

PHARMACOVIGILANCE GUIDANCE FOR COUNTRIES PARTICIPATING IN AMFm PHASE 1

WHO-MMV joint technical consultation on active pharmacovigilance
monitoring with a special focus on AMFm

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Cointrin

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Executive summary

This document provides countries participating in the first phase of the initiative Affordable Medicine Facility for malaria (AMFm) with minimal standard procedures for preparing project plans to submit for funding. It is the product of a consultation on pharmacovigilance among international experts and technical experts from several countries, which was convened by the Global Malaria Programme of the World Health Organization (WHO) and the Medicines for Malaria Venture (MMV) on 6–8 April 2009, in Geneva, Switzerland.

The report describes why countries should prepare a pharmacovigilance strategy that takes into consideration the existing health infrastructure and post-marketing experience with artemisinin-based combination therapies (ACT). Pharmacovigilance systems are needed to monitor and ensure the maximum possible safety of ACT used in the AMFm programme. Their objectives are:

- to monitor the risk for adverse drug reactions associated with ACT made available through the AMFm programme and supplied by
 - the public sector,
 - the for-profit private sector or
 - the not-for-profit private sector (e.g. nongovernmental and faith-based organizations);
- to build a strategy for communication and feedback with health professionals and the public about the safe use of ACT, based on information generated through the pharmacovigilance system;
- to monitor and assess the quality of the components of the pharmacovigilance system; and
- to monitor the safety of ACT in pregnancy by setting up or strengthening a pregnancy register at selected sites (where feasible).

The relevant pharmacovigilance approaches include:

- spontaneous reporting;
- strategies to stimulate spontaneous reporting, particularly by private accredited retailers who are likely to dispense ACT in the context of the AMFm, such as:
 - a patient register,
 - a patient-held card for those prescribed antimalarials,
 - a patient referral form for private accredited retailers and community health workers to refer severely ill patients and patients who have failed to respond to therapy,
 - a simplified adverse drug reaction reporting form and
 - active follow-up of patients to assess the value and validity of data obtained through the reporting systems;
- active monitoring of a cohort of patients exposed to ACT (cohort event monitoring); and
- pregnancy registers.

Communication and feedback should be seen to be as important as data collection and analysis. Approaches to optimizing the benefits of the pharmacovigilance programme through communication, feedback and collaboration with other agencies are briefly described.

The report describes factors for the success of a pharmacovigilance plan, including strengthening existing national infrastructure, obtaining the support of policy-makers, health professionals and the public through advocacy and training, adoption of a phased, pragmatic approach to the plan and monitoring and evaluation of the plan to ensure its effectiveness in meeting the objectives.

Finally, the document provides guidance to countries for completion of the application form, including a budget guideline.

Preamble

This document was prepared after the joint WHO/MMV technical consultation on pharmacovigilance with a focus on the AMFm initiative, held in Geneva, 6–8 April 2009. The consultation involved technical experts from seven of the eleven countries participating in this initiative; international experts on pharmacovigilance; representatives of the secretariats of the AMFm, the Global Fund to Fight AIDS, Tuberculosis and Malaria, the MMV, Roll Back Malaria, the WHO departments of Essential Medicines and Pharmaceutical Policies, the Global Malaria Programme and the Special Programme for Research and Training in Tropical Diseases; and observers from the private pharmaceutical sector (Novartis and Sanofi-Aventis.)

The objective of the consultation was to prepare guidance for pharmacovigilance in countries participating in phase I of the AMFm, to provide minimal standard procedures that countries can use in preparing submissions for funding in the context of the AMFm.

The document represents the outcome of the meeting, which was attended by (in alphabetical order):

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The consultation was co-chaired by A. Dodoo and E. Sevene, and this document was written by U. Mehta in her function as Rapporteur of the meeting.

1. Background

The goal of the AMFm funding scheme is to reduce mortality from malaria and to delay resistance to artemisinin and its derivatives. The initiative seeks to achieve these goals by increasing the affordability and availability of ACT and ensuring that there is enough affordable ACT to replace oral artemisinin-based monotherapy and other antimalarials that are no longer recommended.

Access to affordable ACT will be increased in both the public and the private sector. This goal is especially important in the private sector, where these medicines are currently available in limited amounts and at unaffordable prices. AMFm proposes to increase access to ACT in the private sector by ensuring their sale by accredited retailers with minimal health qualifications and limited skills in diagnosing and managing malaria and its complications. Although most regulatory authorities have registered ACT as 'prescription-only' medicines, the AMFm project will promote their availability through licensed outlets in the private sector. Funders and national regulatory authorities will therefore have greater responsibility for monitoring safety than the pharmaceutical companies that manufacture these medicines. The safety implications of the widespread availability of affordable ACT in the private sector are unknown and must therefore be addressed.

The AMFm project includes interventions to ensure that the improved access to ACT is both effective and safe. These interventions include public education and awareness campaigns on the availability and affordability of antimalarials and training accredited retailers in the correct, safe storage and supply of these medicines to patients with malaria. Pharmacovigilance must accompany these interventions to identify and minimize any risks associated with widespread use of the medicines.

The status of the 11 countries included in the first phase of AMFm with regard to pharmacovigilance varies, ranging from non-functional (Niger), to early development (Benin, Cambodia, Rwanda), well-established with potential for expansion (Kenya, Madagascar, Senegal) and advanced with many years of experience (Ghana, Nigeria, Uganda, United Republic of Tanzania).

Phase I of the AMFm will provide funding for only 24 months. Investment in pharmacovigilance will strengthen existing national activities while at the same time providing additional post-marketing data on the safety of ACT during their use in a

new African setting. Pharmacovigilance plans prepared by countries in line with this proposal can be used to obtain support from multiple sources, resulting in sustainable benefits to the national pharmacovigilance programme and the health system as a whole.

The savings generated from the reduced cost of medicines due to contributions from the AMFm to existing grants (including grants from the Global Fund to Fight AIDS, Tuberculosis and Malaria) could be channeled into pharmacovigilance activities.

This document provides guidance to national health authorities and country coordinating mechanisms in preparing pharmacovigilance plans in order to optimize the safety of the AMFm strategy.

2. Objectives of national pharmacovigilance system as supporting intervention of AMFm

2.1 Overall objective

To develop or strengthen the national pharmacovigilance system to monitor, assess and improve the safety of ACT provided by the AMFm programme
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2.2 Specific objectives

The specific objectives of the pharmacovigilance programmes within the AMFm are:

- to monitor the risk for adverse drug reactions associated with ACT made available through the AMFm programme and supplied by
 - the public sector,
 - the for-profit private sector or
 - the not-for-profit private sector (e.g. nongovernmental and faith-based organizations);
- to build a strategy for communication and feedback with health-care professionals and the public about the safe use of ACT, based on information generated through the pharmacovigilance system;
- to monitor and assess the quality of the components of the pharmacovigilance system; and
- to monitor the safety of ACT in pregnancy by setting up or strengthening a pregnancy register at selected sites (where feasible).

Other interventions to promote rationale drug use will be developed, including training of accredited retailers for rational sales and prescribing practices. Monitoring and evaluation will be required to determine the effectiveness of these interventions, to ensure that there is no under-treatment of severe malaria cases, delayed or non-referral of severe cases or misdiagnosis. Information and communication campaigns will be run to encourage the population to seek early treatment and to increase demand for high-quality, affordable, subsidized ACT. The effectiveness of these interventions will require specific monitoring systems that are not fully covered by the pharmacovigilance strategy.

3. Reporting systems

A country's pharmacovigilance strategy should take into consideration:

- patient factors, such as the population at risk for the disease, potential complications of treatment and treatment-seeking behaviour for fever and suspected malaria;
- the health-care conditions in which the medicines are used, including available human and financial resources, diagnostic capacity, potential for investigating suspected adverse drug reactions, the patient referral system and existing pharmacovigilance activities;
- the epidemiology, diagnosis and clinical manifestations of malaria; and
- the effectiveness and safety of current antimalarial medicines and issues associated with an increased supply and use of ACT in the private sector.

Medicines that have been introduced onto the market recently will require closer monitoring, while older medicines with which there has been extensive post-marketing experience in countries with similar health infrastructure may require less intense monitoring.

3.1 Spontaneous reporting

Spontaneous reporting has been the mainstay of regulatory pharmacovigilance for several decades. It is a relatively inexpensive, simple, sustained means used by national drug regulatory authorities to identify suspected adverse drug reactions and, to a limited extent, signals of reactions and the concerns of local clinicians about all licensed medicines. The elements of spontaneous reporting are described in the WHO publication *A practical handbook on the pharmacovigilance of antimalarial medicines* (www.who.int/malaria/docs/diagnosisandtreatment/Malaria-PharmaVigil.pdf).

National spontaneous reporting systems are, however, usually understaffed and underfunded. While many of the countries in the AMFm scheme already have spontaneous reporting systems in place, the systems are relatively recent and are plagued by underreporting and poor-quality reports, with few financial and human resources. These difficulties can be addressed to some extent by advocacy, especially among policy-makers, by encouraging health professionals to report, giving them training and feedback and building capacity at national level to manage and assess the data derived from spontaneous reporting systems.

Spontaneous reporting does not, however, include the collection of data on denominators or drug use. It does not allow quantification of the risk for a specific adverse drug reaction or identification of the risk factors associated with a particular medicine, nor can it contribute quantitatively to the risk–benefit profile of a particular product.

3.2 Stimulated spontaneous reporting

In most countries, there is only one reporting form for health-care professionals with some training in clinical diagnosis, pharmacology and rational use of medicines. In the AMFm programme, the sale of ACT by private accredited retailers with varying levels of education and training in the clinical care of patients is expected to increase dramatically. Although these retailers will be trained in recognizing, counselling and 'treating' clients suspected of having malaria, there is a risk that they will not

recognize and refer severe cases and that they will make incorrect or miss diagnoses, inappropriately prescribe, underdose or overdose patients, or misdiagnose other causes of fever as malaria. In addition, patients may differ in their treatment-seeking behaviour, purchasing medicine from licensed retailers rather than acquiring them from health professionals in public or private hospitals or clinics, which could delay recognition and management of adverse drug reactions.

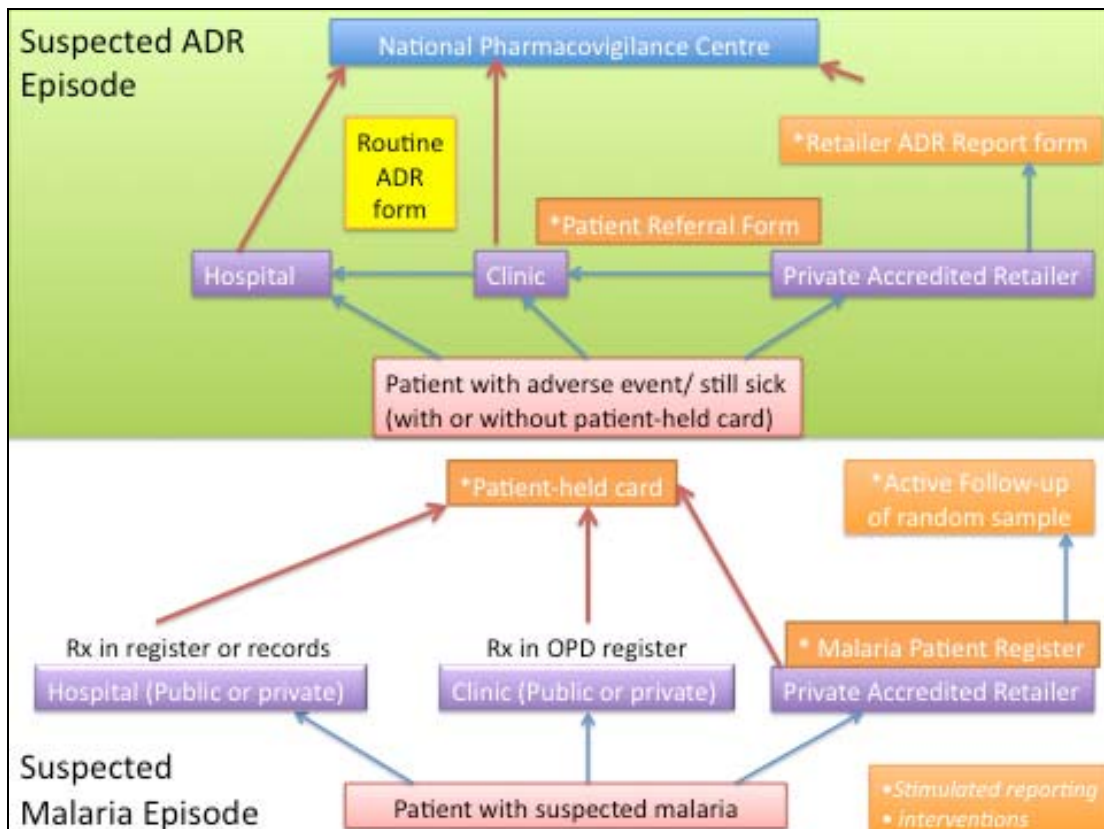
The purpose of the proposed pharmacovigilance system, which may involve procedures to stimulate reporting, is to improve the likelihood of identifying potential additional risks.

Suggested approaches are:

- a malaria patient register kept by private accredited retailers,
- a patient-held card,
- a patient referral form for private accredited retailers,
- a simplified form for reporting suspected adverse drug reactions for private accredited retailers and
- active follow-up of a random subset of patients.

The potential role of these approaches in patient management is illustrated in Figure 1. Each measure can be incorporated into the pharmacovigilance system independently. For instance, some countries may decide not to include a patient register, a simplified reporting form or active follow-up of a subset of patients, or they may decide to include a combination or none of these options, as they deem appropriate for their pharmacovigilance strategy and setting.

Figure 1. Stimulated reporting strategies (in orange boxes with asterisks) in relation to patient care and spontaneous reporting



ADR, adverse drug reaction; Rx, prescription; OPD, outpatient

3.2.1 Malaria patient register for private accredited retailers and reports

A simple malaria patient register could be introduced in a few districts that are likely to be affected by the AMFm strategy. The register would allow private licensed accredited retailers to record the basic details of every patient treated for suspected malaria. It would include columns for some or all of the following items for each patient: date, patient's name, telephone number(s) and address, age, brand name of medicine given, dose and whether referred.

Vendor Name:

Date	Patient/ customer name	Telephone/mobile /address	Age	Brand name of medicine given	Dose	Referred? (Y/N)
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The register would allow assessment of which brands of medicine are being used, whether they are being prescribed at the correct dose and the age distribution of the patients treated. It would also facilitate the tracking of medicines that have been dispensed and allow follow-up of patients.

Similar data can be collected routinely from existing outpatient and inpatient registers in public and private health facilities in most countries. Such registers are usually filled in routinely for all clinic and hospital admissions, usually with the suspected diagnosis at outpatient consultation or admission and the treatment given. Clinical staff and administrative staff responsible for completing such registers in sentinel districts or facilities would have to be trained to complete these registers fully and accurately, including the brand name of the medicine.

Vendors who are allocated these registers might have to be given incentives, training and supervision to maintain them. A system for routine collection, assessment and analysis of the data collected would be incorporated into the plan.

3.2.2 Patient-held cards for all patients treated for malaria

Record linkage (i.e. linking details of a patient's exposure to a medicine and a visit to a health-care facility for an adverse event) remains a challenge, particularly when patients obtained treatment from a different facility or retailer from that in which he or she would go for treatment of a more severe adverse event. A patient-held card indicating that the patient has received antimalarial and any other treatment would help to address this challenge, which is likely to be exacerbated by increased over-the-counter access to ACT.

A card could be given to patients at the time of prescription of any medicine, with an encouragement to present the card to a health professional if they experience any unwanted or untoward event. The card would include the brand name of the medicine prescribed, the date of prescription and the type or name of the supplier, with instructions to patients to take the card with them on any medical visit within one month of receiving it. The card would also bear a reminder to health professionals treating the patient to report to the national pharmacovigilance centre, if they suspect an adverse drug reaction, giving the address of the centre.

The patient-held card would provide health professionals with accurate information on the date of exposure and the exact product to which the patient was exposed.

It would also promote reporting of adverse drug reactions to the medicines.

The success of the approach would depend on patients bringing their cards to subsequent medical visits. Any system that encourages preferential reporting of one medicine or group of medicines is likely to result in a bias in reporting rates, which would have to be taken into consideration by national centre staff and the public. As this targeted approach might spark community concern about the potential risks of these medicines, it is recommended that the patient-held card be given to all patients with suspected malaria and not only to patients receiving ACT or another particular product.

3.2.3 Patient referral form for vendors

One of the anticipated risks of over-the-counter sale of ACT is that patients who are very ill, with vomiting or severe malaria, will not be referred by private accredited retailers to a health facility for further management. One means of addressing this potential problem would be to train retailers to recognize and refer patients who are not eligible for first-line ACT or who require more qualified care. The criteria for referral should be extremely easy to recognize and should be incorporated into the training being planned within the AMFm initiative.

Community health workers and private accredited retailers could be empowered to refer patients to a health facility (clinic or hospital, depending on severity). In order for health staff at neighbouring hospitals and clinics to accept referrals from retailers and community health workers, a simple referral form could be designed.

The usefulness and feasibility of such an approach would have to be assessed in the field and by investigating the acceptability within the community of referral by non-clinicians.

Figure 2 below gives an example of a referral form, which should be simple and include tick boxes to minimize the time required for its completion.

Figure 2. Draft form for referral of patients by private accredited retailers to clinics or hospitals

Accredited retailer referral form °					
Section A (client data)					
Name of patient					Date:
<input type="checkbox"/>	Child	<input type="checkbox"/>	Adult	Age:	
Section B (reason for referral)					
<input type="checkbox"/>	Severe illness	<input type="checkbox"/>	Diagnosis not clear	<input type="checkbox"/>	Not responding to treatment
<input type="checkbox"/>					Other:
Main problem:					
Treatment given (brand name):					
Referred to:					
Section C (person referring)					
Name:					
Signature:					
Name of community unit or district:					
Name of referral health facility for community unit or district:					

° - Adapted from the community health workers' referral form used in Kenya

3.2.4 Simplified form for reporting suspected adverse drug reactions by private accredited retailers

Some patients who have a complication after treatment return to the same private accredited retailer to complain or seek care if they suspect that it is due to the medicine they were sold. In such situations, retailers could serve as a useful source of reports, if the reporting is not too onerous or complicated. This would avoid the possibility of a missed report and might reduce mismanagement of patients, such as the retailer selling an alternative but potentially harmful or ineffective treatment. It would also allow the retailer to report suspected problems of product quality and safety. The reporting process should be as simple as a telephone call to a local or toll-free number or a simple form that could be picked up regularly by a surveillance

officer or by health staff at a nearby pharmacy, health facility or district health centre. The forms should be kept to a minimum and be field-tested before use.

During training, retailers should be told that these reports should not be confused with referral forms and that they should still refer patients to a formal health facility when necessary. The referral note could serve as a reporting form, depending on the system being planned by the country.

In the event of concern by patients or the community and fear of adverse drug reactions directed at the retailer, the retailer must be trained to inform the relevant authorities or other persons identified to assist in investigating and managing such situations. Ideally, this should be the focal person for pharmacovigilance for the area. The person must be easily accessible to retailers and able to provide rapid follow-up and investigation of events.

3.2.5 Active follow-up of a subgroup of patients to validate data

In order to assess whether the reporting system does in fact allow detection of adverse events and to verify the information recorded in the registers, a randomly selected subset of patients treated for malaria (as recorded in the patient register of the clinic, hospital or private accredited retailer) could be followed up either by telephone, at home visits or at follow-up visits by patients requested by a facility. The nature of follow-up will depend on the country and the options available. The follow-up would include the patient's outcome (i.e. still sick, died, recovered or untraceable), information on their adherence to treatment and whether they have a patient-held card. Suspected adverse drug reactions, concern about interactions with health professionals or retailers and information about dose could be collected during a visit.

The most cost-effective methods of follow-up will be decided by each country. If a significant proportion of patients (e.g. > 20%) are lost to follow-up, the results might be difficult to interpret. Patients should be selected for follow-up randomly in order to minimize the possibility of bias. The permission of an ethics committee might be needed to conduct home follow-up or to ask patients to return to a facility after a certain time. Active follow-up can be costly and requires the employment of appropriately trained persons.

3.3 Active monitoring of a cohort of patients given ACT

Cohort event monitoring is a method for pharmacovigilance that involves prospective follow-up of a large population with documented exposure to the medicine in question. Patients are encouraged to return after one week or are followed-up at home or by telephone in order to record any adverse events. There is no control cohort, but events during the week before treatment are recorded. Cohort events would be monitored at sentinel sites within a country.

The approach is particularly useful when new medicines or combinations of medicines with limited post-marketing experience are being introduced into a country. For medicines that have been tested for safety only during clinical development (i.e. in phase I, II and III studies), only a few patient will have been exposed in controlled settings. The cohort event monitoring approach is a targeted, intensive, time-limited method that facilitates the study of new medicines during routine use. The large sample size recommended for this approach would allow the detection of rare

(< 1/1000) adverse reactions and drug–drug, drug–food and drug–disease interactions that are unlikely to be detected during controlled clinical trials.

The method could be used when new antimalarial combinations are being introduced in future phases of the AMFm programme.

Cohort event monitoring has several advantages over spontaneous reporting: the rates and outcomes of adverse events can be determined, which can facilitate the detection of signals; known reactions can be characterized, drug interactions detected, and risk factors and deficiencies in rational drug use identified.

The elements of cohort event monitoring are described in the WHO publication *A practical handbook on the pharmacovigilance of antimalarial medicines*, in which the advantages and disadvantages of this and spontaneous reporting are compared. The monograph lists the minimum standards needed. Data collection tools would have to be adapted to meet the local context, but at the same time recruitment and follow-up procedures and data collection should be standardized to facilitate aggregation of data across sites and countries. In adapting the data collection methods, local contexts of use, language, health-care infrastructure and treatment-seeking behaviour should be considered. Deviations from the recommended cohort event monitoring approach should be rationalized. All adaptations should be clearly specified so that other countries that use the information can understand the context in which data were collected.

Countries should ensure that they have complete ownership of the data generated and the capacity to analyse and interpret them. The WHO Collaborating Centre for International Drug Monitoring (Uppsala Monitoring Centre) is designing an online tool (CemFlow) and database for standardized data entry and analysis of data generated by cohort event monitoring.

Cohort event monitoring is not intended to replace spontaneous reporting; rather, it is a time-limited, targeted programme to complement other initiatives to stimulate or improve existing reporting systems. Countries should consider the feasibility of cohort event monitoring within their national context. This method is more costly and needs more human resources. It does, however, provide high-quality data quickly, many of which cannot be obtained by spontaneous reporting. All recruited patients are requested to return to the treating facility for review; however, this may not be part of routine care and would be difficult to implement for relatively mobile populations. Substantial loss to follow-up has been reported (up to 22% in urban areas in Ghana) but should be minimized as much as possible through contact networks, telephone calls and home visits.

There is likely to be some loss of specificity and sensitivity in the diagnosis of adverse events when staff training and diagnostic facilities are limited. Countries planning to introduce cohort event monitoring should seek the approval of their national ethics committee.

3.4 Pregnancy register

In a few countries where the risk for inadvertent exposure of pregnant women to artemisinins is likely, such as in areas with a high birth rate, a high prevalence of malaria and widespread use of ACT, introduction of a register to monitor the safety of ACT in pregnancy may be warranted.

The countries concerned would have to include in their plans funding for two or three sentinel sites at which a pregnancy registry could be established. The registry should include a control group of women who have not been exposed to ACT in order to

assess the background rate of birth defects in communities where such information is lacking.

Collaboration with other government departments, including maternal and child health services and malaria and HIV/AIDS control programmes, and with specialists in academic departments for obstetrics and gynaecology and neonatology will be essential for the success of the registry.

The key elements for a pregnancy registry are:

- confirmed exposure to a drug and pregnancy status;
- reliable recording of the pregnancy outcome by systematic surface examination at birth;
- clear inclusion and exclusion criteria for birth defects relevant for analysis of teratogenicity (drug-related malformations); and
- data for a control group (not exposed to the medicine under investigation) with which the exposed group can be compared.

The WHO Special Programme for Research and Training in Tropical Diseases and the WHO department 'Making Pregnancy Safer' are assessing the feasibility of setting up a pregnancy registry in Africa. A protocol is available for countries interested in incorporating such a registry into their programmes, which can be obtained from Dr Melba Gomes at WHO (gomesm@who.int). The registry is being tested in several countries, including some involved in the AMFm programme.

The cohort event monitoring approach includes a four-month follow-up of all women of childbearing age exposed to ACT. If a woman is found to be pregnant at this visit, her pregnancy is followed-up to establish the birth outcome. This approach will allow identification of any cluster of similar anomalies, which might suggest a problem that should be investigated further.

Cohort event monitoring does not include a control group, such as pregnant women who are not exposed to ACT, whether this is important when the background rate of birth defects is unknown. Efforts are under way to determine how data on pregnancies and birth outcomes collected by cohort event monitoring can be incorporated into the pregnancy register database.

3.5 Communication and feedback

Most pharmacovigilance centres do not invest as much time and effort into communication and feedback as they do into collecting and analysing the data. The primary purpose of pharmacovigilance is to minimize the risk for harm to patients. If clinicians, nurses and pharmacists are not given feedback on the reports they submit, opportunities to improve clinical practice and patient care are missed. Moreover, they may lose confidence in the programme and lose their motivation to report.

Feedback should be both individual, through telephone calls, e-mails or letters, and collective, in the form of newsletters, articles in local professional media, presentations at professional meetings and other methods appropriate for the local situation.

Individual feedback should include acknowledgement of the report as well as clinical information or feedback, with a request for additional information if needed. Collective feedback could include an analysis of reports received, information on reporting rates, safety signals that might have arisen and suggestions on how the most commonly reported events can be avoided or managed.

National pharmacovigilance programmes should maintain contact with other pharmacovigilance centres (particularly those also involved in the AMFm project), national regulatory authorities, the Uppsala Monitoring Centre, pharmaceutical manufacturers (particularly if the pharmacovigilance centre is part of the national drug regulatory authority) and WHO. International partners might be able to provide additional information on potential signals, guidance on how to manage concerns about safety and experience with specific pharmacovigilance approaches.

National centre staff should build and maintain a culture of adverse drug reaction reporting, by ensuring that health-care professionals are trained, retrained and reminded of the importance of reporting, by the distribution of posters, newsletters and pamphlets. Undergraduate and postgraduate curricula should include training on diagnosis and reporting of adverse drug reactions. Health staff should be retrained periodically, especially in districts targeted for more intense surveillance. Reporting forms should be readily available at all points of patient contact to facilitate reporting. The process for submission of a report to the national centre should be simple and easy.

Regulatory authorities should communicate anonymous information on adverse drug reactions (i.e. respect the confidentiality of the patient and the reporter) to pharmaceutical manufacturers about their products. Standard operating procedures might have to be prepared for such interactions in order to ensure that they are within the legal framework for regulation of medicines. In addition, regulatory authorities should ask pharmaceutical manufacturers to provide any information on safety that they find or new risks related to medicines marketed locally.

National pharmacovigilance centres might also collaborate with partners such as professional societies and academic departments, which could provide training, assist with feedback and encourage reporting within their constituencies. The local media (radio, television, newspapers, Internet websites) can be important in encouraging support for the pharmacovigilance reporting system and for training individuals in the private sector and patients on the safe use of antimalarial medicines.

The media can, however, also propagate rumours, community concern about medicinal products and the pharmacovigilance programme itself. It is advisable to be pro-active, by providing responsible journalists with accurate, authoritative information. National centres, particularly in countries where the local media are dynamic and controversial, should consider setting up a crisis management plan to deal with any crises that might arise during implementation of the AMFm programme and that might receive media attention.

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4. Critical factors for success

4.1 Strengthen the national pharmacovigilance infrastructure

The national centre should prepare a comprehensive strategy to ensure that all the sites selected are adequately supported and monitored. This will require investment to make the sites and site staff easily accessible (e.g. by transport and telephone calls). National centre staff should be trained in improving reporting, management and analysis of data and communicate with reporters, retailers and health professionals.

In many countries, pharmacovigilance (wrongly) focuses on either the public or the private sector. Within the AMFm initiative, both sectors would be supported equally. This will require adaptation and expansion of existing strategies and procedures for more comprehensive coverage of the health sector.

Local clinical experts might have to be recruited to assist in the assessment of certain adverse drug reactions, signals and safety concerns. This could give rise to a national pharmacovigilance committee, if one does not already exist.

National pharmacovigilance systems should be closely linked to national drug regulatory authorities to ensure that the necessary regulatory measures are taken in response to signals or other concerns identified in the programme. When national regulatory authorities are backed-up by national legislation, they should encourage pharmaceutical manufacturers to implement risk management plans for their products, particularly when new products are introduced on a wide scale.

4.2 Advocacy and training

In some countries, pharmacovigilance activities are inadequately supported by policy-makers, which has resulted in limited funding, reduced priority given to safety surveillance and, in some cases, threatened viability of the national pharmacovigilance centre. The AMFm programme gives national programmes the opportunity to demonstrate to policy-makers and opinion leaders the integral role of pharmacovigilance in the use of life-saving medicines and the investment needed to ensure that these medicines gain the confidence of the public. Safe medicines can be assured only with ongoing surveillance of their safety.

A meeting should be held with policy-makers before the launch of an AMFm pharmacovigilance plan. Any milestones and achievements of the national centre should be publicized and brought to the attention of opinion leaders and senior officials. The support of WHO and other international agencies should be enlisted to ensure that the value of pharmacovigilance in the national context is appreciated.

4.3 Phased, pragmatic approach

AMFm is a 2-year programme. As the allocation of pharmacovigilance funding is likely to be limited, countries are encouraged to submit reasonable, achievable plans that are likely to make a meaningful, sustainable contribution to their long-term national pharmacovigilance plans while addressing the more urgent imperative of monitoring the safety of widespread access to ACT in the private and public sectors.

Some of the reporting systems and interventions suggested above might have to be implemented in phases, only a few districts or facilities being selected to participate in more intense monitoring. The programme might be expanded later, after a robust, field-tested strategy has evolved and good-quality data are obtained.

The logistics of strengthening a pharmacovigilance programme should include ensuring that the necessary material, such as adverse drug reaction reporting forms, registers, pamphlets, guidelines and posters, is printed and distributed and that adequate supplies are made available at relevant sites and wards. The system by which reports are returned to the national centre from the public and private sectors should not be too onerous or confusing. The logistics might have to be field-tested, with the introduction of a new system or intervention to ensure that all reporting procedures are appropriate for local conditions.

4.4 Monitoring and evaluation

To ensure the success of reporting systems, the pharmacovigilance programme should include a simple system for monitoring and evaluating the quality of the data and whether the system meets its objectives and continues to evolve with time. Examples of simple indicators that demonstrate the progress made with the funds provided are as follows:

Spontaneous reporting

- number of reports within a specified period and
- completeness of the reporting forms:
 - proportion of forms with identifiable patient, identifiable reporter, medicines reported as brand name and adverse event;
 - proportion of reports with recorded date of onset; and
 - proportion of reports with recorded outcome of event

Stimulated reporting

- registers at private accredited retailers: proportion of vendors who are given the register and who actually use it;
- patient-held card: proportion of patients treated with antimalarials and who retain a patient-held card identified during follow-up;
- simplified reporting form for private accredited retailers: number of forms received per period;
- active follow-up of subset: proportion of patients followed-up who were still sick, had died or had experienced an adverse event; and
- pregnancy register: proportion of women recruited at antenatal care clinics for whom the pregnancy outcome is known and a surface examination has been completed

Cohort event monitoring

- number of patients recruited;
- proportion of patients with complete follow-up:
 - adherence to the protocol;
 - proportion of records in which events in the pretreatment control period were recorded;
 - proportion of records in which information on concomitant medicines was recorded;
 - proportion of records in which information on concomitant diseases is documented;
 - proportion of patients followed-up who missed or failed to return for scheduled follow-up visits;
 - number of women for whom pregnancy status was recorded at the time of treatment;
 - proportion of women of childbearing age enrolled in cohort event monitoring who are followed-up 4 months after ACT treatment, with pregnancy status recorded; and
 - proportion of fatal cases for which the cause(s) of death is recorded;
- total event reporting rate (for comparison across sites).

Communication and feedback

- proportion of adverse drug reaction reports for which individual feedback (e.g. e-mail, letters, telephone calls) was given to the reporter; and
- description of collective feedback outputs (e.g. newsletters, publications, professional meetings and reports) by the national centre over a specific period.

5. Guidance on completion of the application form

It is essential that pharmacovigilance focal points work closely with other persons involved in the country coordinated mechanism in preparing the submission to AMFm for funding. This will avoid duplication of activities and give pharmacovigilance staff a perspective of their role within the grant application. As part of their submission, countries should describe the weaknesses of existing pharmacovigilance programmes, including:

- the history and background of the national pharmacovigilance centre (when started, location within the ministry of health or elsewhere, goals and objectives, human resources, full or associate member of the WHO International Drug Monitoring Programme, current budget);
- whether current laws and regulations support pharmacovigilance activities and decisions;
- the number of reports received per annum (proportion of those related to antimalarial products);
- any forms, guidelines, standard operating procedures or national strategic plans for pharmacovigilance; and
- a list of all other existing or planned pharmacovigilance projects, in particular any registers, cohort event monitoring or research projects.

The existing system should be analysed to identify areas in which additional investment is required in order to meet the common goals of the national plan and more immediate plans for the AMFm initiative. The areas could be categorized as:

- advocacy and training,
- data collection methods,
- data management,
- assessment and
- communication and feedback.

These areas could be expanded by the addition of specific activities, schedules for completion and the budget required. The submission should consist of a summary of a more complete plan that is realistic and feasible within the context of AMFm.

6. Proposed budget outline

Appendix 1 gives a list of possible financial line items for a proposed budget, which countries can adapt for their own needs. The guideline is designed to assist countries in structuring their budgets and to highlight the need for specificity and clarity in allocating financial resources for planned activities.

Not all the line items listed in Appendix 1 will be relevant for all countries. The proposal is not intended to create a parallel pharmacovigilance system for ACT or to duplicate existing activities in pharmacovigilance. Rather, it is meant to strengthen and build on what already exists. The budget submitted should be in line with the proposed approach of the country and the additional resources needed to achieve the plan of action. Applicants should keep in mind the short time frame of this project when considering staff employment, reallocation of staff and the resources allocated to the AMFm project. They should map existing efforts within their territory to ensure that no duplication or redundant work is included in the proposal.

Funds will have to be allocated to the coordinating unit or institution, i.e. the national pharmacovigilance centre. Expedited transfer of funds from the Global Fund will be required if countries are to meet their goals within the time frame of the AMFm. To minimize delays in the receipt of funds, applicants should work closely with their country coordinating mechanism in preparing their applications, to ensure that the mechanism for rapid fund disbursement is agreed and identified in the proposal. Alternatively, applicants might be considered independently as sub-recipients of funds.

AMFm Pharmacovigilance Budget

Enhanced Spontaneous Reporting

Personnel

National Level Staff

- National co-ordinator (% time)
- National Administrator (% time)
- National data capturer
- Staff development programme

- District level co-ordinator remuneration
- Follow-up staff (e.g. nurse, midwife or CHW) remuneration
- Data collection staff

Materials development, printing and dissemination

- ADR forms
- Patient cards

- Training manuals and reporting guidelines
- Vendor registers

- Vendor reporting forms (where applicable)

- Newsletter/Bulletin/update reports
- Posters and Pamphlets

Equipment

Cell Phones (2 per district)
Fax Machine
Computer
Bicycle/motor bike
Scanner / Photocopier
Internet access (if applicable)

Training and Advocacy Costs (food, venue hire, equipment hire)

Vendor Training

Initial training course
Refresher courses (include number)
Annual feedback meeting

Health Professional Training

Initial training course
Refresher courses (include number)
Annual feedback meeting

National District Co-ordinating staff training

Initial training course
Refresher courses (include number)
Annual feedback meeting

National staff development programme

Advocacy and stakeholder's involvement

Running costs

Internet access at sites
Cell phone and land line costs (phone and fax)

Travel allowance for data collection staff (fuel and maintenance costs)

Field testing of data capture tools

Database development and IT support

Quality Assurance visits

National Investigator's Quarterly Site Visits
Travel/ Per Diem

Field transport (Car Hire and Petrol)
National committee meetings

International Communication and Collaboration

Training of trainer workshops

National Co-ordinator training & mentorship

AMFm PCV Annual Workshop

Travel/ Per Diem

Email Discussion group

Website