

National Pharmacovigilance Systems: Ensuring the Safe Use of Medicines August 16–18, 2010 Nairobi, Kenya



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About SPS

The Strengthening Pharmaceutical Systems (SPS) Program strives to build capacity within developing countries to effectively manage all aspects of pharmaceutical systems and services. SPS focuses on improving governance in the pharmaceutical sector, strengthening pharmaceutical management systems and financing mechanisms, containing antimicrobial resistance, and enhancing access to and appropriate use of medicines.

Recommended Citation

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Strengthening Pharmaceutical Systems (SPS) Program. 2010. *National Pharmacovigilance Systems: Ensuring the Safe Use of Medicines August 16–18, 2010 Nairobi, Kenya*. Submitted to the U.S. Agency for International Development by the Strengthening Pharmaceutical Systems (SPS) Program. Arlington, VA: Management Sciences for Health.

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CONFERENCE SUMMARY AND WAY FORWARD

Medicines-related problems can be the result of several different types of challenges (e.g., poor product quality, previously unidentified adverse drug reactions, and medication errors). In addition to these issues, the increasing availability of new essential medicines as a result of several global initiatives (including the U.S. President's Emergency Plan for AIDS Relief [PEPFAR]) and the safety data that can better inform decisions in treatment guidelines have highlighted the need for an increased awareness of pharmacovigilance systems at the local level.

Pharmacovigilance systems include all organizations, institutions, and resources that contribute to ensuring medicine safety through efficient and timely collection, assessment, and communication of risks and benefits to support decision making at various levels of the health care system. Comprehensive pharmacovigilance systems are those that use both passive (e.g., spontaneous reporting) and active (e.g., cohort event monitoring) surveillance methods to achieve these goals. Such systems, when implemented nationally, will help to ensure that signals of public health importance generated through spontaneous reporting mechanisms can be evaluated with active surveillance methods and that subsequent harm can be prevented through risk management practices.

The U.S. Agency for International Development-funded Strengthening Pharmaceutical Systems Program advocates that countries should establish national, comprehensive pharmacovigilance systems to best protect public health.

Until recently, most global pharmacovigilance initiatives have focused on supporting passive surveillance systems, such as the World Health Organization (WHO) Programme for International Drug Monitoring. These systems add value by encouraging the reporting of pharmacovigilance data, compiling these (mostly voluntary) reports from around the world, and sharing this information widely. This data aggregation has been valuable as countries with limited resources have struggled to staff and fund their own national programs. However, sentiment suggests that more locally developed approaches to pharmacovigilance would complement the global initiatives and lead to better risk management; for example, providing information about the total number of patients (that is, the denominator of the ratio) exposed to the medicine and determining the incidence of adverse events. There is currently momentum for augmenting spontaneous reporting with active systems for collecting, analyzing, and using information directly in the country or region.

SPS has been collaborating with WHO and donors (USAID, the Global Fund to Fight AIDS, Tuberculosis and Malaria) to provide assistance in developing comprehensive country-owned, national pharmacovigilance systems focused on adding active surveillance mechanisms to complement the local passive surveillance strategies. As part of this work, a conference entitled **National Pharmacovigilance Systems: Ensuring the Safe Use of Medicines** was held August 16–18, 2010, in Nairobi, Kenya, to provide a platform for discussion of national strategies for comprehensive pharmacovigilance implementation. More than 100 participants representing Ministries of Health, medicines regulatory authorities, nongovernmental organizations (NGOs), donors, universities, and other partners from more than 30 different countries participated in the conference, which was conducted in English with simultaneous French translation.

The Nairobi conference began with a discussion of global pharmacovigilance initiatives, and then focused on systems-based approaches to comprehensive strategies. Country, disease, and methodological examples of pharmacovigilance initiatives and the lessons learned from these were then discussed. Next, participants generated information about country-level barriers, opportunities, stakeholder roles, and sustainability issues in the realm of pharmacovigilance. Donor perspectives were also addressed with particular emphasis on how countries can include pharmacovigilance activities in their Global Fund applications and how USAID can support activities for Global Fund recipients. Finally, an outline for a step-wise plan of action for transitioning to national, comprehensive pharmacovigilance systems (described hereafter) was developed.

Complete proceedings of the conference, including a participant list, resource inventory, and slide presentations are available from <http://www.msh.org/projects/sps/Resources/Conferences/SPS-PV-Conference.cfm>.

STEPS FOR INITIATING OR ENHANCING NATIONAL, COMPREHENSIVE PHARMACOVIGILANCE SYSTEMS

Step 1. Determine where the country is now with regard to establishing and maintaining a national, comprehensive pharmacovigilance system.

- A. Because of nonstandard terminologies and variations in individual country infrastructure, comprehensive pharmacovigilance activities (in particular, the capability for active surveillance) may exist, but be relatively unrecognized within a country. For this reason, it is important to **assess the country's current medicines safety situation** to develop an individualized assessment of actual and potential support for pharmacovigilance activities.

One model available for this mapping is the **SPS Pharmacovigilance Framework** (below), which helps identify and illustrate relationships between people, functions, and structures available to support pharmacovigilance activities within the country context.

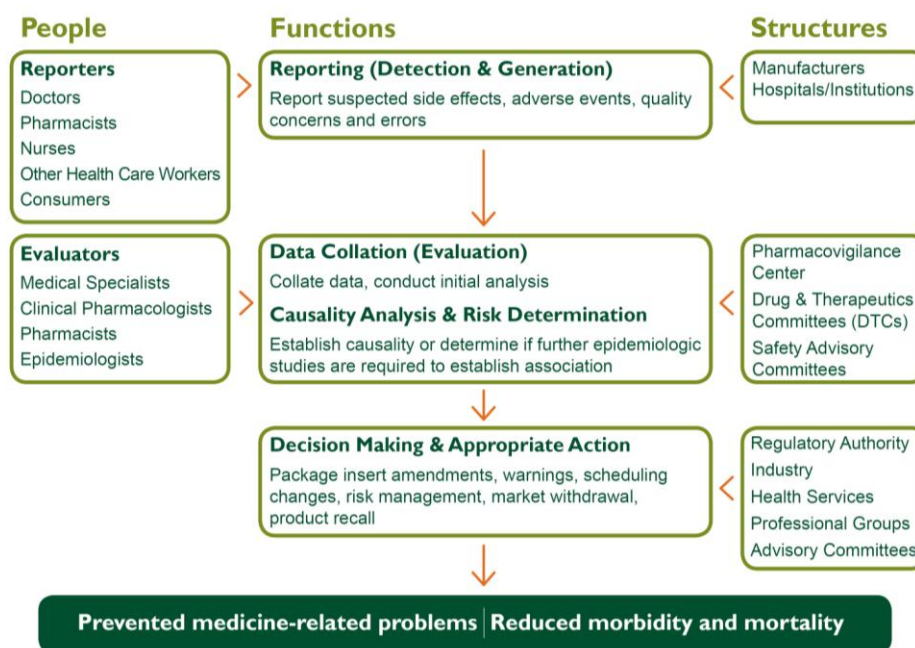


Figure 1. The Pharmacovigilance Framework

More information about this framework is available in English, French, and Spanish from <http://www.msh.org/projects/sps/Pharmaceutical-Management/Pharmacovigilance.cfm>.

- B. Use **stakeholder analysis** methods to assess how the people and structures identified in Step 1, Section A (e.g., health care workers, regulatory authorities, industry) can be engaged in the national pharmacovigilance strategy. Key stakeholders are those groups or individuals who are important to or can significantly influence the success of the project. This analysis should inform a **stakeholder engagement plan** with directed interventions to optimize the strengths of the current country system while building a strategy designed to bridge gaps in areas of weakness.

There are many good techniques available for stakeholder mapping, but a general approach is to categorize stakeholders by their levels of importance (technically) to the system and influence in facilitating (or blocking) the strategy.¹ For example, within a specific country situation, a university partner may be important for analysis of data from sentinel sites; however, their political influence for garnering support for the system may be quite low. Basic stakeholder analysis using this technique might look something like the matrix (with associated engagement strategies) shown below.

Importance (technical)	High	High importance Low influence MANAGE (consult with these)	High importance High influence INVOLVE (partner with these)
	Low	Low importance Low influence MONITOR (control these)	Low importance High influence ACKNOWLEDGE (inform these)
		Low	High
		Influence (support)	

Figure 2. Stakeholder Analysis Matrix

Across countries, the stakeholder analysis may include a listing of similar individuals and organizations, but the relative influence of these stakeholders may vary widely, which means the mechanisms for engaging them may also vary. For example, in a country where the medicines regulatory authority is both particularly skilled and politically savvy, this group should be a key partner that is highly involved in coordinating national medicines safety activities. In another country, where the medicines regulatory authority is relatively weak, another stakeholder (e.g., Ministry of Health or university) may take on the leadership role, but keep the medicines authority informed of the systematic changes.

- C. Determine the country’s **pharmacovigilance system baseline effectiveness** by considering the operational strategy for reporting and managing adverse drug reactions, medication errors, product quality concerns, and claims of therapeutic ineffectiveness. Tools are available for reviewing the following components of the national pharmacovigilance system—policy, law, and regulation; systems, structures, and stakeholder coordination; signal generation/data management; risk assessment and evaluation; and risk management and communication.

¹ Developed at Imperial College London. (Note that this information has been added to this discussion of stakeholder analysis based on feedback from the conference.)

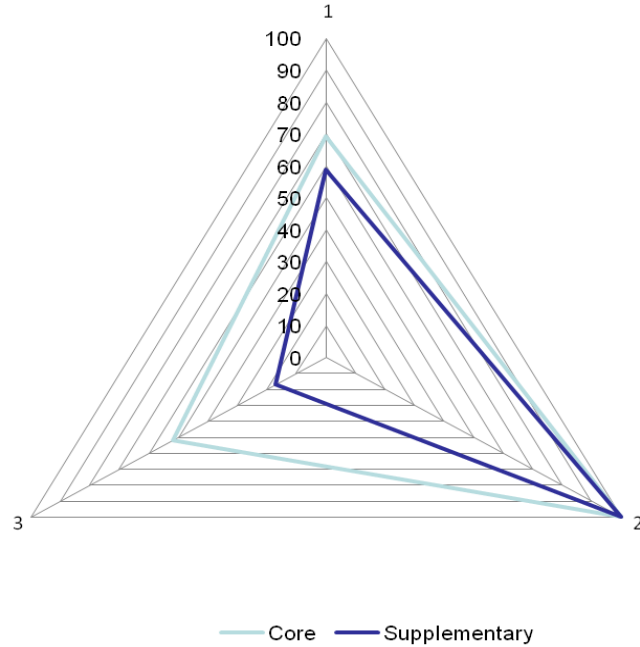


Figure 3. Radar Chart of Pharmacovigilance Effectiveness

One such tool is the **Indicator-based Pharmacovigilance Assessment Tool (IPAT)**. The IPAT includes 43 indicators (26 core and 17 supplementary) categorized as to being reflective of the structures, processes, or outcomes of the pharmacovigilance system being examined. Once the assessment is completed, radar charts (also known as spider graphs), such as the one in the adjacent figure, can then be used to display visually how well the country is performing on the specific indicators selected for evaluation.

This analysis and visualization can be repeated periodically to track system changes over time.

- D.** Determine at what level interventions are needed to build capacity for enhanced pharmacovigilance. This is critical because the resources required for active surveillance can be more complex than those required for spontaneous reporting. In addition, systems changes are often required so that information collected can be more easily used for local decision making.

The **Pharmacovigilance Capacity Building Pyramid**² is one tool that illustrates why creating functional capacity within the system includes much more than equipment, training, and funding (the most commonly requested areas of pharmacovigilance assistance among low- and middle-income countries).³

² Adapted from Potter, C. and R. Brough. 2004. Systemic Capacity Building: A Hierarchy of Needs. *Health Policy and Planning* 19(5):336–335.

³ Olsson, S., S. N. Pal, A. Stergachis, and M. Couper. 2010. An Analysis of Pharmacovigilance Activities in 55 Low- and Middle-Income Countries. *Drug Safety* 33(8):689–703.

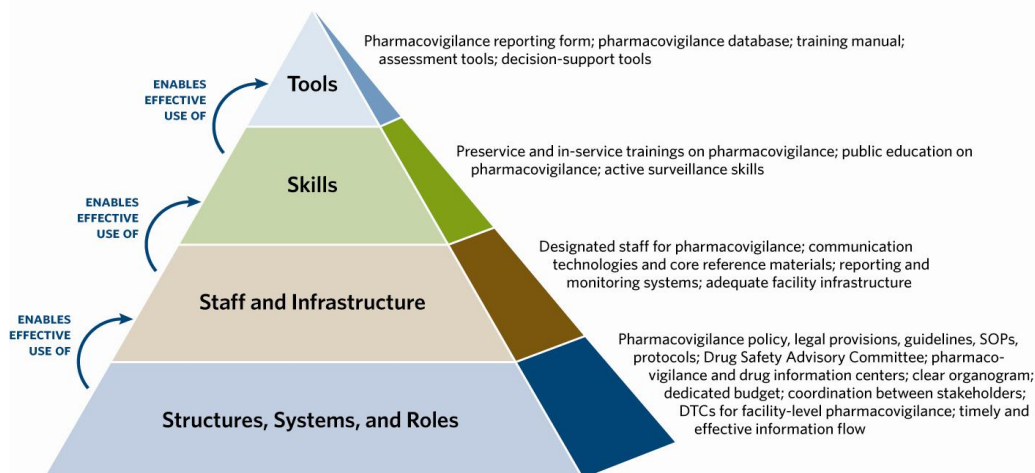


Figure 4. Pharmacovigilance Capacity Building Pyramid

In this pyramid model, interventions at the upper levels (tools and skills) are typically focused on individuals whereas those at the lower or foundation levels (staff and infrastructure; structures, systems, and roles) are typically focused on institutions. The pyramid emphasizes that even an adequate number of well-trained pharmacovigilance staff will be unlikely to compensate for poorly defined roles, policy and legal hurdles, and lack of adequate facilities. Therefore, investments in the foundation of the pyramid should be prioritized, recognizing that building true capacity at this level may require substantial time and political buy-in, but can lead to more sustainable results.

Step 2. Determine and implement interventions that will improve the country's pharmacovigilance system.

A. Consider sustainability from the start

Currently, few low- and middle-income countries allocate budget to pharmacovigilance; these activities are primarily supported through public health programs and donors.³ Historically, the transition from donor-supported to government-owned public health activities has been challenging, particularly if not well planned.

Medicine safety and pharmacovigilance infrastructure are integral to strengthening the overall health system, and so it is important to consider sustainability from the outset, even at the expense of implementation speed.

B. Decide what to do based on what is already in place

For countries in the early phases of pharmacovigilance activity, achieving a minimum functional system is a good initial goal. WHO and the Global Fund have created a partnership for establishing global minimum standards for national pharmacovigilance systems.⁴

⁴ Pal, S. and S. Xueref. WHO-GFATM Partnership for Pharmacovigilance in Global Health Initiatives. Conference presentation from National Pharmacovigilance Systems: Ensuring the Safe Use of Medicines. August 2010. Nairobi, Kenya.

Recommended minimum national pharmacovigilance requirements include—

- A pharmacovigilance center with at least one full-time staff member, stable basic funding, clear mandates, a well-defined structure or roles, and active collaboration with the WHO Programme for International Drug Monitoring
- A spontaneous reporting system (including forms)
- A database or system for collating and managing reports
- An advisory committee able to provide technical assistance on causality assessment, risk assessment, risk management, case management, and crisis management
- A clear strategy for routine and crisis communications

Although active surveillance methods are not included specifically in these minimum national requirements, the emphasis on assessment and risk management implies that inclusion of these activities is necessary. The Nairobi conference highlighted that many active surveillance and related risk assessment activities and studies are already taking place in developing countries. These studies were largely informed by local needs and safety concerns. Clearly, countries understand the need to evaluate safety signals particularly when they are of public health importance. The fact that both spontaneous reporting and active surveillance are currently ongoing in some developing countries, but are not being recognized, may be attributed to the lack of coordination of pharmacovigilance activities at national pharmacovigilance centers as well as gaps in communications among various stakeholders.

C. Agree on how to do it

Each country's mapping of pharmacovigilance activities and stakeholder analysis (Step 1, Sections A and B) will drive the determination of roles and responsibilities for capacitating the comprehensive national pharmacovigilance system.

The WHO/Global Fund partnership aims to develop and communicate best practices for pharmacovigilance in global health initiatives. The draft strategy for these activities is currently being finalized, with the goal of initiating field testing of interventions in 20 or more priority countries. Based on the results of this field testing, the pharmacovigilance strategy will be implemented across all countries beginning in 2012. More detail about this strategy is forthcoming.

The WHO/Global Fund partnership has developed an implementation toolkit (including tools from a variety of sources) that includes pharmacovigilance activities in public health programs. Developing medicine safety activities by building on disease-specific mechanisms may be the most expedient pathway to initiating a comprehensive national system. It also suggests that linking pharmacovigilance to other highly supported and visible activities (e.g., procurement and supply management planning) is a potential mechanism for anchoring these value-added activities to the standard national infrastructure and processes.

D. Determine how to fund it

Funding can be leveraged from donors while local government support increases incrementally. For this reason, it is important to have a clear understanding of the flow of funds surrounding all services (e.g., procurement, medicines regulation, and pre- and in-service education) that may influence stakeholder engagement in the national pharmacovigilance system.

The lack of emphasis on developing pharmacovigilance systems in recipients of donor support in the area of pharmaceutical management⁵ has resulted in a need for active direction in this area. The Global Fund, in collaboration with its partners and with technical guidance from WHO, is defining and will implement a clear pharmacovigilance strategy in its grants. Countries should begin preparation now (Step 1) to include pharmacovigilance activities in their Global Fund applications.

Complementing this initiative, USAID will continue to work with Global Fund applicants, recipients, and other interested countries to plan, develop, and implement appropriate pharmacovigilance strategies and activities.

E. Set targets and timelines

Targets are an important quality assurance mechanism because they indicate whether an intervention will likely yield the anticipated results, allowing for adjustment, expansion, or termination (if necessary) before funding is exhausted. It is important that the targets be realistic, however, taking into account resources available at the country level. As increasing attention is paid to pharmacovigilance, the need for performance metrics (process and outcomes) is also being recognized. The IPAT includes indicators that can be used to set targets and monitor achievements longitudinally. Timelines for yielding results must also be reasonable and reflect that systemic change often occurs slowly, but an incremental approach is better linked to future sustainability.

For references on targets and timelines, see <http://www.msh.org/projects/sps/Resources/Conferences/SPS-PV-Conference.cfm>. However, some of this may require extrapolation to be most useful in the developing world context. Recognizing that such information is often deemed politically sensitive, better mechanisms for publicly sharing specifics about implementation costs, targets, and timelines are needed to improve the planning process.

F. Implement interventions with the goal of sustainability

Interventional activities focused on strengthening the national pharmacovigilance system will depend greatly on the baseline assessment (Step 1, Section C). Although there may be many actions that could be undertaken, the specific country-level and indicator-based analyses will reveal those that should be undertaken. Some examples of potential interventional activities from the USAID-funded SPS Program can be found in Annex 1.

As stated earlier, interventions associated with training are among the most commonly requested areas of pharmacovigilance assistance,³ but without careful planning (Step 1, Section D), funding can be misallocated to training that has not been fully linked to deliver measurable outcomes. Although much can be learned from following the results of similar national models, if the interventions are not mapped directly to the baseline pharmacovigilance assessment and do not reflect the stakeholder analysis and engagement plan, it is likely that the interventions will not be powerful, efficient, or sustainable.

⁵ Stergachis, A., R. J. K. Bartlein, A. Doodoo, et al. 2010. A Situational Analysis of Pharmacovigilance Plans in Global Fund Malaria and US President's Malaria Initiative Proposals. *Malaria Journal* 9:148.

Step 3. Measure to determine if pharmacovigilance interventions are successful and efficient.

A. Objective measurements of performance

Too often, inexact terms like “strengthened” are used when describing the specific results of pharmacovigilance systems in the global health context. Such vagaries lead to challenges when determining the value of specific interventions and can be complicated by misaligned expectations and political will. For this reason, when preparing national, comprehensive pharmacovigilance strategies, it is critical to have a good understanding of the baseline (Step 1) and the timeframe (Step 2, Section E) to develop a specific assessment plan for measuring results.

One way to present the assessment plan is to format it as a table that includes the indicators as individual rows set vertically and have the data source or collection method, the baseline value, the target change value in natural units or percent change, the timeframe for measurement, and the unit of responsibility as column heads set along the horizontal. Ensuring that these outcomes are transparent and that all stakeholders are clear on how success will be measured will minimize the risk of misunderstanding later.

B. Total cost

Although cost-effective is often used to describe pharmacovigilance activities, interventions cannot actually be determined to be cost-effective unless accurate details about the total cost of intervention and measures of effectiveness are clear. Obtaining this information can be challenging, particularly when existing governmental resources (e.g., staff and facilities) are being leveraged as part of the support for the intervention.

Costs can be divided into groups based on their role in the pharmacovigilance intervention—

- Start-up and establishment (e.g., training and equipment)
- Stabilization (subscriptions to important information resources, marketing to raise awareness as pilot programs are expanded)
- Sustainability (e.g., transitional issues such as rebranding); all costs, whether based on donor or government support, should be included in the costing exercise

As an example, the Roll Back Malaria partnership has estimated that a national pharmacovigilance program for antimalarial drugs should cost USD 150,000–250,000 for start-up with recurrent costs of approximately USD 50,000 per year.⁶

C. Answering the “so what” question

National comprehensive pharmacovigilance systems help countries to better understand the benefit and risk balance of medicines in the population. When combined with rational use initiatives, the benefit and risk profile of a medicine can be tilted so that the maximal benefit is derived and the overall risks are reduced. This can and should subsequently inform the revision of the country’s treatment guidelines.

⁶ Roll Back Malaria: RBM Country Needs Assessment Template 2008. Available from <http://www.rollbackmalaria.org/docs/rbmttoolbox>. Accessed September 19, 2010.

With all the layers of measurement in an effective national pharmacovigilance system, countries can become distracted with gathering metrics and compiling statistics, rather than the actual patient- and population-level results. For example, the number of adverse event reports received and processed is only a crude preliminary marker of a quality system; these are essentially outputs, not outcomes.

What is more important is how the information in these reports is acted upon, i.e., what risk management interventions have been implemented in response to the information and what harm has been avoided. This information might include details about products recalled, products restricted for use in specific populations, manufacturers banned from doing business within the country, and other elements that contribute to safer use. Data may also reveal previously unknown, but beneficial effects of medicines.

We need more evidence-based work on metrics for pharmacovigilance. These types of metrics contribute to the assessment of the total value of the intervention to the system. This information should be considered along with the total cost (Step 3, Section C) to determine which activities are most powerful and efficient and should therefore be prioritized for the future.

Step 4. Share information about successes and failures widely.

National pharmacovigilance centers can be resource-intensive, so it is important for the key stakeholders, including the public (Step 1, Section B), to see the results of the activities and, consequently, to feel that the country's medicines system is safer overall because of them. Success stories should be shared widely to garner political support so that sustainability and replication can be prioritized. Countries must not forget, however, that there is as much to learn from what doesn't work as from what does. Although it is human nature to focus on the positives, careful review of the negatives is very important. Transparency and open discussions about unintended (negative) consequences or challenges to good methodology in national pharmacovigilance systems could save other countries from making similar missteps. Just like the medication error literature suggests, creating a culture where "near misses" (in this case, interventions that weren't successful in achieving their goals) can be discussed and shared is an important part of the strategy.

**ANNEX 1. SPS COUNTRY-LEVEL PHARMACOVIGILANCE CAPACITY-BUILDING ACTIVITIES
(THROUGH OCTOBER 2010)**

Country	Structure, System, and Roles	Staffing and Infrastructure	Skills	Tools
Ethiopia	Support to achieve membership in the WHO Programme for International Drug Monitoring		Training	
Ghana	Assessment using IPAT; recommendation for organizational structure for post-marketing surveillance directorate			Revised reporting form
Kenya	Support to achieve membership in the WHO Programme for International Drug Monitoring		Training materials and training	Reporting form
Namibia	Established Therapeutic Information and Pharmacovigilance Centre (TIPC) with functional structure, framework, guidelines, standard operating procedures, and mandate; conducted retrospective data linkage study on AZT and anemia; secured Global Fund funding for prospective active surveillance	Provided staffing, office space, infrastructure	Training materials and training	Reporting form
Nigeria	Recommended structural changes; provided technical assistance for Global Fund round 10 application for pharmacovigilance		Training materials and training	Revised reporting form
Rwanda	Developed framework for medicine safety system based on assessment using IPAT; support to achieve membership in the WHO Programme for International Drug Monitoring; supporting development of active surveillance for artemisinin-based combination therapy and antiretrovirals		Training	Reporting system
South Africa	Assessment using IPAT for industry and public sector; supported protocol development for Antiretroviral Cohort Adverse Event Monitoring programme In KwaZulu-Natal [ACADEMIK] study; initiated development of active surveillance system	Staffing for KwaZulu-Natal active surveillance activities	Training materials and training	Electronic tool for active surveillance study
Tanzania			Training materials and training	Revising reporting form
Vietnam	Framework for national system; introduced active surveillance and supported development of protocol and sentinel surveillance sites		Training materials and training	Revising reporting form