

**FIELD GUIDE FOR
COHORT EVENT
MONITORING (CEM) OF
ANTIMALARIALS IN
NIGERIA**

*Abridged format adapted from WHO “Practical handbook on the
pharmacovigilance of antimalarial medicines”*

PHARMACOVIGILANCE

Definition

Pharmacovigilance has been defined as: The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem (WHO).

Pharmacovigilance of antimalarials

Malaria is the greatest killer disease of all time. Unfortunately, after a period of relatively good control in many countries with the use of insecticides and antimalarials such as chloroquine, there has been a resurgence of this disease. This is due to the development of resistance of mosquitoes to insecticides and resistance of parasites to the antimalarials, thus producing an increase in malaria morbidity and mortality. WHO is promoting the use of artemisinin combination therapies (ACTs) as a therapeutic tool to treat uncomplicated acute falciparum malaria. It is known to be effective, but its safety under large-scale operational use has not been fully assessed. Children and pregnant women are the most vulnerable to falciparum malaria and least is known about safety in these populations. A range of ACTs is becoming available and it is important that these are carefully monitored.

Passive or Active Pharmacovigilance

Passive pharmacovigilance

Passive surveillance means that no active measures are taken to look for adverse effects other than the encouragement of health professionals and others to report safety concerns. Reporting is entirely dependent on the initiative and motivation of the potential reporters. This is the most common form of pharmacovigilance. It is commonly referred to as “spontaneous” or “voluntary” reporting. In some countries this form of reporting is mandatory.

Active pharmacovigilance

Active (or proactive) safety surveillance means that active measures are taken to detect adverse events. This is managed by active follow-up after treatment and the events may be detected by asking patients directly or screening patient records. It is best done prospectively. Active pharmacovigilance is sometimes very descriptively referred to as, “hot pursuit”. The most comprehensive method is cohort event monitoring (CEM). Examples of this are the Intensive Medicines Monitoring Programme (IMMP) in New Zealand and Prescription Event Monitoring (PEM) in England. Other methods used include the use of registers, record linkage and screening of laboratory results in medical laboratories.

Methods for both passive (spontaneous reporting) and active pharma-covigilance (CEM) will be described. The essential and interesting tasks of causality assessment and signal identification are applicable to both methods of surveillance and will be covered in detail after the individual methods have been discussed.

Cohort event monitoring

✓ Event monitoring

An event is any new clinical experience that occurs after commencing a medicine regardless of its severity or seriousness and without judgement on its causality. (Favourable events may be recorded as an indication of an unexpected therapeutic effect.)

Event monitoring involves

- Actively asking for reports of the events
- Systematically asking for reports of the events.

✓ Adverse event

An adverse event (sometimes called an adverse experience) is defined as, “Any untoward medical occurrence temporally associated (i.e. associated in time) with the use of a medicinal product, but not necessarily causally related” (WHO).

Cohort Event Monitoring (CEM) records all clinical events and not just suspected adverse reactions.

Cohort event monitoring (CEM) is a prospective, observational, cohort study of adverse events associated with one or more medicines.

This methodology is often referred to as prescription event monitoring (PEM), but this terminology is inappropriate when individual prescriptions with subsequent dispensing by pharmacists are not part of the process of supplying medicines to patients. In most malaria-endemic countries, the treatment of malaria is not provided on a prescription basis. Examples of CEM methodology are the Intensive Medicines Monitoring Programme (IMMP) in New Zealand and the PEM run by the Medicine Safety Research Unit in England.

A CEM programme is essentially an observational study of a new medicine in the early post marketing phase, but it can be used for older medicines. Its basic function is to act as an early warning system of problems with new medicines, although it will provide much more.

The aims of CEM include the following:

- Provide incidence rates for adverse events as a measure of risk.
- Characterize known adverse reactions.
- Detect signals of unrecognized reactions.

- Detect interactions with other medicines, complementary and alternative medicines, foods and concomitant diseases.
- Identify risk factors and thus provide evidence on which to base effective risk management.
- Assess safety in pregnancy and lactation.
- Provide a measure of comparative risks between medicines.
- Provide cohorts for further study of safety issues if required in the future.
- Detect inefficacy, which might be due to:
 - faulty administration;
 - poor storage conditions;
 - poor quality product;
 - counterfeit product;
 - interactions

Selection of medicines to monitor

- ✓ It is intended to monitor artemisinin combination therapies (ACTs).

Basic processes:

- ✓ Establishing a cohort of patients for each medicine and/or medicine combination.
- ✓ Recording adverse events experienced by patients in the cohort(s) for a defined period.

Programme duration:

- ✓ CEM is done for a limited length of time. The length depends on the time it takes to achieve the cohort size that is necessary and this will depend on the incidence of malaria in the population being studied. The target sample size is usually around 10,000 patients.
- ✓ If there is particular interest in certain subgroups e.g. pregnant women or children or those who experience an event of concern, then monitoring may need to continue for a longer period to get sufficient numbers to evaluate these subgroups at a satisfactory level of statistical significance.
- ✓ A practical approach is to review the data monthly. Trends will be observed that may indicate the need for an extension of monitoring.

Epidemiology

The key epidemiological features of CEM studies are that they are:

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 are treated for malaria with the medicine being monitored are included. 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 the monitoring is planned before the patients are treated and the patients are studied and followed up from the time they begin their treatment.

3. *Inceptional*

This has a similar meaning to prospective: that every patient is studied 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 patients are studied over a period of time. For antimalarials used for acute treatment this is a matter of only a few days although monitoring may continue longer if looking for delayed effects.

6. *Descriptive*

In terms of a CEM malaria study, this means that the events are identified and described, their frequency is measured and their distribution in different subgroups of the cohort is recorded.

First step – Implementation

The implementation step has to be done well if a CEM study is to succeed. (Refer main document)

Second step – Establishing the cohort(s)

Numbers of patients

A cohort of 3000 patients gives a 95% chance of identifying a single event with an incidence of 1:1000.

Total numbers

In general, the aim is to have 10 000 patients in the cohort. This gives a 95% chance of identifying a specific event with an incidence of 1:3000 (uncommon or rare). Normally several events are needed to alert to a signal, or help evaluate a problem.

If a comparator study is being undertaken, greater numbers will be needed if the background incidence in the community is high (as with diarrhoea) and it may be desirable to detect statistically significant differences between the comparators.

Selection of patients

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

Logistics

- The patients might be recruited from all health facilities involved in the malaria programme.
- Patients might be recruited from selected health facilities that are representative of the whole country, designated as "sentinel monitoring sites".

Inceptional

Patients must be monitored from the inception of treatment. Patients not seen at the beginning of treatment should be excluded from the study.

Subgroups of interest

Children: In order to determine any risk factors specific to children, the whole population of users will still need to be monitored to enable comparison of children with the adults in the cohort, and to detect risk factors specific to children.

HIV/AIDS: In order to determine any risk factors specific to patients with HIV/AIDS, the whole population of users will still need to be monitored to enable comparison with the cohort members who do not have HIV/AIDS.

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

Patient identification

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

Other patient data

Age at the time of treatment. (date of birth to help identification).

Sex.

Weight and height.

Background data

History of significant illness (e.g. liver disease, kidney disease).

Other diseases present at the time of treatment (e.g. HIV/AIDS, tuberculosis, anaemia).

Acquiring the data

The medicines

Details of administration of antimalarial medicine

The following should be recorded:

- brand name, e.g. Coartem;
- dose and schedule of administration;
- date of commencement of treatment;
- date of completion of course of therapy or date of withdrawal;
- record of incomplete adherence;
- record reason(s) for incomplete adherence.

Concomitant medicines

All medicines taken during the 2 weeks prior to treatment and at any time from day 0 of treatment until the follow-up appointment should be recorded (first day of treatment is day 0)

Record the following information on concomitant medicines:

- name: brand (preferred) or generic;
- any traditional medicine(s) (“yes” or “no”);
- indication for use;
- dose and frequency of administration;
- date started;
- date stopped (record “continues” if not stopped).

The events

Principles of event reporting

- All adverse events are requested to be reported and not just suspected adverse reactions. Clinicians should be asked to make no judgement on causality.
- “Adverse events” are requested to be reported because there are always unexpected or unrecognized adverse reactions. If only suspected reactions are reported, then those which are unexpected and unrecognized are likely to be missed.
- All clinical events experienced by each patient should be recorded on the questionnaire provided. This includes unexpected improvement of concomitant disease (favourable event) as well as adverse events.
- Pretreatment: Each patient who attends a health care facility with an attack of malaria should be asked if any health events have occurred in the previous 7 days and these

should be recorded as having occurred during the control period. These should include diseases such as otitis media, tonsillitis, measles and abscess.

- Post-treatment: At the follow-up visit any new events or worsening of pre-existing conditions that have occurred since treatment began should be recorded.

Reporting requirements

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

- All new events even if minor.
- Change in a pre-existing condition.
- Abnormal changes in laboratory tests.
- Persistent positive tests for malaria.
- Admission to hospital with date and cause.
- Pregnancy of any duration.
- Accidents.
- All deaths with date and cause.
- Possible interactions.
 - o Include pharmaceutical or traditional medicines.
 - o Remember oral contraceptives and alcohol.

Recording event details

A brief description of each event is usually all that is necessary. These event descriptions will be reviewed later by pharmacovigilance staff and standard adverse event terminology will be applied by them. The clinician does not need to know the standard event terminology.

Reporting forms (questionnaires)

The CEM questionnaires have two parts:

- Side A is the Pretreatment questionnaire. This information is used to record patient details, treatment and the events during the pretreatment control period.
- Side B is the post-treatment (or follow-up) questionnaire. This provides the follow-up information on events and outcomes of treatment since treatment began.

It is important to make the recording of data as easy as possible.

Who should report?

- Health workers with clinical responsibility should record the events.

It is desirable that the health worker who treated the patient at the first visit should also see the patient at follow-up.

Follow-up

- At the time of treatment and enrolment in the study, each patient should be given a follow-up appointment for monitoring purposes and asked to return on the 3rd and 7th day after commencement of treatment in order to record any adverse events.
- When the patient returns to the health facility, the same clinician who made the pre-treatment assessment should, in principle, also be responsible for making the post-treatment evaluation.
- Defaulters should be actively traced at home/village level by visits of support staff who will interview the patient or care-giver and refer back all patients presenting with “new events, even if minor” or “deterioration in a pre-existing condition”.
- A special form for patient tracking should be drawn up, with the following information:
 - o patient identification;
 - o date of home/follow-up visit;
 - o name of health worker;
 - o outcome of visit, indicating:
 - o no new event;
 - o improvement of clinical condition;
 - o the presence of new adverse events and subsequent referral to the treatment centre for clinical assessment;
 - o reasons for referral.
- The timing of follow-up of defaulters should be not later than 7 days after the missed follow-up appointment.
- Events that become obvious after the 7-day follow-up period, and which appear to be reactions to the ACT, should be reported on a spontaneous reporting form.
- To facilitate this, spontaneous reporting forms should be stamped ‘CEM’ and placed, where possible, with the patient’s record, or otherwise be readily available in the health facility.
- Completed and stamped CEM forms would be collected by the CEM programme supervisors and forwarded to the Pharmacovigilance Centre.
- Reasons for non-adherence

It is important to record any of the following, or other reasons, for non-adherence to the treatment schedule.

- Persistent vomiting.
- Other adverse events.
- Patient felt better quickly.
- Patient felt worse (possible inadequate response).
- Patient wished to keep some of the tablets.

Completed Questionnaires would be collected weekly from the study sites by the supervisors.

General advice and information

- Don't ask for too much
 - The more you ask for the less you will get.
 - Assess the necessity for every data item requested.
 - Increased data increases the workload and the cost.
 - Some information is best requested by follow-up when the necessity for it can be explained and interest created by the problem being explored.

Non-serious events

It is important to include these because:

- They might indicate a serious problem.
- They might affect adherence, e.g. nausea.
- If common, they might be more important to public health than rare, but serious problems.

Be open-minded

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

Privacy

- Given basic precautions to maintain confidentiality, patients give greater priority to safety concerns.
- Security and confidentiality of data is the essential requirement. Other ethical requirements should not prevent CEM taking place or reduce its functionality,

because it is unethical not to pursue those methods that are essential to safety assessment and the protection of patients.

Special types of event

Serious events

- Details of serious events should be sent immediately to the Pharmacovigilance Centre where they will be fully assessed and appropriate action taken.

Deaths

- All deaths should be followed up to assess the cause, even if it seems most unlikely that death was related to the medicine.
- With CEM, death rates can be calculated. This has particular advantages:
- Importantly, death rates can be used to measure changes in outcomes.
- Death rates can be compared between comparators.

Lack of efficacy

Lack of efficacy should always be recorded.

The following terms should be used as appropriate:

- “medicine ineffective”;
- “therapeutic response decreased”.

Reasons for lack of efficacy

These are important events to record. Possible reasons for lack of effect are as follows:

- did not retain the medication because of vomiting or severe diarrhoea;
- lack of adherence to treatment schedule;
- inadequate dose;
- poor quality medication;
- counterfeit medication;
- incorrect diagnosis;
- interactions reducing blood levels;
- medicine resistance.

Concomitant morbid conditions

Patients may be more susceptible to adverse reactions if they also have other health problems, either because of the concomitant condition or from the interaction of malaria medicines with

those being used to treat the other illness. The following are examples of concomitant illnesses that may result in such problems:

- HIV/AIDS
- tuberculosis
- malnutrition
- anaemia.

Concomitant conditions should therefore always be recorded.

Clinical details

- Concomitant disease.
- Relevant patient history, e.g. liver disease; renal disease.
- Previous exposure to same medicine(s). - Yes/no?
- Any reaction to previous exposure – yes/no.
- If “yes”, record the reaction term(s) for previous reaction(s).

Good data are essential

- The data in the report(s) need to be of good quality if a signal of a new adverse reaction is to be considered.
- There should be sufficient data to fully assess the relationship of the medicine to the event.

Differences between spontaneous reporting and cohort event monitoring

Cohort event monitoring

- Advantages
 - the ability to produce rates;
 - the ability to produce a near complete profile of the adverse event and/or adverse reaction for the medicines of interest;
 - very effective in identifying signals at an early stage;
 - the ability to characterize reactions in terms of age, sex and duration to onset and thus produce risk factors. Other relevant data may be collected such as weight, or co-morbidity in order to provide the opportunity for determining other risk factors;
 - the ability to make accurate comparisons between medicines;
 - the ability to establish a pregnancy register and define and measure rates of any abnormalities;
 - because of the routine follow-up, the method can detect with confidence reduced or failed therapeutic effect and thus raise suspicion of inaccurate diagnosis of

disease, poor prescribing, inadequate adherence to treatment, emerging resistance or poor quality or counterfeit medicines;

- the ability to record and examine details of all deaths and provide rates of death;
- the ability to produce rapid results in a defined population;
- this method collects comprehensive and near-complete data that will provide for the special needs of the malaria programme, including effects of malaria treatment in pregnancy, specific toxicities, safety in children;
- because the method looks intensively at new medicines of great interest in a specific area of need, and provides clinically significant results rapidly, it stimulates interest in medicine safety in general;
- the method provides sound evidence with which to deal with any medicine scares.

- Disadvantages

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

Spontaneous reporting

- Advantages

- It is administratively simpler and less labour intensive than CEM.
- It is less costly than CEM.
- It is the most common method of pharmacovigilance used.
- National Pharmacovigilance Centres and health professionals (to a certain extent) will be familiar with this method.

- Disadvantages

- The data collected by this method are incomplete. In developed countries less than 5% of reactions are reported. A report from the WHO filariasis programme suggests that compliance with reporting is likely to be much lower than this, leaving many unanswered questions.
- Reliable rates cannot be calculated and so risk cannot be measured and risk factors cannot be established with confidence.
- There are strong biases in reporting.
- Deaths are poorly reported.
- Special studies will need to be set up to obtain accurate information on areas of particular interest e.g. pregnancy, children and specific events of concern. These

special studies add to the cost and in turn reduce the cost advantage of spontaneous reporting.

Ethical issues

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

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

Security of data and confidentiality must be ensured.

Confidentiality

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