Chapter Three

Literature Review

Literature Review

3.1 Pharmacovigilance

Pharmacovigilance has been defined as:"The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem[2]" It aims at getting the best outcome of treatment with medicines. Good pharmacovigilance will identify the risks in the shortest possible time after the medicine has been marketed and will help to establish and/or identify risk factors. This information when communicated effectively allows intelligent, evidence-based prescribing with potential for preventing many adverse drug reactions and will help each patient to receive optimum therapy at lower cost to the health system.

The processes involved in the clinical development of medicines are illustrated in Figure 1. Once put onto the market, a medicine leaves the secure and protected scientific environment of clinical trials and is legally set free for consumption by the general population. At this point, most medicines will only have been tested for short-term safety and efficacy on a limited number of carefully selected individuals. In some cases as few as 500 subjects, and rarely more than 5000, will have received the product prior to its release, therefore, it is essential that new and medically still evolving treatments are monitored for their effectiveness and safety under real-life conditions post release. More information is generally needed about use in specific population groups, notably children, pregnant women and the elderly, and about the efficacy and safety of chronic use, especially in

combination with other medicines. Experience has shown that many adverse effects, interactions (i.e. with foods or other medicines) and risk factors come to light only during the years after the release of a medicine (Table 1) [11]

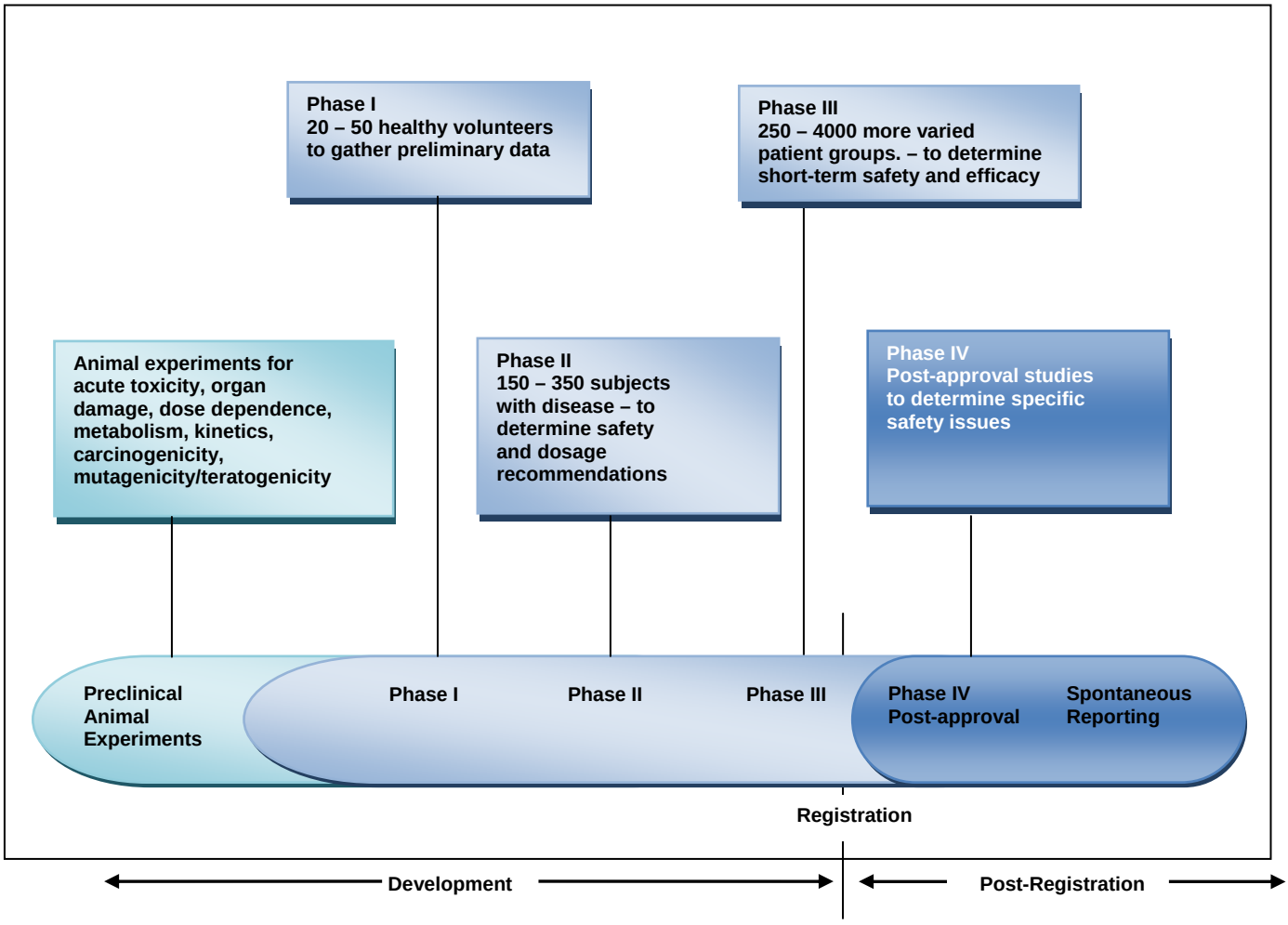

Figure 1: Clinical development of drugs

Table 1: Classical examples of serious and unexpected adverse reaction

Medicine	Adverse reaction
Chloramphenicol	Aplastic anaemia
Methyldopa	Haemolytic anaemia
Oral contraceptives	Thromboembolism
Reserpine	Depression
Statins	Rhabdomyolysis
Thalidomide	Congenital malformations

The scope of pharmacovigilance covers product quality; medication errors, including therapeutic ineffectiveness; and previously known or unknown adverse drug reactions (ADRs) as depicted in figure 2.

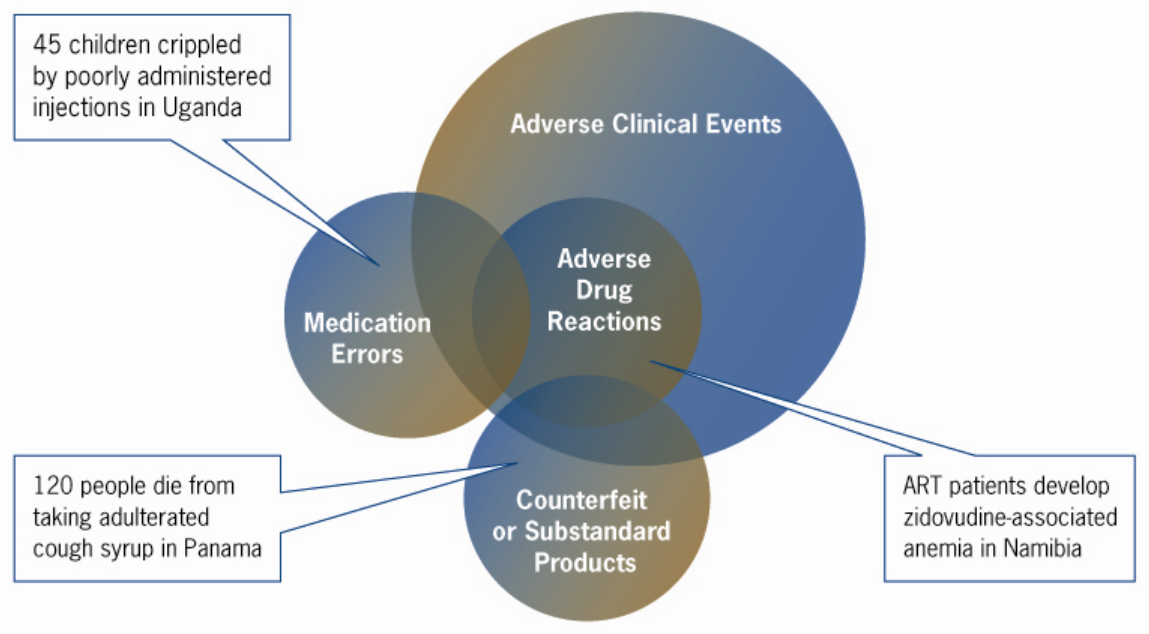

Figure 2: Scope of Pharmacovigilance

Figure 3 illustrates the components of a comprehensive, pharmacovigilance system describing the people, functions, and structures of a pharmacovigilance and medicine system. The outcome of a pharmacovigilance system should be decreased medicine-related problems, with the ultimate impact being a reduction in medicine- related morbidity and mortality. This framework presents a comprehensive systems perspective of the medicine safety system. (IPAT)

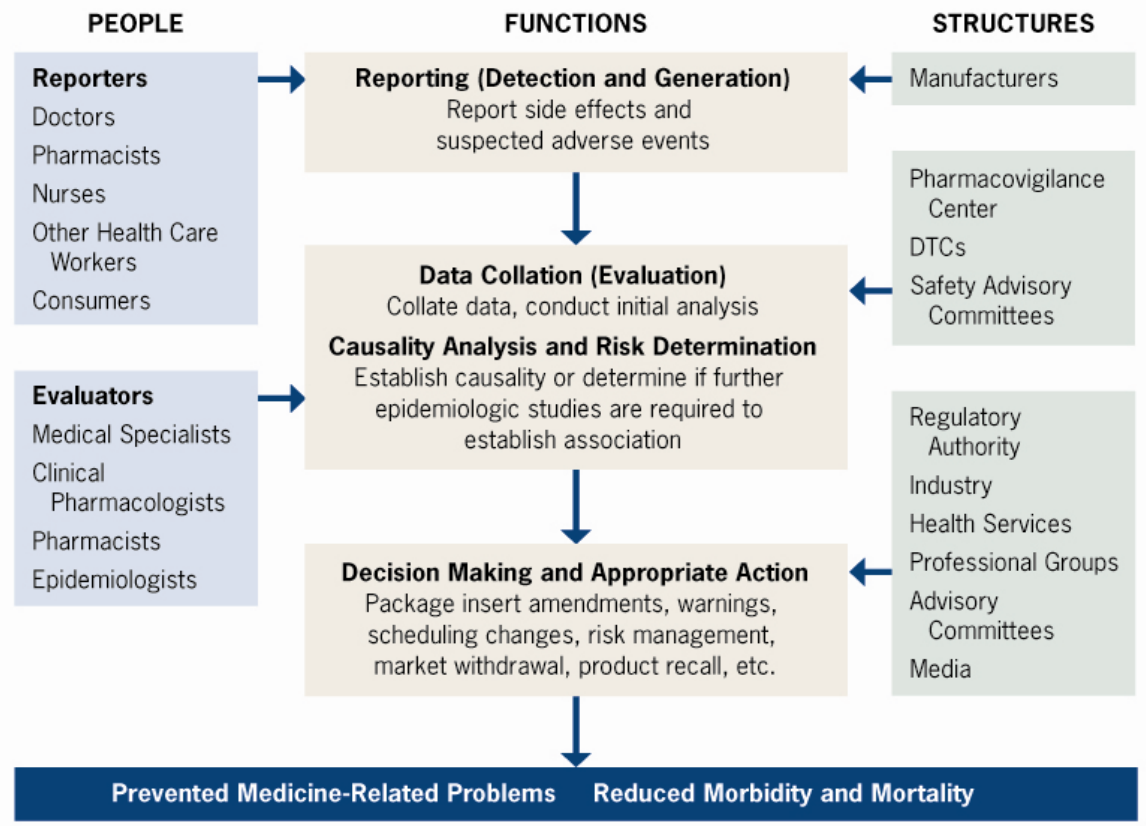

Figure 3: Pharmacovigilance framework

3.2 Specific aims of pharmacovigilance: [12]

Pharmacovigilance has specific aims as follows:

• improve patient care and safety in relation to the use of medicines and all medical and paramedical interventions,

• improve public health and safety in relation to the use of medicines,

• contribute to the assessment of benefit, harm, effectiveness and risk of medicines, encouraging their safe, rational and more effective (including cost-effective) use, and

• promote understanding, education and clinical training in pharmacovigilance and its effective communication to the public.

3.3 Methods of pharmacovigilance

The Pharmacovigilance methods that can be used in specific circumstances depend on the local situation, experience, expertise, and resources available to achieve these objectives.

Active surveillance

This method involves active follow-up of patients after treatment, and all adverse events are detected either by asking patients directly or by screening patient records.

a. Cohort event monitoring: Cohort studies are studies that identify subsets of a defined population and follow them over time, looking for differences in their outcome. Cohort studies generally are used to compare exposed patients to unexposed patients or one exposure to another. [13]

Cohort studies have many advantages. They are the best way to ascertain both the incidence and natural history of disorder, temporal sequence between cause and outcome is usually clear, useful in investigation of multiple outcomes that might arise after a single exposure, useful in the study of rare exposure. It also has some disadvantages such as selection bias is built into such studies, follow up can be difficult. [14]

Cohort event monitoring can be done with different epidemiological designs[15]as follows:

1. Observational

This means that the studies are "*non-interventional*" and are undertaken in real-life situations. Patients are not selected according to any criteria: all patients who receive treatment are included until the desired cohort size is achieved. This includes patients of all ages, those with other diseases and those on other medicines. Treatment is given according to the usual local guidelines.

2. Prospective

This means that CEM is planned before the patients are treated and treatment is monitored until the end of the programme, or until they cease to receive treatment for whatever reason.

3. Inceptional

This has a similar meaning to prospective: that every patient is followed-up for adverse events from the time of commencement of their treatment.

4. Dynamic

This means that new patients are added as the study continues until such time as there are sufficient numbers in the cohort.

5. Longitudinal

This means that the occurrence of any events in patients are observed over a period of time until the end of the programme, or until they cease to receive treatment with the monitored medicines.

6. Descriptive

This means that all events are identified and described, their frequency is measured and their distribution in different subgroups of interest in the cohort is recorded and analyzed.

b. Sentinel Sites [16]

Active surveillance can be achieved by reviewing medical records or interviewing and/or physicians in a sample of sentinel sites to ensure complete and accurate data on reported adverse reactions from these sites. The selected sites can provide information, such as data from specific patient subgroups that would not be

available in a passive system and information on the use of a drug, can be targeted at sentinel sites.

c. Registries

A registry is a list of patients presenting with the same characteristics. This characteristic can be a disease (disease registry) or a specific drug exposure. Pregnancy is also recorded as an event as part of the cohort event monitoring study. This helps to estimate the exposure to medicines during pregnancy.

Deaths

As part of cohort event monitoring, all deaths can be recorded, and their causes assessed by verbal autopsy. Where possible the data will be cross-tabulated with data from governmental records of deaths. In a study done by U.Mehta,[17] they have carried out confidential enquiry into malaria related deaths which proved to be useful tool for identifying the preventable factors ,health system failures, and adverse events affecting the malaria case management.

Passive surveillance [18]

Passive surveillance or spontaneous reporting is reporting of adverse events that are entirely dependent on the initiative and motivation of the reporters.

Spontaneous reporting is the most common method, easy to establish, cheapest to run, but reporting rates are low. In districts where active surveillance cannot be done due to constraints of manpower and funds, passive surveillance can be done

by spontaneous reporting using National ADR reporting forms if available, suitably modified if necessary.

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

Spontaneous reporting is dependent on clinicians and other health professionals who need to be trained and encouraged to report details of suspected adverse reactions in patients on ART treatment. Under-reporting is a serious problem with this method, but reporting can be intensified in selected units e.g. hospitals.

3.4 Adverse Drug Reactions (ADRs)

An adverse drug reaction is “a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function”.[19]

Classification and mechanisms of adverse drug reactions

There are different types of classification of adverse drug reactions and all are necessary different purposes.

Pharmacological Classification [20,21,22]

ADRs have traditionally been classified into two broad categories.

Type A: (Augmented)

This is commonest type of ADR which is predictable by pharmacological mechanisms. It includes an exaggerated therapeutic response at the target site (e.g. hypoglycemia with a sulphonylurea), a desired pharmacological effect at another site (e.g. headache with GTN), and secondary pharmacological effects (e.g. orthostatic hypotension with a phenothiazine). These reactions are usually dose dependent and predictable, and are often recognized before a drug is marketed. However, some effects occur after a long latency, such as carcinogenesis or effects on reproduction. An example is vaginal adeno carcinoma in the daughters of women exposed to diethylstilbestrol during pregnancy.

Type B: (Bizzare)

Type B reactions are unrelated to the known pharmacological actions of the drugs in question. These reactions are often caused by immunological and pharmacogenetic mechanisms. Type B reactions are generally unrelated to dosage and, although comparatively rare, they are more likely to cause serious illness or death. Immonologic reactions such as anaphylaxis with penicillins, aplastic anaemia with chloramphenicol are some examples of type B reactions.

Type C: (Continuous drug use)

This type of ADR occurs as a result of continuous drug use.Such type of ADR may be irreversible, unexpected, unpredictable e.g. dementia by anticholinergic medication.

Type D: (Delayed)

This type of ADR is charactrised by the delayed occurrence even after the cessation of treatment. E.g. corneal opacities after thioridazine

Type E (End of dose)

This type of ADR is usually characterized by withdrawal reactions. These ADRs occur typically with the depressant drugs.E.g. Seizures on benzodiazepines withdrawal.

Type F (Failure of therapy)

This ADR results from the ineffective treatment.

These classification is also not applicable to all the reactions, thus a new system has been proposed which takes into account properties of both the reaction and the affected individual, as well as those of the drug itself. The three dimensional classification system, known as DoTS, is based on dose relatedness, time course and susceptibility.[23]

2. Adverse drug reaction can be classified into two main types based on mechanism of reaction.

A. Non-immunologic type

Predictable ADRs: Reactions are dose dependent and affect the majority of individuals who ingest a sufficient amount of the drug. Examples of dose dependent hepatotoxins are paracetamol (acetaminophen), salicylates, tetracycline and methotrexate.

Unpredictable ADRs or Idiosyncratic: Reactions are generally less frequent, typically occurring in between 1 in every 1000 and 1in every 100000 patients. Examples of drugs involved are chlorpromazine, halothane and isoniazid.

B. Immunologic type

These reactions are generally classified into the four types.

Type I reactions are caused by the formation of drug /antigen-specific IgE that cross-links with receptors on mast cells and basophils. This leads to immediate release of chemical mediators, including histamine and leukotrienes. Clinical features include pruritus, urticaria, angio-oedema and, less commonly, bronchoconstriction and auaphylaxis. The drugs most commonly responsible for type I hypersensitivity are aspirin, opioids, penicillins and some vaccines.

Type II or cytotoxic reactions are based on IgG or IgM-mediated mechanisms. These involves binding of antibody to cells with subsequent binding of complement and cell rupture. This mechanism accounts for blood cell dyscrasia such as haemolytic anaemia and thrombocytopenia.

Type III reactions are mediated by intravascular immune complexes. These arise when drug antigen and antibodies, usually of IgG or IgM class, are both present in the circulation, with the antigen present in excess. Slow removal of immune complexes by phagocytes leads to their deposition in the skin and the microcirculation of the kidneys, joints and gastrointestinal system. Serum sickness and vasculitis are examples of type III reactions.

Type IV reactions are mediated by T cells causing “delayed” hypersensitivity reactions. Typical examples include contact dermatitis or delayed skin tests to tuberculin. Drug-related delayed-type hypersensitivity reactions include Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN). Recent work has proposed that type IV reactions be divided into four subtypes based on the T-lymphocyte subset and cytokine expression profile involved. Delayed-type hypersensitivity reactions include Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN). Recent work has proposed that type IV reactions be divided into four subtypes based on the T-lymphocyte subset and cytokine expression profile involved.

3.5 Adverse drug reaction monitoring system:[24]

The information collected during the pre-marketing phase of drug development is inevitably incomplete with regard to possible ADRs. This is mainly because tests in animals are insufficient to predict human safety; patients used in clinical trials are selected and limited in number, the conditions of use differ from those in clinical practice and the duration of trials is limited;

By the time of licensing exposure of less than 5000 human subjects to a drug allows only the more common ADR to be detected; . At least 30,000 people need to be treated with a drug to be sure that you do not miss at least one patient with an ADR which has an incidence of 1 in 10,000 exposed individuals.

Information about rare but serious adverse reactions, chronic toxicity, use in special groups (such as children, the elderly or pregnant women) or drug interactions is often incomplete or not available; Thus, post-marketing surveillance is important to permit detection of less common, but sometimes very serious ADRs. Therefore health professionals worldwide should report on ADRs as it can save lives of their patients and others.

Following steps are followed in adverse drug reaction monitoring:

Detection of ADRs [25]

1) Improve detection and accurate diagnosis of ADRs by healthcare providers and patients.

2) Encourage active surveillance of specific drug safety concerns through epidemiological methods such as case control studies, record linkage and epidemiological studies.

3) Consider special activities and expertise required for the detection of safety concerns related to vaccines, biologicals, veterinary medicines, herbal medicines, biotechnology products and investigational drugs.

4) Improve signal detection systems by facilitating the rapid availability of ADR data that may have international relevance.

5) Revisit the definitions of terms used within the field of pharmacovigilance including the definitions of specific ADRs to ensure reliability and universal understanding of data obtained through ADR reporting systems.

6) Develop and implement ADR detection systems that could benefit populations with restricted access to health care.

Assessment of ADRs[25]

7) Further development of automated signal detection systems used in spontaneous monitoring programmes.

8) Improvements in assessment of drug safety concerns that are of international relevance.

9) Foster collaborative links both at local and international level that could allow countries to assess and respond appropriately to drug safety crises.

10) Consider methods by which information on local patterns of drug use can be integrated with pharmacovigilance information during assessment of benefit and harm at a national level.

Prevention[25]

11) Improve access to reliable and unbiased drug information at all levels of health care.

12) Improve access to safer and more effective medicines for neglected diseases prevalent in developing communities.

13) Encourage awareness of drug safety and rational drug use among health professionals and the public.

14) Integrate pharmacovigilance activities into national drug policies and the activities arising from these (e.g. standard treatment guidelines, essential drugs lists etc.).

15) Further incorporation of pharmacovigilance principles into clinical practice and academic medicine.

16) Encourage the principles of product stewardship among the various partners in health care.

17) Improve regulation and pharmacovigilance of traditional and herbal medicines.

18) Develop systems which assess the impact of preventive actions taken in response to drug safety problems.

Communication [25]

19) Improve communication and collaboration between key partners in pharmacovigilance both locally and internationally.

20) The principles of good communications practice in pharmacovigilance and drug regulation should be encouraged, and the resources and expertise to deliver coopted. Different solutions are likely to be developed in different countries and regions, and the experience should be shared.

21) Develop a better understanding of patients, their expectations of medicines and their perception of risk associated with the use of medicines in order to facilitate programmes that will better inform the public on the benefit and harm associated with medicine.

22) Develop sustained and active relationships with the media in order to facilitate effective and accurate communication of drug information to the public.

23) Encourage harmonization of drug regulatory and pharmacovigilance activities by incorporating the wider international community in the development of harmonization policies.

Outcomes and Impact [25]

24) Conduct on-going research to assess the cost-effectiveness of contemporary pharmacovigilance systems in contributing to patient welfare and public health.

25) Consider the sensitivity and specificity of current signal detection and assessment methods and the extent to which contemporary pharmacovigilance systems have been successful in detecting and preventing potential disasters while avoiding the premature withdrawal of safe and useful medicines from the market.

3.6 Assessment of Adverse Drug Reactions:

a. Causality: [26]

There are different scales are available for causality assessment.

1. WHO criterion of causality
2. Naranjo's algorithm
3. ABO system

1. The causality categories described by WHO-UMC are as follows:

Certain : a clinical event , including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

Probable/Likely: a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.

Possible: a clinical event, including loboratory test abnormality, with a reasonable time sequence to administrations of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

Unlikely: a clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

Conditional/Unclassified: a clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment, or the additional data is under examination.

Unassessable/Unclassifiable: a report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

2. Naranjo algorithm: [27]

Question	Yes	No	Don't know
Are there previous conclusive reports on this reaction?	+1	0	0
Did the adverse event appear after the suspected drug was administered?	+2	-1	0
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0
Did the adverse reaction reappear when the drug was re-administered?	+2	-1	0
Are there alternative causes (other than the drug) that could solely have caused the reaction?	-1	+2	0
Was the drug detected in the blood (or other fluids) in a concentration known to be toxic?	+1	0	0
Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
Was the adverse event confirmed by objective evidence?	+1	0	0
Total score			

Total score categories are defined as follows: ADR is:

Certain > 9;

Probable 5-8;

Possible 1-4;

Unlikely 0

3. ABO system:[28]

Category A: "Reports including good reasons and sufficient documentation to assume a causal relationship, in the sense of plausible, conceivable, likely, but not necessarily highly probable".

Category B: "Reports containing sufficient information to accept the possibility of a causal relationship, in the sense of not impossible and not unlikely, although the connection is uncertain and may be even doubtful, e.g. because of missing data, insufficient evidence or the possibility of another explanation".

Category O: "Reports where causality is, for one or another reason, not assessable, e.g. because of missing or conflicting data.

b. Seriousness: [29]

A serious adverse event or reaction is any untoward medical occurrence that at any dose;

-results in death,

- is life-threatening

- requires inpatient hospitalization or prolongation of existing hospitalization

- results in persistent or significant disability

- is congenital anomaly

c. Severity: Hertwig and Seigel scale[30]

Severity levels	Definition
1	Required no change in treatment with suspected drug.
2	Drug dosing or frequency changed ,without antidote or treatment for exhibited symptoms
3	Required treatment or drug administration discontinued
4	Resulted in patient transfer to higher level of care
5	Caused permanent harm to the patient or significant hemodynamic instability.
6	Directly or indirectly resulted in patient's death.

Level 1&2 = Mild

Level 3&4 = Moderate

Level 5&6 = Severe

d. Preventability: [31]

Schumock and Thornton scale of preventability:

Answering “yes” to one or more of the following implies that an ADR is preventable:

1. Was the drug involved in the ADR inappropriate for the patient’s clinical condition?

2. Was the dose, route, or frequency of administration inappropriate for the patient’s age, weight, or disease stage?

3. Was required therapeutic drug monitoring or other necessary laboratory test not performed?

4. Was there a history of allergy or previous reaction to the drug?

5. Was a drug interaction involved in the ADR?

6. Was a toxic serum drug concentration (or laboratory monitoring test) documented?

7. Was poor compliance involved in the ADR?

e. Avoidability of adverse drug reactions: [32]

Definitely avoidable - the ADR was due to a drug treatment procedure inconsistent with current knowledge of good medical practice.

Possibly avoidable - the ADR could have been avoided by an effort exceeding the obligatory demands of current knowledge of good medical-practice.

Unavoidable - the ADR could not have been avoided by any reasonable means.

3.7 Risk minimization:[33]

A risk minimization tool is a process or system intended to minimize known risks. Tools can communicate particular information regarding optimal product use and can also provide guidance on prescribing, dispensing, and/or using a product in the most appropriate situations or patient populations.

A variety of tools are currently used in risk minimization plans. These fall within three categories: (1) targeted education and outreach, (2) reminder systems, and (3) performance-linked access systems. A RiskMAP might include tools from one or more categories, depending on its risk minimization goals.

1. Targeted Education and Outreach

Tools in this category employ specific, targeted education and outreach efforts about risks to increase appropriate knowledge and behaviors of key people or groups (e.g., healthcare practitioners and consumers) that have the capacity to prevent or mitigate the product risks of concern. This tool is used for products where the benefit/risk balance does not necessarily warrant a RiskMAP

Examples of tools in this category are as follows:

- healthcare practitioner letters
- training programs for healthcare practitioners or patients

- continuing education for healthcare practitioners such as product-focused programs developed by sponsors and/or sponsor-supported accredited CE programs
- prominent professional or public notifications
- patient labeling such as Medication Guides and patient package inserts
- promotional techniques such as direct-to-consumer advertising highlighting appropriate patient use or product risks
- patient-sponsor interaction and education systems such as disease management and patient access programs

In addition to informing healthcare practitioners and patients about conditions of use contributing to product risk, educational tools can inform them of conditions of use that are important to achieve the product's benefits. For example, a patient who takes a product according to labeled instructions is more likely to achieve maximum product effectiveness. On the other hand, deviations from the labeled dose, frequency of dosing, storage conditions, or other labeled conditions of use might compromise the benefit achieved, yet still expose the patient to product-related risks. Risks and benefits can have different dose-response relationships. Risks can persist and even exceed benefits when products are used in ways that minimize effectiveness. Therefore, educational tools can be used to explain how to use products in ways that both maximize benefits and minimize risks.

2. Reminder Systems

Tools in the reminder systems category be used in addition to tools in the targeted education and outreach category when targeted education and outreach tools are known or likely to be insufficient to minimize identified risks.

Tools in this category include systems that prompt, remind, double-check or otherwise guide healthcare practitioners and/or patients in prescribing, dispensing, receiving, or using a product in ways that minimize risk. Examples of tools in this category are as follows:

- Patient education that includes acknowledgment of having read the material and an agreement to follow instructions. These agreements are sometimes called consent forms.
- Healthcare provider training programs that include testing or some other documentation of physicians' knowledge and understanding.
- Enrollment of physicians, pharmacies, and/or patients in special data collection systems that also reinforce appropriate product use.
- Limited number of doses in any single prescription or limitations on refills of the product.
- Specialized product packaging to enhance safe use of the product.
- Specialized systems or records that are used to attest that safety measures have been satisfied (e.g., prescription stickers, physician attestation of capabilities).

3. Performance-Linked Access Systems

Performance-linked access systems include systems that link product access to laboratory testing results or other documentation. Tools in this category, because they are very burdensome and can disrupt usual patient care, should be considered only when (1) products have significant or otherwise unique benefits in a particular patient group or condition, but unusual risks also exist, such as irreversible disability or death, and (2) routine risk minimization measures, targeted education and outreach tools, and reminder systems are known or likely to be insufficient to minimize those risks.

Examples of tools in this category include:

- prescription only by specially certified healthcare practitioners
- product dispensing limited to pharmacies or practitioners that elect to be specially certified
- product dispensing only to patients with evidence or other documentation of safe-use conditions (e.g., lab test results)

3.8 Pharmacovigilance of antiretrovirals: [34]

There is considerable experience in the developed world with the use of antiretroviral medicines. These medicines are associated with significant safety concerns including serious ADRs, with both short- and long-term effects. The outcome of these long-term adverse effects is unknown. The major events linked to the use of antiretroviral medicines include altered body fat distribution (lipodystrophy), anaemia and neutropaenia, hypersensitivity reactions, hepatic

disorders, acute pancreatitis, altered bone structure (osteopaenia and osteoporosis), muscle damage (myopathy) of the newborn and lactic acidosis. These may damage confidence in any national ART programme and affect patient adherence. Poor adherence is known to lead to failure of therapy in the patient and in addition, to increase the possibility of development of drug-resistant viral strains leading to reduced efficacy.

Little is known about the toxicity profile of ART in developing countries. These countries have special factors and conditions that are very different from those of the developed world and medicine use and its safety may therefore vary considerably. The relevant factors and conditions include the existence of comorbid conditions such as a high prevalence of tuberculosis (TB), malaria and other infections of all types; malnutrition; reliance on traditional and/or alternative therapies; insufficient numbers of trained doctors and pharmacists; irrational use of prescription medicines; and likelihood of medicine interactions. In addition, some local systems for the delivery of health care may rely on people who have limited training, knowledge or expertise, and medicine regulatory systems that are either rudimentary or nonexistent and are not adequately equipped to deal with medicine safety issues.

3.9 Antiretroviral Therapy and antiretroviral centres:

Antiretroviral therapy (ART) is the method of fighting HIV virus with drugs. It does not kill the virus but only suppresses it by slowing down growth and reproduction of the virus.[5] Antiretroviral treatment for HIV infected patients was first introduced in 1986 and Zidovudine , a nucleoside reverse transcriptase inhibitor was the first drug used for the treatment. It was observed that Single drug therapy was short lived and thus later combination of 2-3 drugs was used as it gives sustained benefit.[6]

Goals of the ART are improved quality of life, reduction of HIV-related morbidity and mortality, restoration and/or preservation of immunologic function and maximal and durable suppression of viral load. These goals can be achieved through different tools such as by preventing vertical transmission and transmission to sexual partners, selecting proper ART regimen, maximizing adherence towards treatment and by use of resistance testing. Current ART regimen available are NRTI (Nucleoside reverse transcriptase inhibitors) which includes zidovudine, lamivudine etc , NNRTI (Non Nucleoside reverse transcriptase inhibitors) which includes nevirapine, efavirenz, Protease inhibitors, fusion inhibitors and many more.[35]

These treatment are very costly and once started patient need to take this medication throughout his/her life and thus it becomes duty of Government to make these drug available for the middleclass people who can't afford to buy these drugs.

The Government of India launched free ART initiative on 1st April 2004 at 8 Government hospitals in six prevalence states i.e. Andhra Pradesh, Karnataka, Maharashtra, Tamil Nadu, Manipur and Nagaland and now the count stands at 270 ART centres in 31 states and union territories. Patient fulfilling WHO criterion to start ART only advise to start the medication. Patients diagnosed with clinical AIDS or having CD4+ cell count below 200/mm^3 or Total Lymphocyte Count (TLC) under 1200/mm (Stage II or III) only started with the ART. Patients whose CD4 cell count is good or more than 200 are advice not to take ART and these patients are registered for pre ART care. [36]

Pre ART period where an HIV positive person does not medically require the initiation of ART. Patients are counseled to maintain healthy/positive living and be linked to care and support services. These patients are followed up for the early detection of OIs and initiation of ART before the CD4 count falls below 200 cells. Following ART regimen are available at ART centre.

- Stavudine (30 mg) + Lamivudine (150 mg) + Nevirapine (200 mg)
- Zidovudine (300 mg) + Lamivudine (150 mg) + Nevirapine (200 mg)
- Stavudine (30 mg) + Lamivudine (150 mg) + Efavirenz (600 mg)
- Zidovudine (300 mg) + Lamivudine (150 mg) + Efavirenz (600 mg)

At patient's first visit to ART clinic, patient's complete medical history, physical examination, screening for TB, behavioral/psychosocial assessment, educational level, employment history, financial resources, social support, family/household

structure, disclosure status, readiness to disclose, understanding of HIV/AIDS, transmission, risk reduction, treatment options, nutritional assessment, family/household assessment to determine if there are other HIV-infected family, members who may need care, Investigation: baseline Blood profile, CD4 count, other test as necessary are performed. [37]

During second visit, patient is put on co-trimoxazole prophylaxis and adherence counseling is done. In third visit, ART is initiated if patient is stable on Co-trimoxazole and is ready to start with the therapy. First choice given is zidovudine+lamivudine+nevirapine (for patients with Hb > 8 g/dl) and second choice: stavudine+lamivudine+nevirapine. Assessment for ART tolerability and adherence assessment is done at fourth visit and patient is tole to come every month for follow up. In case of CD4 and viral load failure in patients of stage 3 and 4, patients are shift to second line therapy.[37]

3.10 Adverse effects of ART:

Antiretroviral therapy can have a wide range of adverse effects on the human body. Common but mild adverse effects occurring early in most antiretroviral regimens include gastrointestinal effects such as bloating, nausea and diarrhea, which may be transient or may persist throughout therapy. Other common nuisance adverse effects are fatigue and headache caused by AZT and nightmares associated with EFV.

Several uncommon but more serious adverse effects associated with antiretroviral therapy, including AZT-associated anemia, d4T-associated peripheral neuropathy, PI-associated retinoid toxicity (exemplified by pruritus and ingrown toenails) and NNRTI-associated hypersensitivity reactions, are treated according to accepted therapy for these conditions in patients not receiving HAART. This treatment also results in development of some serious nature of adverse effects such as lactic acidosis, hepatic steatosis, hyperlactatemia, hepatotoxicity, hyperglycemia, fat maldistribution, hyperlipidemia, bleeding disorders, osteoporosis and skin rash.[34]

Various National and International studies have been done to support antiretroviral therapy induced adverse effects. A study on Iranian patients observed the hematological ADRs as the most common cause of ART interruption.[38] Another study showed that 37.5% of the patients were non-adherent to the treatment because of adverse effects. [39]

Adverse drug reaction due to antiretroviral therapy was observed to be having significant impact on the incidence and nature of ADRs in hospital setting. [40]

3.11 Pharmacovigilance of antidiabetic drugs:

Diabetes is the single most important metabolic disease which can affect nearly every organ system in the body. It has been projected that 300 million individuals would be affected with diabetes by the year 2025.

In India it is estimated that presently 19.4 million individuals are affected by this deadly disease, which is likely to go up to 57.2 million by the year 2025.Diabetes

mellitus is a group of metabolic diseases characterized by high blood sugar (glucose) levels, which result from defects in insulin secretion, or action, or both.[41]

These anti-diabetic drugs are associated with many adverse drug events. Hasford and Schneeweiss et al[42] reported that 69% and 30% patients on insulin and about 57% and 40% patients on oral hypoglycemic agents developed hypoglycemia and hypoglycemic coma respectively. The anti-diabetic drugs such as Metformin belonging to the class of biguanides had major side effects such as lactic acidosis and hepatotoxicity[43]. Glibenclamide, an antidiabetic drug induced erythema multiforme and photodermatitis[44].Sulphonyl urea shows side effects like hypoglycemia, nausea, vomiting, cholestatic jaundice, agranulocytosis, aplastic and hemolytic anemias, generalized hypersensitivity reactions. A study reported that the use of rosiglitazone was associated with a slightly increased risk(About 20 %) of heart attack.[45]