



SAFETY FIRST



O3i/RaPID PHARMACOVIGILANCE PROGRAM

STATUS REPORT 2008





The RaPID Pharmacovigilance Program
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Acronyms

ACT	Artemisinin-based Combination Therapy
ADR	Adverse drug reaction
AIDS	Acquired immunodeficiency syndrome
CEM	Cohort Event Monitoring
CHAI	Clinton HIV/AIDS Initiative
DFID	United Kingdom Department for International Development
EPN	Ecumenical Pharmaceutical Network, Kenya
Global Fund	Global Fund to fight AIDS, Tuberculosis, Malaria
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IHMR	Institute of Health Management Research, India
MIT-ZLP	Massachusetts Institute of Technology—Zaragoza International Logistics Program, Spain
MOU	Memorandum of Understanding
MSH	Management Sciences for Health
MOH	Ministry of Health
NDRA	National drug regulatory authority
NMCP	National Malaria Control Program
O3i	Organization for Innovation, Implementation and Impact
PHP	Public Health Program
RaPID	Rapid pharmacovigilance program implementation in developing countries
RBM	RBM Partnership
TFDA	Tanzania Food and Drugs Authority
UMC	Uppsala Monitoring Center, Sweden
UGMS	University of Ghana Medical School, Ghana
WHO	World Health Organization
WHO-ART	WHO Adverse Reaction Terminology



1. Preamble

Adverse drug reactions (ADRs) are a relatively common phenomenon despite stringent drug safety regulations. Experience has shown that drugs, although meant to save lives, can have significant untoward effects, if not administered and used properly; and even when used properly, potential for unavoidable adverse reactions to medicines exist. Yet, in most developing countries, there is practically no culture of pharmacovigilance and drug safety. For example, some developing countries collect less than 100 ADRs per year, which is less than 1% of their target. The current global status of ADR reporting¹ to Uppsala Monitoring Centre (UMC) database is presented in the figure below:

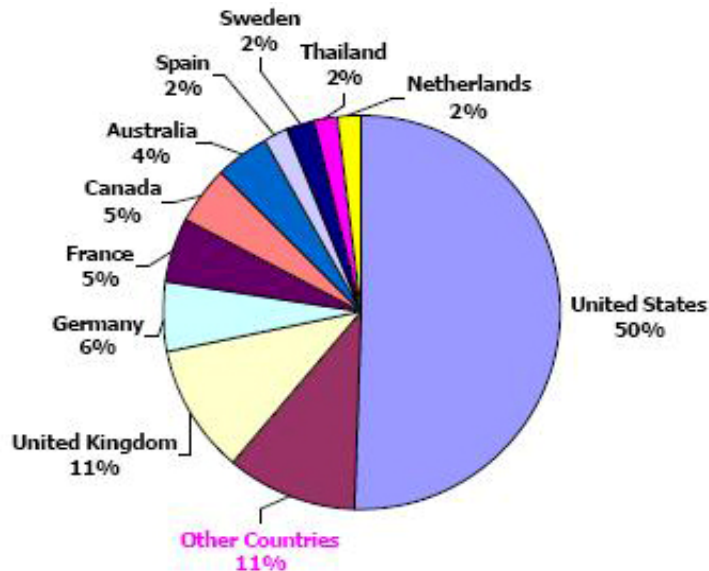


Figure 1: Top ten contributors to WHO database

A robust, practical and relevant pharmacovigilance system entailing detection, assessment and prevention of adverse effects is therefore, vital to ensure patient safety, particularly in the developing countries.

Building health systems' capacity for pharmacovigilance can be time-consuming and resource-intensive. In order to address the urgent need for a well-functioning pharmacovigilance in developing countries towards ensuring patient safety, a 'ready-to-use' solution called RaPID² was developed by a consortium of organizations: 'O3i'--Organization for Innovation, Implementation and Impact, a non-profit organization based in USA; Uppsala Monitoring Center (UMC)--the WHO Collaborating Center for International Drug Safety in Sweden; and other technical partners that include Massachusetts Institute of Technology--Zaragoza International Logistics Program (MIT-ZLP) in Spain, University of Ghana Medical School (UGMS) in Ghana--a premier institution for higher education and research in Africa; Ecumenical Pharmaceutical Network (EPN) in Kenya--an independent apolitical non-profit organization with 80 Pan-African members providing healthcare in 31 African countries; and Institute of Health Management Research (IHMR) in India--a leading academic and research institution focused on health systems management. Briefs on the RaPID's Technical partners are enclosed as annexure 1.

¹ Top Ten Contributors to WHO Database. Sourced from: Uppsala Monitoring Centre, Sweden

² RaPID is an acronym for 'Rapid Pharmacovigilance Implementation in Developing Countries'



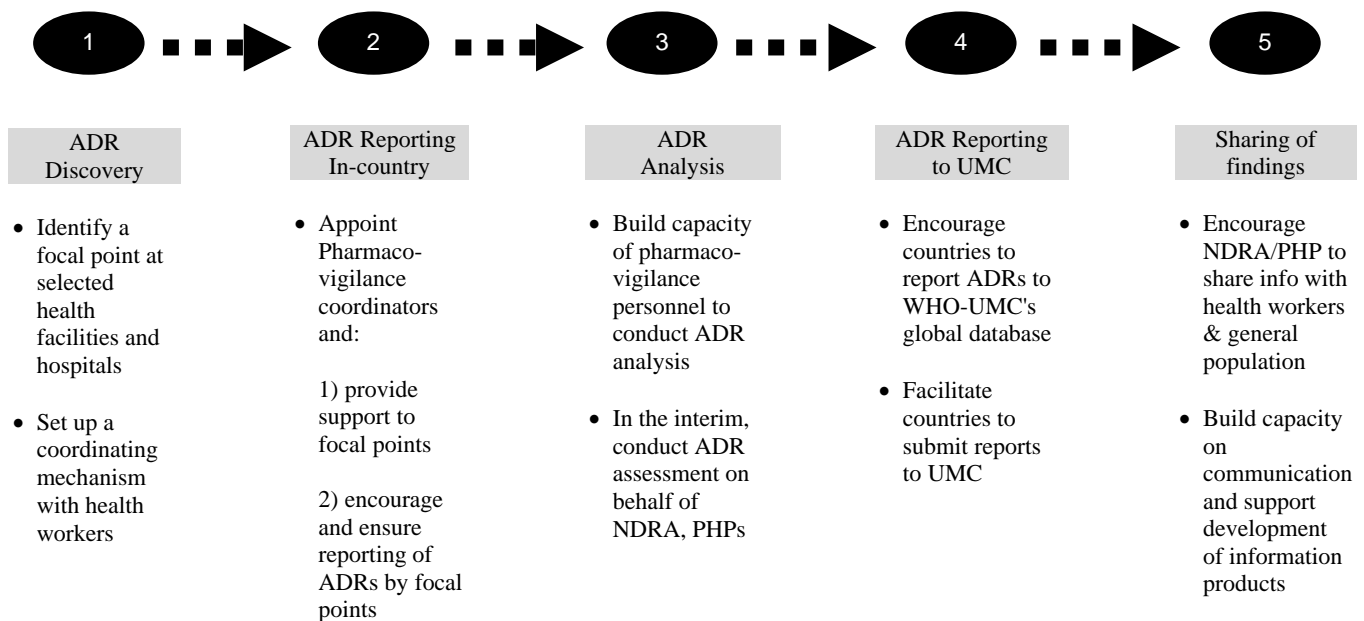
1.1 Convergence between National Drug Regulatory Authority and Public Health Program

Historically, pharmacovigilance has been seen as the responsibility of the national drug regulatory authority (NDRA) and there has been very little interface with the public health programs (PHPs). As a result, there is almost no evidence on the safety of drug use in public health programs. However in recent years, there is an increasing awareness regarding the need for stringent drug safety monitoring systems to complement the massive scaling up of public health programs for HIV/AIDS, Tuberculosis and Malaria control, especially since many of the drugs used for treating these diseases are consumed long-term, have narrow therapeutic windows, and could lead to a significant number of ADRs, especially in highly-vulnerable groups like pregnant women and young children. A recent WHO report stated that, “*adverse effects associated with antiretroviral medicines...occur in up to 30% of HIV-infected children on antiretroviral therapy*”,³ which then leads to poor adherence and a higher drop-out rate from the treatment program.

The RaPID Pharmacovigilance Program’s mission is to conduct pharmacovigilance on behalf of public health programs and to strengthen national pharmacovigilance capacity in developing countries.

The RaPID Pharmacovigilance Program is therefore, complementary to the work done by the Uppsala Monitoring Centre for the WHO Program for International Drug Monitoring, facilitating implementation of many of its stated goals.

A diagrammatic representation of the approach and functions of the RaPID Pharmacovigilance Program is shown below:



³ WHO report “Promoting Safety of Medicines in Children, Sep 2007



2. Actions/Impact of RaPID Pharmacovigilance Program

The focus of the RaPID Pharmacovigilance Program is on three major topical areas:

**Policy &
Coordination**

**Technical Assistance
& Capacity Building**

Partnership Building

Activities under each of these focus areas are planned and implemented in close collaboration with the RaPID's technical partners including Uppsala Monitoring Centre.

2.1 Policy & Coordination

Challenges: As mentioned earlier, pharmacovigilance to date has received relatively little attention in public health programs, which in turn, resulted in minimal focus and funding by donors and national governments. Assessment conducted by RaPID showed that in many countries, funding for pharmacovigilance is less than US\$ 10,000, which is inadequate for any program to run effectively. In addition, very little coordination occurs between the public health programs and the national drug regulatory authorities. This scenario is now changing as the public health programs and donors are increasingly focusing on establishing/strengthening pharmacovigilance health systems as part of overall health systems strengthening. For example, pharmacovigilance is now a part of Global Fund's policy on quality and safety and has been recommended as part of the Procurement and Supply Chain Plan.

Potential solution: To undertake proactive advocacy efforts to inform and influence policy/decision makers of public health programs, national drug regulatory authorities and donor organizations to focus on pharmacovigilance and promote better coordination between public health programs and national drug regulatory authorities.

Actions/impact:

- RaPID's advocacy and resource mobilization efforts facilitated better coordination between the public health programs—the national malaria control programs (NMCP) in Nigeria and Tanzania towards harmonized planning and implementation of drug safety monitoring. The action was funded by RBM Partnership.
- In Tanzania, RaPID provided a common platform to the in-country key players in public health, viz., MSH, CHAI, Ifakara Health Research and Development Centre, WHO, to engage in a strategic discussion with global experts from Uppsala Monitoring Centre on strengthening pharmacovigilance. A major focus of the discussion was on the development of protocol of: Active Surveillance using Cohort Event Monitoring (CEM) of artemisinin-based combination therapies (ACTs). The event was co-hosted by TFDA, NMCP (Tanzania) and RaPID Pharmacovigilance Program with support from RBM Partnership.
- Ongoing discussions in country and with international donors, like the Bill and Melinda Gates Foundation, World Bank, Global Fund, RBM Partnership to ensure dedicated funding for pharmacovigilance through appropriate budget heads (example, health systems strengthening).



2.2 Technical Assistance & Capacity Building

Challenges: In many countries, ADR discovery, reporting, and analysis are minimal due to insufficient financial and physical capacity. These elements are vital to accelerate pharmacovigilance to ensure patient safety, particularly in public health programs for HIV/AIDS, Tuberculosis and Malaria control, which are rapidly scaling up access to newer drugs or drug combinations for treatment, often long-term. In this context, even though capacity building and self-reliance are the ultimate aims for all pharmacovigilance activities, in the short-term, the objective is to provide immediate support to PHPs and NDRA's by way of technical assistance.

Potential solution: Public health programs in many countries need and seek technical assistance to implement ADR data reporting and analysis as well as strengthen in-country capacity on pharmacovigilance. Even national drug regulatory authorities are now increasingly seeking disease focused support for pharmacovigilance.

Actions/Impact:

- RaPID's technical assistance and capacity building is focused on the following:
 - **Assessment of pharmacovigilance capacity.** In order to understand the current status, identify needs and gaps, and recommend the way forward, RaPID has successfully concluded assessment of national drug regulatory authority with a focus on pharmacovigilance capacity in public health programs. The assessments are complimentary to the UMC's efforts related to in-country assessments.

Examples include:

- Rapid assessment of pharmacovigilance capacity in Kenya, Tanzania, Uganda
- In-country consultation on development of protocol on CEM in Tanzania in collaboration with NDRA, PHP, global experts
- In-country consultation on development of protocol on CEM in Nigeria in collaboration with NDRA, PHP, global experts
- Completion of project "Rapid Pharmacovigilance Assessment of Adverse Drug Reaction (ADR) Reporting in Botswana, Ghana, Sierra Leone, Sudan, Zambia, Zimbabwe"

- **Application of innovative models for ADR data analysis.** Most developing countries have limited or no capacity for ADR data analysis. Hence, this remains as one of the critical topics for which RaPID provides consulting support.

Examples include the project "Rapid Pharmacovigilance Assessment of Adverse Drug Reaction (ADR) Reporting in Botswana, Ghana, Sierra Leone, Sudan, Zambia, Zimbabwe." Specifically, the project steps included:

- Contacting the NDRA of Botswana, Ghana, Sierra Leone, Sudan, Zambia, Zimbabwe.
- Collation of a total of 161 ADR reports from the selected countries followed by uploading onto the RaPID website by UGMS. The reports were received by a multi-specialty O3i/RaPID assessment team comprising pharmacists, medical doctors and post-graduates with expertise in internal medicine, paediatrics, pharmacology. This assessment team, which had been previously validated by the UMC for entering data into VigiFlow efficiently, then carried out technical



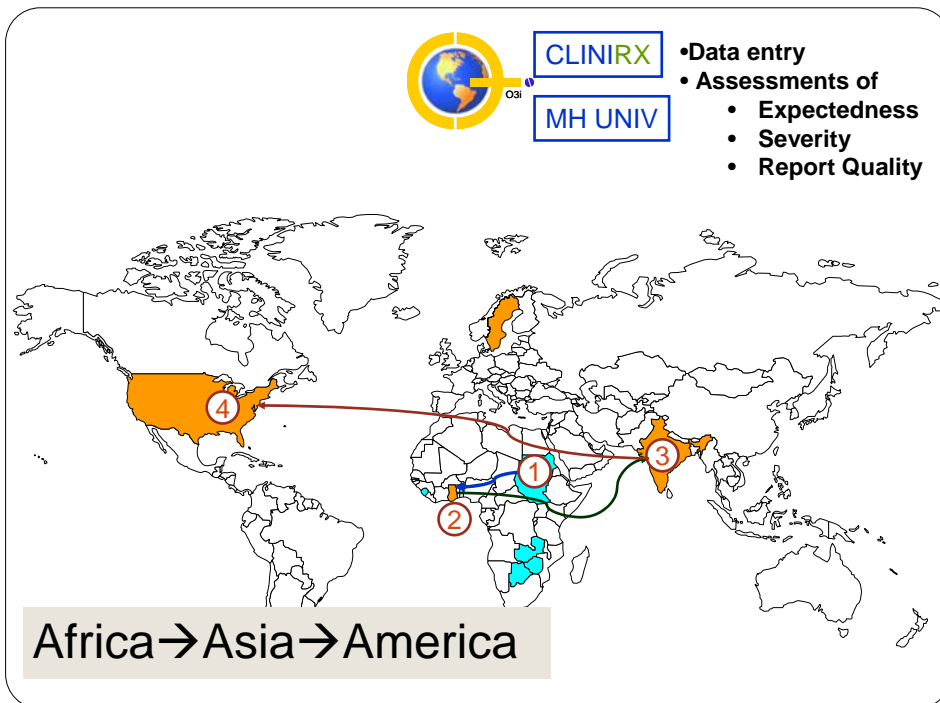
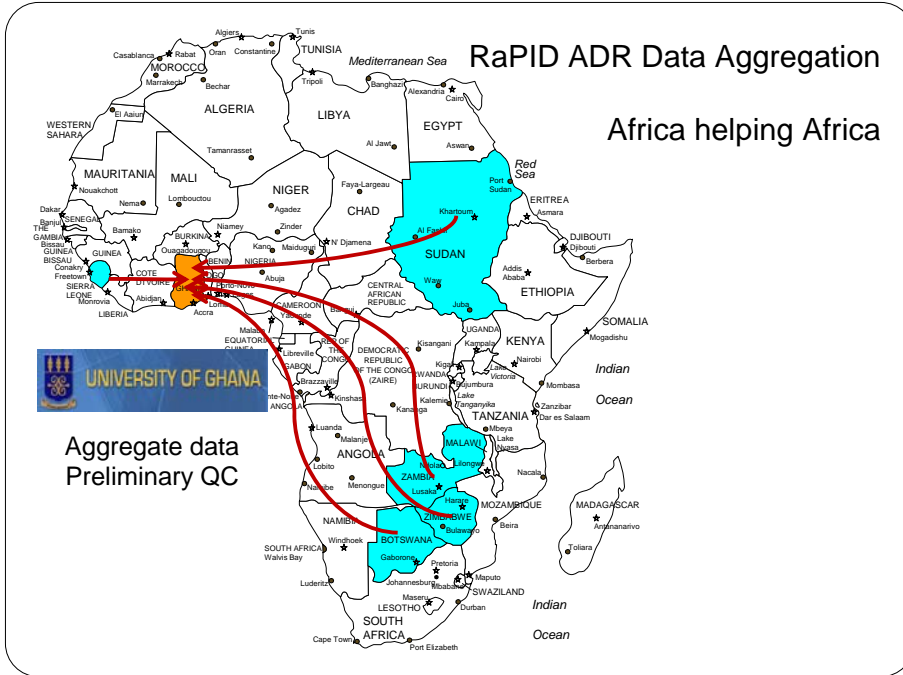
assessment and analysis of the reports. Upon receipt of the data, the team performed the following tasks:

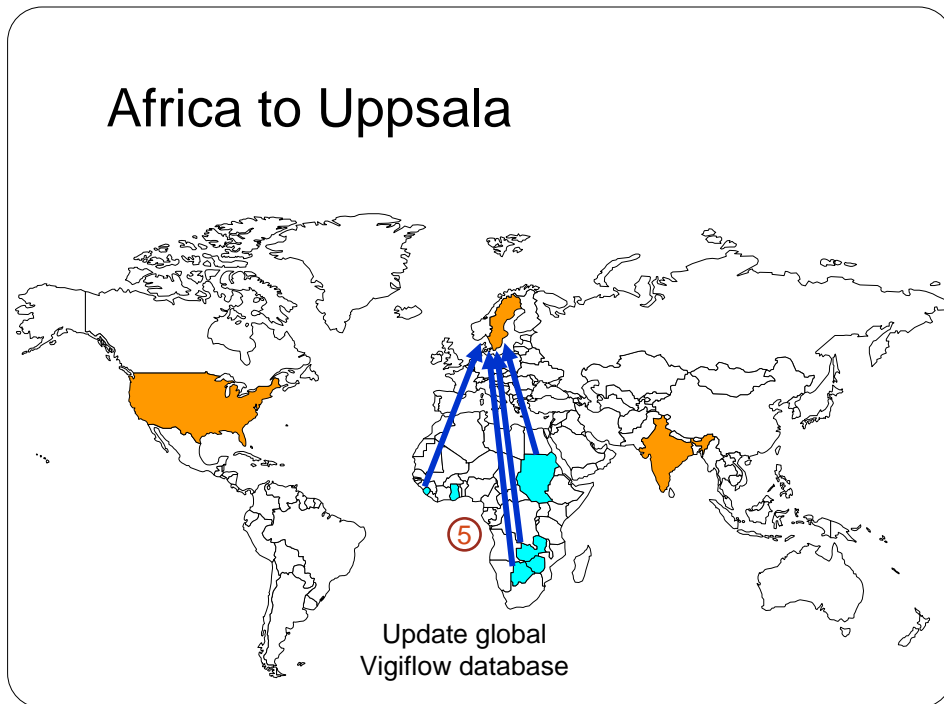
- 1) At the outset, quality of the ADR reports was assessed for completeness and accuracy to ensure that minimum information required for reporting was filled in. A summary on quality of ADR reporting was then prepared.
 - 2) If an ADR report had the required minimum information, it was entered in the online VigiFlow system by the trained and validated O3i/RaPID professionals.
 - 3) The O3i/RaPID medical reviewer then assessed the data entered in the VigiFlow system. WHO-ART coding was done for the reported ADRs in the system.
 - 4) Evaluation of the expectedness of ADRs was done (i.e. whether the nature, severity and specificity of the reported adverse reaction were consistent with the adverse reaction terms mentioned in the standard text of Martindale: The Complete Drug Reference & Physician's Desk Reference).
 - 5) A brief medical narrative of the ADR cases was prepared.
 - 6) Subsequently, a VigiFlow report was generated for each ADR case.
 - 7) A causality assessment report based on WHO causality assessment grading was prepared.
 - 8) All the reports including the causality assessment reports were further reviewed and analyzed by O3i/RaPID medical experts.
 - 9) Finally, line listings and a consolidated summary of ADR assessment were generated.
 - 10) The final step of committing the reports to Uppsala's VigiFlow® database was conducted by the countries directly.
 - 11) Further, completed questionnaires related to ADR reporting capacity assessment were also communicated electronically to O3i/RaPID team by the National Drug Regulatory Authority/Pharmacovigilance department in selected countries, except Sierra Leone. This information was analyzed and a summary was prepared.
 - 12) All security and confidentiality arrangements were strenuously maintained at each step of the project, which followed ICH guidelines. Any personal identifiable data pertaining to patients and reporters were not shared with any third party.
- Preparation of project report and dissemination to project countries and partners.

The project catalyzed Sudan's (and will catalyze Zambia's) introduction into the UMC's WHO Program for International Drug Safety Monitoring as a ***permanent member***.



The key steps are illustrated below:





- **Direct country support.** RaPID has initiated efforts to catalyze multiyear funding from several donors (examples, Global Fund, World Bank, DFID) to technically support the pharmacovigilance department of the NDRAs. Examples include:
 - Several countries are being supported directly or indirectly, including, Tanzania, Nigeria (who have signed MOU with O3i), Zambia amongst others.
 - In Nigeria, RaPID is supporting the development of an operational plan for pharmacovigilance in malaria in consultation with National Malaria Control Program and NDRA.
 - Other key countries being targeted for RaPID support include Zambia, Tanzania, Mozambique, Kenya, and Angola.

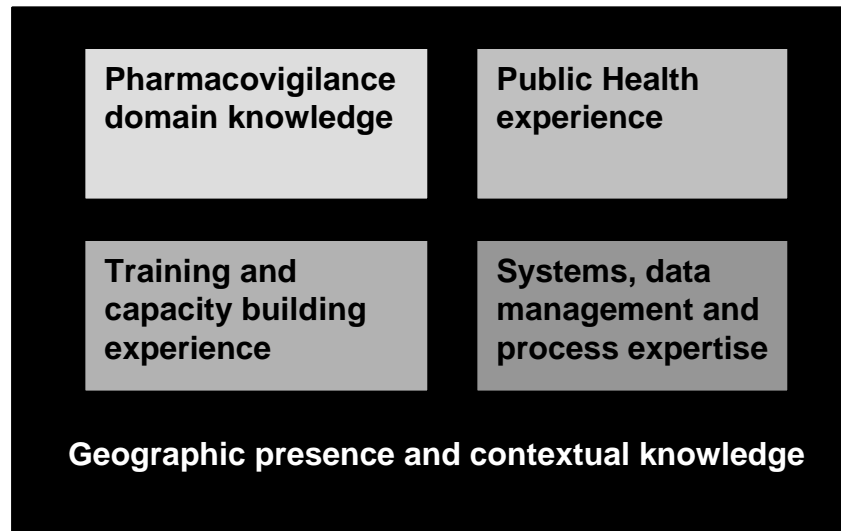
- **Capacity building/training.**
 - RaPID has successfully bid for and won the contract for training/capacity building on pharmacovigilance in Botswana. Subsequently, UMC and RaPID have jointly conducted training on pharmacovigilance in Botswana.
 - RaPID has helped to catalyze a new process of validation of individuals interested in building expertise in VigiFlow® data entry.

Outline of key Technical Assistance/Capacity Building activities provided/planned by the RaPID Pharmacovigilance Program is presented in annexure 2.



2.3 Partnership Building

For effective planning and implementation of pharmacovigilance, an organization needs expertise in several technical areas and must have geographic presence in order to better understand the local context.



For each of the above areas, RaPID has teamed up with a leading institute.

- Uppsala Monitoring Centre, Sweden: Pharmacovigilance domain knowledge; pharmacovigilance experience; training and capacity building experience
- O3i, USA: Public health experience; training and capacity building experience
- MIT—ZLP, Spain: Systems, data management and process expertise
- University of Ghana Medical School, Ghana: Pharmacovigilance domain knowledge, public health experience, geographic presence and contextual knowledge
- EPN, Kenya: Public health experience, geographic presence and contextual knowledge



Annexure 1

Technical Partners of the RaPID Pharmacovigilance Program

- Uppsala Monitoring Center (UMC), Sweden. UMC is a centre of scientific excellence and is field-name of the WHO Collaborating Center for International Drug Monitoring. UMC offers essential resources for drug regulatory agencies, health professionals, researchers, and pharmaceutical industry.
- Massachusetts Institute of Technology—Zaragoza International Logistics Program (MIT-ZLP), Spain. MIT-ZLP is a research and education partnership established by the MIT Centre for Transportation and Logistics, University of Zaragoza, Government of Aragón, in Zaragoza, Spain. MIT-Zaragoza provides support to countries, international agencies on public health supply chain issues.
- University of Ghana Medical School (UGMS), Ghana. UGMS is a premier institution for higher education and research with a mission to develop world-class human resources and capabilities to meet national development needs and global challenges through quality teaching, learning, research and knowledge dissemination.
- Ecumenical Pharmaceutical Network (EPN), Kenya. EPN is an independent apolitical non-profit organization that works in a context of increasing poverty and need for health services towards sustainable quality pharmaceutical care. It is a growing network with over 100 member organizations in over 30 countries.
- International Institute of Health Management Research (IIHMR), India. IIHMR is an academic and research institution recognized by the Government of India and accredited to the International Hospital Federation & Association of University Programs in Health Administration. IHMR is solely focused on health systems management towards improving the standards of health.



Annexure 2

Table: Outline of key Technical Assistance/Capacity Building activities provided/planned by the RaPID Pharmacovigilance Program

Key activities	Partners' roles	Source of funding	Timeline--Year
Technical assistance			
Rapid assessment of pharmacovigilance capacity in Kenya, Tanzania, Uganda	Uppsala Monitoring Centre: Technical input	WHO	November 2007
Conducted in-country consultation and developed protocol on CEM in Tanzania in collaboration with NDRA, global experts	Uppsala Monitoring Centre: Technical collaboration	RBM Partnership	February to April 2008
Conducted in-country consultation and developed protocol on CEM in Nigeria in collaboration with NDRA, global experts	Uppsala Monitoring Centre: Technical collaboration	RBM Partnership	February to April 2008
Completion of project "Rapid Pharmacovigilance Assessment of Adverse Drug Reaction (ADR) Reporting in Botswana, Ghana, Sierra Leone, Sudan, Zambia, Zimbabwe". Catalyzed introduction of Sudan in the WHO Program for International drug Monitoring	University of Ghana Medical School & Uppsala Monitoring Centre: Technical collaboration	WHO	December 2008
Catalyzed introduction of Sudan into the Uppsala Monitoring Centre's WHO Program for International Drug Safety Monitoring	University of Ghana Medical School & Uppsala Monitoring Centre: Technical collaboration	WHO	December 2008
Successfully bid for and won contract for training/capacity building on pharmacovigilance in Botswana	Uppsala Monitoring Centre: Technical collaboration	O3i/RaPID	June 2008
Jointly conducted training on pharmacovigilance in Botswana	Uppsala Monitoring Centre: Technical collaboration	MOH, Botswana	November 2008
Helped to catalyze a new process of validation of individuals interested in building expertise in ADR data entry in VigiFlow software	Uppsala Monitoring Centre: Technical collaboration	O3i/RaPID	February-May 2008



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