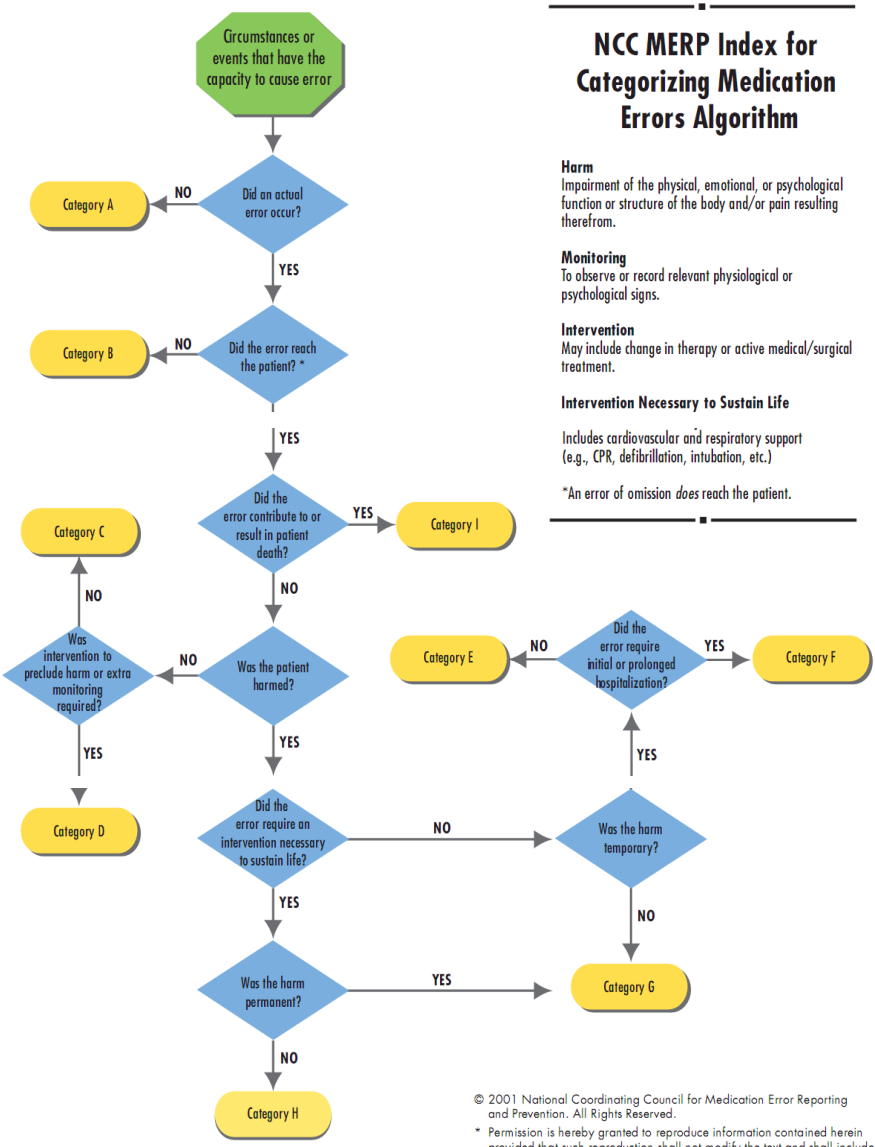
Harm
Impairment of the physical, emotional, or psychological function or structure of the body and/or pain resulting therefrom.

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.)

Annex 12. Medication Errors Algorithm



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