

Towards a global strategy¹ on Pharmacovigilance (PV)

A joint document by the GF and WHO²

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¹ The focus was initially on the Global Fund, but it is now expanded to other Global Health Initiatives as the World Bank and UNITAID are interested to join this effort. Discussions are still on-going with PEPFAR and other Partners.

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Executive Summary:

Pharmacovigilance (PV) is an indispensable public health activity for the monitoring and prevention of adverse drug reactions (ADR), which represent the fourth to sixth leading cause of death in the USA and cause an estimated 197 000 deaths per year in Europe. PV is critical for the review of treatment guidelines, and it can unveil problems of irrational use of medicines, medication errors and medicine quality issues.

Until date, it appears that few Global Fund (GF) grants consider PV, and most of the countries benefiting from GF resources seem not to have functioning PV systems in place.

The GF Board expressed in 2002 that *'It is strongly recommended to Recipients that they (...) monitor adverse drug reactions (ADRs) according to existing international guidelines and, if necessary, drawing on budgeted requests for financial support from the Fund'*.

The Global Fund Secretariat with technical guidance from WHO and key inputs from Partners is launching an initiative 'towards a strategy on PV', to enable countries (including PR) to implement functioning PV systems. This concept note introduces what are the driving principles of this initiative, such as a transversal system strengthening approach, seeking the sustainable development of existing PV systems already in place in countries and encouraging innovative strategies. We also promote the concept of countries reaching 'minimum PV standards' as defined by WHO, before moving beyond, and countries will be offered tools and processes gathered into a user-friendly PV toolkit so they can easily implement and benefit from a functional PV system.

We propose roles for different Partners, including countries, technical agencies or private manufacturers. Other Global Health Initiatives (GHI) are invited to join and co-own this initiative, so it could become a 'GHI strategy on PV'.

The rolling-out of the PV strategy will follow a phased approach, with a 18-month first phase of "proof of principle" in 10-20 invited countries that will aim at documenting cost-effective PV approaches for low and middle-income countries, reflecting on their past PV activities (what has worked, what has not worked and why?), and field testing new PV techniques. Based on lessons learned, the future strategy on PV will be finalized and proposed for a global roll-out in all countries receiving GF resources.

1- Background

1.1 The importance of pharmacovigilance

Pharmacovigilance is defined as “the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems”.

Pharmacovigilance (PV) is a core component of the pharmaceutical management system, and represents an arm of patient care. It aims at making the best use of medicines for the treatment or prevention of disease. No one wants to harm patients, but unfortunately any medicine can sometimes do just this. Good pharmacovigilance will identify the risks and the risk factors of adverse risk reactions in the shortest possible time so that harm can be avoided or minimized. When communicated effectively, this information allows for the intelligent, evidence-based use of medicines and has the potential for preventing many adverse reactions. This will ultimately help each patient to receive optimum therapy, and on a population basis, will help to ensure the acceptance and effectiveness of public health programmes.

Significant harm to a few patients can destroy the credibility, adherence to and success of a treatment programme. Rumours and myths about the adverse effects of medicines can spread rapidly and are difficult to refute in the absence of good data³. Pharmacovigilance can provide data, improve public awareness of adverse drug reactions (ADRs) and compliance⁴. It can also provide evidence of other types of medicine-related problems including treatment failure / therapeutic ineffectiveness⁵, poor quality and counterfeit medicines⁶, interactions between medicine and food and the incorrect use of medicines. Good pharmacovigilance practice can generate the evidence that will inspire public confidence and trust.

Pharmacovigilance promotes ethical practices and quality of care. Several studies show that many ADRs are preventable⁷. PV can help understand the types of medicines that are associated with ADRs, the risk groups affected and the circumstances under which these preventable ADRs occur, the types of medicines that are associated with these preventable ADRs and identify best practices for protecting patients from preventable harms⁸.

³ Dodoo A, Adjei S, Couper M, et al. When rumours derail a mass deforming exercise. *Lancet* 2007; 370:465-466.

⁴ Gunawardena et al. 2008: Pharmacovigilance through consumer feedback (reporting) in the mass treatment of lymphatic filariasis using diethylcarbamazine and albendazole in two districts of Sri Lanka. *Tropical Medicine and International Health* Vol 13 Issue 9, pgs 1153 - 1158

⁵ Meyboom et al. *Drug Safety* Volume 23, Number 2, August 2000 , pp. 95-99(5): The Value of Reporting Therapeutic Ineffectiveness as an Adverse Drug Reaction

⁶ Dora Akunyili and Ijeoma Nnani. *The International Journal of Risk and Safety in Medicine*. Vol 16, No. 3/2004, 181 - 190. Risk of medicines: Counterfeit drugs; Meyboom et al. *PV in perspective*. *Drug safety* 1999 Dec 21 (6): 429 - 447

⁷ Ducharme MM, Boothby LA. An analysis of adverse reactions for preventability. *Int J Clin Pract*; 2007; 6 (1) 157-61
Ruiz B, Garcia M et al. Factors predicting hospital readmissions related to adverse drug reactions. *Eur J Clin Pharmacol*; 2008; 64(7) 715-22.

M^cDonell PJ, Jacobs MR. Hospital admissions resulting from preventable adverse drug reactions. *Ann Pharmacother*; 2002; 36(9) 1331-6.

⁸ Detecting medication errors in pharmacovigilance database: capacities and limits. L Alj et al, 2007, *International Journal of Risk and Safety in Medicine*

Pharmacovigilance promotes sound principles of public health. Pharmacovigilance involves training of health workers in the identification of adverse reactions, data collection and recording, processing and analysis. Based on the interpretation of the analysis of data and available evidence, it promotes the development of communication strategies to inform the general public, the health providers, the regulatory authorities and the pharmaceutical companies concerned.

All new medicines are developed through well-conducted Phase I-II-III clinical trials, involving approximately 2000-3000 closely monitored patients. But these clinical trials phases have major shortcomings:

- The incidence of adverse events and toxicity is relatively low and requires very large cohorts of patients to identify rare, new and unexpected adverse events: this condition being rarely met in premarketing clinical control trials, are identified through cohorts of patients treated over a sufficient period of time in observational studies.
- These studies almost always exclude young infants and pregnant women, older patients and those with co-morbidities and concomitant treatment. For this reasons, new medicines may enter in the market with limited knowledge of the frequency of rare and serious side-effects, which may occur under real-life use. Moreover for all new medicines there are very limited data on exposure in infants and pregnant women, which for certain diseases, like malaria, are important vulnerable population groups.
- These clinical trials do not fully consider populations living in area where the disease burden exists:
 - o Our knowledge of antiretroviral medicines toxicity from post marketing studies is largely based on information and data collected in developed countries from populations whose demographics, genetic background, nutritional status and background co-morbidity vary substantially from those of populations which are most in need of treatment. In addition, in low and middle income countries, most patients on antiretroviral treatment receive fixed drug combination and generic medicines, not addressed in these studies.
 - o Although the burden of the three major diseases weighs heavier on resource limited settings than the rich, information on ADRs may be disproportionately influenced by reports from the higher income countries. The experience with use of second line drugs in "naïve" populations, having a different co-morbidity pattern, may differ substantially. The detection of such events may be subject to unnecessary delays. Thus, for instance, the occurrence of fatal cutaneous hypersensitivity reactions to thiacetazone among people with HIV in Africa which was only reported in the early 1990s.

In summary, pharmacovigilance is an indispensable public health activity that can identify previously undetected adverse drug reactions. The information collected allows the assessment of the risks and benefits of deploying new medicines for large scale use and provides compulsive evidence for an effective risk management plan. PV is critical for the review and update of international and national treatment guidelines. In addition to ADRs monitoring and prevention, an effective pharmacovigilance system can also unveil problems of irrational use of medicines, medication errors and drug quality issues. A sound PV system can thus strengthen Public Health programs and

improve quality of care. Ultimately it brings value for money in the investments of Global Health Initiatives.

1.2 The burden of adverse drug reactions (ADRs)

Adverse drug reactions represent a severe burden for the society:

ADR are the fourth to sixth leading cause of death in the USA⁹ while in Europe, it is estimated that 197 000 deaths per year are due to ADRs¹⁰. In the UK, it is estimated that 6.5% of hospital admissions are due to ADRs¹¹.

The associated costs of medicine related morbidity and mortality exceeded \$177.4 billion in 2000 in the USA¹², while the total annual cost to society due to ADRs in the EU is €79 billion. In the UK, the cost of ADR is being around £446 million per year.

Few data is available from low or middle income countries. Still, a study in India reports that the average cost of managing a single ADR of moderate severity in patients is \$15¹³.

1.2.1. ADRs in Tuberculosis

Pharmacovigilance is commonly considered irrelevant for tuberculosis given that the drugs in use have been available for decades and their associated adverse effects are generally well known. However, ADRs remain very frequent, even in patients on currently available first-line anti-TB medications: a study from Iran demonstrated that 45% of patients with respiratory TB admitted to a teaching hospital had ADRs induced by anti-TB drugs.¹⁴ Many of these ADRs were preventable. Another study from Canada found that among 1061 patients receiving treatment 318 (30%) had at least one major ADR.¹⁵ Thus, the monitoring of ADR should be considered as important for the safety of tuberculosis patients embarking on treatment lasting from 6 months to 2 years. However, while monitoring and evaluation have been central components of the WHO-recommended framework for TB care for many years, pharmacovigilance is not specified in the Stop TB Strategy¹⁶. In contrast to HIV and malaria, no WHO document exists dedicated to PV in TB. The standard WHO guidelines on programmatic management of drug resistant TB gives a brief mention of pharmacovigilance.¹⁷ The experts who will be

⁹ Lazarou et al, 1998

¹⁰ Memo from Brussels, 10 Dec 2008.

¹¹ Adverse drug reactions as a cause of admission to hospital: a prospective analysis, Pirmohamed M *BMJ* 2004; 329: 15-19

¹² Ernst FR & Grizzle AJ, 2001: *J American Pharm. Assoc*

¹³ Ramesh M et al. *Pharmacoepidemiol Drug Safety* 2003; 12 (8): 687 - 692. Adverse drug reactions in a South Indian hospital - their severity and cost involved

¹⁴ Javadi MR, Shalviri G, Gholami K *et al.* (University of Medical Sciences, Tehran, Islamic Republic of Iran). Adverse reactions of anti-tuberculosis drugs in hospitalized patients: incidence, severity and risk factors. *Pharmacoepidemiol Drug Saf.* 2007 Oct;16(10):1104-10.

¹⁵ Marra F, Marra CA, Bruchet N, Richardson K, Moadebi S, Elwood RK, Fitzgerald JM. Adverse drug reactions associated with first-line anti-tuberculosis drug regimens. *Int J Tuberc Lung Dis.* 2007 Aug;11(8):868-75.

¹⁶ whqlibdoc.who.int/hq/2006/WHO_HTM_STB_2006.368_eng.pdf

¹⁷ whqlibdoc.who.int/publications/2008/9789241547581_eng.pdf (p.210)

revising this document in 2010 intend to strengthen this dimension and elaborate more on the mechanisms for improved reporting.

Recent developments in the management of tuberculosis should be viewed as new opportunities to reconsider this position, and to couple these developments with a commensurate scale-up in tracking of side-effects. To mention some of the more pertinent factors:

- Patients are being treated with a different armamentarium of drugs
- Treatment is typically longer with drugs like fluoroquinolones, indicated for much briefer duration for the management of other infectious diseases
- The wider use of drugs belonging to different classes would be expected to increase the likelihood of side effects, including rarer ones
- The prospect of having new drugs on the market in DR-TB regimens in the next couple of years represents a novel experience for many TB specialists
- The expansion of treatment projects among populations whose age-structure, genetic stock, nutritional status and background co-morbidity may influence the expression of ADR
- Co-morbidities are more likely to accentuate toxicity because of interference with metabolism (e.g. liver pathology) or due to concomitant use of drugs with overlapping toxicity (e.g. HIV)
- The acknowledgement among clinicians that side-effects are frequent and a major determinant of poor patient adherence and failure ...
- ...while at the same time having very little data and little knowledge of the mechanisms in place for notifying episodes.

1.2.2. ADRs in HIV/AIDS

The HIV/ART programs launched to improve ART access in resource limited settings have now reached 4 millions of patients; the majority of them live in sub Saharan Africa. This scale up has not been matched by a proportionate development in pharmacovigilance. As of end 2008, only 3,000 of the 60,000 ADRs reports linked to the use of ARVs were sent to the Uppsala drug Monitoring Centre from developing countries. If evidences of ADR linked to ART exist in low and middle income countries, these would require improved specific detection, assessment, understanding and prevention.

Lack of national or regional data has been problematic so far to functioning regulators that recognize the need to more actively be involved in ART scale-up. Data are also needed by Industry (brand and generic) as products are rolled out in at risks groups or in different settings than the pre marketing studies and in much larger patient numbers where rare adverse events will be seen.

Numerous new ARVs are available and ART has significantly led to decreased morbidity and mortality from HIV infection. Clinicians agree that the benefits of ART, far outweigh-through decreased mortality and morbidity-ARVs toxicities impact. There is however increasing recognition of existing toxicities leading to drug substitution or serious ADRs linked to acute and long-term toxicities and mortality.

In existing treatment cohorts, and in spite of a high level of adherence, the proportion of HIV patients who discontinue the first-line ART due to toxic adverse events varies considerably according to the context, gender metabolic conditions: for example, lactic

acidosis incidence is of 16.2 cases by 1000 of patients-years in women, and of 1.2 cases by 1000 of patients-years in males. Treatment-limiting toxicity (15 to 30% on average) is an important cause of treatment failure, arising often early after treatment initiation, but also accumulating over time, such as lipodystrophy linked to stavudine.

In a study¹⁸ in Cambodia, among patients without specific risk factors, switching from stavudine to AZT, 21.9% developed anaemia of any grade, of which 7.1% developed severe anaemia. Drug-related anaemia was cited as the reason for switching among 38 of the 51 patients who switched from AZT within one year, and one of the four deaths during the study was due to severe anaemia.

It is notable that for most ADRs, risks factors and at risks populations sub-groups are identified and therefore these ADRs may be preventable.

In addition to the general considerations for improving pharmacovigilance, the specific aspects of ART that is a life long treatment, based on multi drugs combination, with a wide range of brand and generic formulations need to be addressed in PV for ARVs programmes. In addition, the fact that most treatment programmes are naturally organized in cohorts calls for innovative reporting system such as the cohort Event Monitoring Tool proposed by WHO-UMC. The WHO ART recommendations are widely based on risks-benefits assessment and consideration for drug related toxicities.

Pharmacovigilance is critical for HIV patients' safety, well being and adherence to antiretroviral therapy that is life long. It also has major implications at population level, in public health programmes, linked to cost, effectiveness, prevention of drug resistance, sustainability and improved treatment monitoring. Pharmacovigilance is a tool leading to a rationale choice of treatment regimen and improved national programmes management.

1.2.1. ADRs in malaria

The identification and reports of unexpected drug reactions may have major impact on the reputation of antimalarial medicines, especially if this occurs at the time of large introduction of relatively new medicines:

For example, in Ghana, the reports in 2005 of a series of dystonic reactions following the introduction of 6 new brands of artesunate+amodiaquine received major attention by the national press. Despite these reactions being transient in nature and responding to treatment with diazepam, the nature of these unexpected events (involving spasms of the oro-facial muscles) created a major reaction of panic. The association between these neurological reactions and the introduction of new 1st-line antimalarial treatment moved the public into questioning the need for ACT adoption and created strong pressure to revert back to the use of highly ineffective chloroquine for the treatment of malaria. This major disaster was averted by the very active pharmacovigilance center in this country, which was instrumental in conducting immediate investigations, gathering additional evidence, with a good crisis management strategy already in place.

Following the decision of Ministry of Health to withdraw from the market all the brands containing high dose amodiaquine (600 mg tablets), the frequency of reports of dystonic

¹⁸ Isaakidis P et al. *Evaluation of a systematic substitution of zidovudine for stavudine-based HAART in a program setting in rural Cambodia.* J Acquir Immune Defic Syndr 49:48 – 54, 2008

reactions decreased. Since 2006, artesunate+amodiaquine is the 1st-line treatment of malaria in Ghana and over 9 million patients have been treated with this medicine, mainly in the public sector.

In most malaria endemic countries, however, with limited exceptions, pharmacovigilance is still in its early phase of development. Most of the functioning centers are mainly based on spontaneous reporting systems, which are inexpensive, relatively easy to establish and are sustainable. However, in public health programmes particularly in resource-limited settings, it is important to complement this method with active surveillance methods, which will provide denominator data. Well conducted cohort event monitoring (CEM) programmes are currently being piloted in a few Sub Saharan countries. Pregnancy registries to assess the safety of inadvertent exposure to artemisinin-based antimalarial medicines during the first trimester of pregnancy are in the final stage of field evaluation.

1.3 The international nature of pharmacovigilance

A strength of pharmacovigilance is its international nature. Under the stimulus and coordination of the World Health Organization (WHO) and its Collaborating Centre for International Drug Monitoring (the Uppsala Monitoring Centre), there are currently 126 national centres networking in a strong international programme. These national centres collaborate in the WHO Programme for International Drug Monitoring, to collect reports of suspected adverse drug reactions (ADRs) and after review, send them to the Uppsala Monitoring Centre for entry into the WHO database. This is the largest database of ADR reports in the world (over 5 million case reports) and is a prime resource for generating signals of previously unrecognized ADRs and for the study of questions on the safety of medicines. This database reflects the reporting activity of national PV centers, which, in resource-limited settings are often poorly resourced and under-staffed. For these reasons the reports about medicines used in public health programmes in developing countries are still limited and most of the reports are not reflecting the situation in high disease burden countries.

This database would have added value if it included more reports about medicines used in public health programmes and could also be a valuable resource for the programmes themselves.

1.4 Overviews of methods in pharmacovigilance

With the current global focus on priority diseases, several new medicines with limited post-marketing safety data are being introduced into countries with little or no capacity to monitor the safety of these medicines. Spontaneous reporting is the principle PV method used. It is cheap and easy to establish, and can detect early signals of unknown adverse drug reactions but cannot estimate the incidence of these reactions or the frequency of risk factors associated to them.

In view of the above, the WHO Programme for International Drug Monitoring, along with its dedicated Collaborating Centre in Sweden and partners in the WHO disease programmes has engaged in developing, adapting and introducing new and innovative methods of active surveillance (including cohort event monitoring and pregnancy registers) that can **complement** spontaneous reporting methods. These innovative methods have the potential to effectively establish the rates of adverse events and identify specific risk factors and groups. These methods can provide in a time-limited

period a valid clinical assessment of the problems associated with the use of new medicines for priority diseases in endemic countries.

There is an urgent need to leverage these new tools to address priority diseases such as malaria, TB and HIV AIDS. We need to advance the lessons learnt from these early experiences to strengthen PV systems and provide proof of concept that, if successful, can serve as a model for adoption in other developing countries, as well as for safety monitoring of new medicines deployed to fight other priority diseases in developing countries.

The ultimate goal is to strengthen health systems by building sustainable and truly global PV systems that inform policies and treatment guidelines, to reduce patient deaths and morbidity arising from undetected adverse drug reactions.

1.5 Overview of past GF approach on pharmacovigilance (Round 1 to Round 9):

In 2002, the GF Board expressed that it ‘strongly recommend Recipients (of GF grants) to monitor adverse drug reactions’.

The Board decision GF/B4/2 (4th Board meeting, October 2002) expresses that *‘It is strongly recommended to Recipients that they implement mechanisms to encourage adherence to treatment (...), to monitor and contain resistance, and to monitor adverse drug reactions (ADRs) according to existing international guidelines and, if necessary, drawing on budgeted requests for financial support from the Fund’*.

Thus, advocating for the monitoring of adverse drug reactions has been in GF guidelines almost since its inception, and the GF decided to emphasize in its new Risk Management framework (November 2009)¹⁹ that the organization faces an ‘ethical’ risk if medicines procured by the GF principal recipients, and delivered to patients, are of poor quality. Several ‘upstream’ mechanisms are in place to ensure that the medicines are in compliance with the GF policy (‘QA policy’). In addition to these existing processes, pharmacovigilance represents a ‘downstream’ (or ‘bottom-up’) process that needs to be enforced so risks linked to medicines and poor quality drugs can be identified and corrective actions taken.

It can be stressed that in addition to the ‘ethical’ risk, the fact that the GF would support the wide-scale procurement and use of medicines in countries without a functional PV system could affect the GF in term of other types of risk, such as the ‘reputational’ risk, ‘accountability’, ‘fiduciary’, and/or ‘epidemiological’ risks.

For example if an African country would widely use, thanks to GF resources, a new quality-assured pediatric formulation of an anti-malaria medicine, a functioning PV system at country level is needed to ensure that sufficient post marketing data are available in this African environment.

If no functional PV system is in place, and in case the new formulation is later found to be associated with adverse events such as adverse drug reaction or ineffectiveness of the treatment, the GF may be held responsible among different stakeholders for not supporting countries in preventing (i): ‘damage health of children’, (ii): ‘waste of public resources’, (iii): ‘creation of resistances to active pharmaceutical ingredient’...

¹⁹ GF/FAC12/15

From Round 1 to Round 9, countries applying for GF grants have not systematically included PV in their programmes, and the GF itself has not been taken a pro-active role to thoroughly enforce the implementation of PV systems: it has mainly been encouraging countries to include PV as part of their grant applications process. But even with such 'encouragement', the GF so far has not held countries responsible for implementing any PV plans, nor does it include appropriate indicators for monitoring PV inclusion in progress reports.

In addition, a certain lack of clarity existed in the GF application process, as several distinct pharmaceutical components are mixed. This may have diluted any specific activities directed towards strengthening PV.

- Specific guidance to countries to include PV in their grant applications:
 - The Round 9 guidelines²⁰ expressed that *'The Global Fund expects Principal Recipients (...) to procure products of assured quality (...) in accordance with national laws and applicable international obligations. Specific topics which are relevant to this section include the existence of well-functioning transparent procurement systems, QA systems and QC activities, intellectual property rights, supply management, and ensuring appropriate use and patient safety (pharmacovigilance system).'*
 - The specific guide on pharmaceuticals²¹ reflects the GF Board decision GF/B4/2 as indicates that it *'strongly recommends (countries) to implement mechanisms to monitor adverse drug reactions according to existing international guidelines. The cost of such activities may be included in the Global Fund grant budget.'*

- Lack of visibility and monitoring of any PV activities:
 - The official indicator depository of the GF and Partners (i.e. The M&E Toolkit) for HIV, TB, Malaria and HSS available at http://www.theglobalfund.org/en/me/guidelines_tools/?lang=en#for do not propose to countries that are running GF grants any specific indicator for PV. It only contains one indicator that reflects indirectly a certain aspect of PV, in the section Health products, vaccines and technologies (HSS-HP8): *'Percentage of health facilities that have procedures in place to report product quality issues'*.
 - A very few number of countries report on PV activities, and this is probably a consequence to the above point: a rapid review of the GF portfolio grant performance frameworks reported that out of 600 grants scanned, only 7 grants were or are reporting on PV activities (and/or management of adverse events).
It is possible than more grants are implementing PV activities than the 7 identified, but these PV would not be reported to the GF

²⁰ Guidelines for Proposals - Round 9 Call for Proposals (page 40/67),

http://www.theglobalfund.org/documents/rounds/9/CP_Pol_R9_Guidelines_Single_en.pdf

²¹ Guide to the Global Fund's Policies on Procurement and Supply Management (page 9/11)

http://www.theglobalfund.org/documents/psm/pp_guidelines_procurement_supplymanagement_en.pdf

Secretariat, and the quality and the outcomes of their PV efforts are unknown to the GF and the majority of its Partners.

- The PSM plan of the GF asked the following question to the countries: *Is there a system for monitoring adverse drug reactions and drug resistance? If yes, describe briefly how the system works. If no, describe plans to establish a system.* A first overview of different PSM plans that are available on the Country Program SharePoint indicates that there may be a certain heterogeneity in:
 - (i) Availability of PV information
 - (ii) Quality of information on PV

One could wonder who is making the optimal use of the information on PV in the PSM plan, when available. In addition, the role of the Local Fund Agent regarding PV could also be clarified and specified.

The PMAS Team in the Pharmaceutical Management Unit of the GF is in the process of strengthening the PSM plans through the 'Country Profile' initiative. These country profiles will include a strong section on PV, and synergies will be ensured between the country profile workstream and our effort dedicated to strengthening PV.

- Lack of clarity on PV, and mix with other pharmaceutical topics:
 - In their report of Round 8 proposals²², the Technical Review Panel (TRP) and the Secretariat of the GF indicate that *'there was relatively limited space provided for applicants to provide details regarding their health system strengthening request and implementation arrangements compared with the disease specific arrangements. This may have encouraged some countries to limit the scope of their description of each of the interventions that comprised their overall HSS request, or led to some level of duplication between them. For example, Cote d'Ivoire proposed three interventions under the 'Medical products and technologies' building block: capacity building of district pharmacies; pharmacovigilance; and drugs quality assurance.'*
 - We can re-iterate the fact that the PSM plan asked for the description, in the same section, of 'a' system for monitoring adverse drug reactions and drug resistance: while these two pharmaceutical sciences have some links, their *modus operandi* are very distinct and specific from the other one.
 - The same comment can be applied to the guidelines for the Affordable Medicine Facility-malaria (AMFm), as it was expected from the applicant countries to implement *'activities to ensure appropriate national drug monitoring (including pharmacovigilance, drug quality surveillance and resistance monitoring).'* Thus applicant countries must in the same section *'describe efforts to strengthen the national system of*

²² The Report of the TRP and the Secretariat on Round 8 proposals (page 59/66)
http://www.theglobalfund.org/documents/board/18/GF-B18-10_TRP_ReportToBoard_and_Annexes2-5-6.pdf

pharmacovigilance, quality surveillance and/or resistance monitoring relevant to the AMFm’.

- Additional information:
 - It is unclear within the Secretariat of the GF if the information shared on PV by the PMU team is optimally used by targeted recipients such as the Fund Portfolio Managers (who are in charge of interfacing with the countries). Maybe more specific materials, documentation, sensitization sessions on PV should be shared or performed, as it could be the case with the Technical Review Panel.
 - The promising collaboration on PV with key technical partners such as WHO needs to be specified and systematized, instead of having some joint activities implemented in an ad-hoc basis: For example, information on PV in GF grants should be transparently made available to Partners, and the GF would need to learn from its partners with field presence about the implementation status of PV in countries. The GF and WHO (and other Partners) should be able to track and report key figures such as ‘*Out of 140 countries supported by the GF, only XX (%) meet the minimum requirement on PV as defined by WHO.*’

1.6 New initiative from the GF Portfolio Implementation Committee, for R10:

In March 2010, the Portfolio Implementation Committee (PIC) of the GF tasked its sub-working group on PV, led by WHO, to incorporate PV issues in R10 proposal guidelines and form.

The Sub-Working Group (SWG) on PV was established to advise the PIC on

- 1- Incorporation of PV issues in Round 10 Proposal Guidelines and Form, and
- 2- Provide recommendation on inclusion or revision of Board decision GF/B4/2 to Committee and Secretariat.

Membership includes Private Sector, USA and WHO (lead) with support from the Secretariat.

Following guidance from the SWG, Round 10 Proposal Forms and Guidelines have been updated to give higher visibility to PV and to ensure consistency with WHO standards (<http://www.theglobalfund.org/en/applynow/>).

There is also guidance for countries to submit costed PV plans as part of the Procurement and Supply Management plans.

The Secretariat also developed a specific information note for applicants (http://www.theglobalfund.org/documents/rounds/10/R10_InfoNote_Pharma_en.pdf).

Based on recommendations from the SWG, the Secretariat will also work with partners on issuing a PV technical fact sheet for countries, informing TRP about PV and reviewing how PV can be captured in the performance framework.

Finally, the Secretariat and the PIC SWG on PV will also continue to work on strengthening the 2002 Board decision point on PV (GF/B4/2) and present recommendations to the PIC in its next meeting (October 2010).

- **Conclusion of the overview of GF approach on PV:**

Issues with the quality of medicines and adverse drug reactions are considered as a potential risk for the GF. To ensure that this potential risk is mitigated, actual PV management practices in the GF are in the process of being reviewed and strengthened as appropriate, with gaps identified and addressed. Also, partnerships on PV should be enhanced both in countries and at global level.

All PV activities should be coherently organized and implemented according to a comprehensive GF strategy on PV.

2- Overall goal of this PV initiative in general, and of this paper in particular:

The overall goal is to review GF approach on PV and to define a GF strategy on PV: the GF aims at having a sound PV strategy that would specify the positioning of the GF towards PV, a description of the roles and responsibilities of the various stakeholders involved (GF bodies, Countries, Technical Partners, Manufacturers...) and an operational plan for its implementation.

This paper describes the way toward obtaining such a GF strategy on PV, by

- a): highlighting the dichotomy between desired situation in PV management and the actual practices
- b): proposing key concepts that would lay the foundations of the future strategy
- c): proposing what would be the role of Partners in PV
- d): suggesting an operational plan for the next 2 years, to mature the GF strategy on PV

This paper will be used with Partners for inputs, and within the GF for inputs and clearance, so GF resources can be invested in this effort.

- One of the key objectives of the GF strategy on PV would be to ensure that all grants implement minimal PV requirements, as defined by the normative technical agency (WHO). Countries will need to meet these minimal PV requirements, before moving beyond to more mature PV systems.
- It is expected that countries will use the vehicle of GF resources to strengthen their existing PV systems as part of the strengthening of their comprehensive Pharmaceutical System. Efforts in PV will be designed to avoid competing with more critical priorities in the setting-up of comprehensive Pharmaceutical System. Core information about the status of each country Pharmaceutical Management system will be obtained through the Country Profiles (a joint effort between WHO, GF and Partners).
- This initiative is the opportunity for the GF to collaborate with a technical agency such as WHO to strengthen disease control and health system strengthening programmes in countries, as PV improves patients' safety and treatment programmes effectiveness. It is also an opportunity for technical agencies to review the PV tools, upgrade those and ensure the conducive processes so they can be effectively used.

- It is proposed that the future GF strategy on PV will be finalized once the first phase of this initiative would have been conducted in 10-20 countries with field lessons learnt. It will describe the 'why' and 'what' the GF and its Partners will ensure, so countries can meet these expectations. In particular, the future GF strategy will provide:
 - o A description of roles and responsibilities on PV (at country and global levels), with the description of expected tasks to be implemented and specification of required resources
 - o A clarification of GF business procedures on PV for the GF different levels and associated processes (e.g. TRP and grant application review, Secretariat and grant management...)

3- Driving principles of a GF strategy on PV²³

The GF strategy on PV and all preparatory activities on PV will be aligned with the GF mission and vision, and will respect key pillars of the GF such as 'Partnership', 'Country Ownership' and 'Performance-base funding'. It will participate in the mitigation of one of the corporate risks identified in the GF Risk Management Framework.

It will promote a transversal system strengthening approach, seeking the sustainable development of existing PV systems already in place in countries and encouraging innovative strategies. It will promote the concept of countries reaching 'minimum PV standards' as defined by WHO, before moving beyond, and countries will be offered tools and processes gathered into a user-friendly PV toolkit so they can easily implement and benefit from a functional PV system.

The rolling-out of the PV strategy will follow a phased approach, with a 18-month first phase of "proof of principle" in 10-20 invited countries that will aim at documenting cost-effective PV approaches for low and middle-income countries, reflecting on their past PV activities (what has worked, what has not worked and why?), and field testing new PV techniques.

- 3.1 The GF strategy on PV will be **aligned with the GF vision and mission**: as reported in Annex 1, the GF vision and mission stresses that the organization aims at making a sustainable and significant contribution to the reduction of infection, illness, and death, thereby mitigating the impact caused by (the 3 diseases), and contributing to poverty reduction as part of the MDG. As part of the founding principles that are guiding the GF in the conduct of its business, the GF 'supports the substantial scaling up and increased coverage of **proven and effective interventions**, which strengthen systems...'

It can be emphasized that PV, as a part of the national Pharmaceutical Management system (or national Pharmaceutical strategy), is an essential tool to reflect the effectiveness of medicine-related interventions: the GF needs to

²³ This section will be updated if other major Global Health Initiatives such as UNITAID, PEPFAR, WB...fully join the effort: if such is the case, more emphasis will be put on 3.3, 3.4, 3.5, 3.6, 3.7 and 3.8. The three first concepts would appear in another section that will be specific to the GF.

ensure that functional PV systems are in place in countries to improve medicines safety and treatment programmes effectiveness.

3.2 The GF strategy on PV will **respect GF business model**, and will be conceptualized and implemented taking into account the GF architecture: GF is a financing institution, an organization without field presence that relies on technical Partners for delivery of technical assistance, technical mentoring and stewardship. **The GF is a partnership in essence**, and the GF strategy on PV will endeavor respecting this core principle by defining clear roles and responsibilities for each core PV stakeholder, including Countries, UN agencies, Manufacturers...

Other key business processes of the GF will be reflected in the strategy, such as the respect of **country ownership** and **performance-based funding (PBF)**, with the proposition of a light but effective PV reporting framework.

3.3 As introduced in the section '**Overview of PV management within the GF**', the GF specified in its 2009 Risk management framework that that the organization faces an 'ethical' risk if medicines procured by the GF principal recipients, and delivered to patients, are of poor quality. Such strategy on PV is aiming at participate in the mitigation of one of the corporate risks.

3.4 **Transversal approach:** the GF PV strategy will directly consider the 3 diseases in an integrated manner when relevant. It will have a generic section applicable to each of the 3 diseases, followed by specific tools addressing the specificities of each diseases (e.g. longitudinal medical records for patients on ART represent a source of information for ADR that is usually not available for malaria patients, health facilities to recruit patients treated for malaria and tuberculosis may be different...)

3.5 The GF strategy on PV will be based on a **health system strengthening approach:**

- It will consider PV as **part of the comprehensive pharmaceutical management system** and the treatment programmes, not as a stand alone project. It will respect the interrelations between PV and the other components of the pharmaceutical management system, as well as the potential need to temporally prioritize other components of such global system over PV activities.
- It will aim at strengthening local existing systems to meet WHO minimum standards on PV; as much as possible, all activities on PV will also use pre-existing systems and tools, preferentially **using existing systems and information** ('secondary data' such as IMAI records and ART cohorts) over initiating new data collection mechanisms.
- It will seek to ensure **self sustainable PV systems**, defining, testing and promoting PV approaches that could be used by countries themselves without external support, once the PV system has reached a sufficient level of maturity.
- Even if the GF will base its approach of ensuring that countries receiving GF resources shall implement the minimum PV standards recommended by WHO (see 'stepwise approach below'), the GF PV strategy will recognize that **flexibility for PV activities** is required based on particular in-country and disease related situations, capacities and priorities. Specific approaches

reflecting needs of countries will be developed, e.g. "enhanced spontaneous reporting" with patient cards to record treatment exposure in the private sector will be proposed for countries participating to the Phase I of the Affordable Medicine Facility for malaria (AMFm).

3.6 'Stepwise approach': the GF strategy on PV will be based on the concept of 'minimum standards (requirements) for PV' that each country receiving GF grants shall implement in a sustainable manner (before eventually moving beyond).

- The first level, that would be mandatory to attain, will reflect '**minimum PV requirements**²⁴' ('functional PV systems'), as recommended by WHO following a consultation to be held with in-country PV experts (Jan 2010).
- Upper levels refer to more mature status of the national PV system that would come with the implementation of more sophisticated approaches (e.g. cohort event monitoring, registers for adverse events in pregnancy, longitudinal data sets such as patient records that complement current methodologies, risk-management plans, ...) and tools (e.g. advanced data mining tools to enable better and broader use of adverse events data thereby promoting a more evidence-based approach to policy making and treatment guidelines).

3.7 Building on existing efforts, and seeking country friendliness:

- WHO will build on its experience as a normative and technical agency. With the GF, it will ensure interactive relationships between stakeholders involved in PV, including the countries as main beneficiaries. WHO with Partners will optimize existing PV tools and processes, to be reviewed and strengthened as needed: a specific workstream will be ensured to analyze the reasons why basic PV activities such as spontaneous reporting are functioning poorly in countries, even if resources are available.
- In order to define the best PV approaches, the GF with technical guidance from WHO will analyze what has been working, what has not been working and why in countries with on-going PV activities. We will thus learn from the past to define PV best practices. To complement this effort, WHO will also define innovative PV approaches, to be tested by volunteer countries during an 18-month period.
- WHO will compile the PV tools and processes into one **PV toolkit** for easy usage from Countries: it will consist in a package of simple PV tools and description of supporting processes (including the requirements of a functioning PV system, the required PV tools such as PV cards, a generic PV system strengthening workshop to be held at country level to identify and analyze gaps to be filled, to define an action plan with clear accountability framework...). This 'PV package' will be offered to countries to adapt to their specific requirements so they can take ownership and make it operational. The toolkit will have a specific section for the GF as it will propose processes and resources so PV can be effectively implemented in GF grants (including role and responsibilities of key GF bodies and functions such as the technical review panel -TRP-, the country coordinating mechanisms -CCM-, local fund agents -LFA-, GF Secretariat...).

²⁴ To be defined by WHO in 2009, in consultation with in-country experts (from NDRA...)

3.8 The strategy will be operationalized following a **phased approach**: Preparation phase, Phase 1 and then Roll-out phase (see 'Operational Plan' in section 6 below).

4- Partnerships **COMMENT SX: this needs to be updated w UNITAID and WB positioning**

The GF, as an organization with the mission 'to attract, manage and disburse additional resources through a new public/private partnership' (hereby a 'financing entity'), is relying on a variety of Partners to successfully develop, implement and mature its strategy on PV.

Country representatives (National Drug Regulation Authorities, National PV Centers, the National programmes to fight HIV/AIDS, TB and malaria), and technical partners such as WHO are fundamental in the process in order to ensure key tasks such as the definition of minimum standards for PV (normative role) and delivering technical support (setting up the PV toolkit and delivering in-country technical assistance-TA).

Other technical agencies would be invited to participate in the effort by delivering effective TA for participating countries, including mentoring/twinning activities.

Other financing entities may join the initiative, providing strong strategical inputs and even expending this effort to their portfolio thanks to additional resources.

Private manufacturers' inputs will be actively sought, especially in relation to data collection tools and validation: their role will be jointly defined with all other parties taking into account 1- the need to build regulatory capacities in countries so the manufacturers can meet their PV obligations 2- the management of the conflict of interest of the pharmaceutical sector when reporting drug safety information.

This initiative will benefit from the expertise of PV stakeholders, gathered into a technical advisory group.

In general, this GF strategy on PV will be co-developed by the GF and WHO with strong inputs from the Countries and other Partners, each stakeholder taking advantage of the other's skills.

The GF will propose to other Global Health Initiatives (GHI) to join and co-own this initiative, so it could become a GHI strategy on PV. If such is the case, this paper will be updated to reflect this partnership and enhanced collaboration on PV.

In addition, other organizations' inputs will be sought to define and mature the plan, with some organization joining this initiative for delivering certain goods and/or services. For example, certain organizations may be interested to support some specific tasks and to directly fund certain activities such as the PV workshop for Phase 1 countries (June 2010). The GF will actively seek to define a strong partnership with UNITAID that has highlighted PV as one of its key strategic topic for the years to come.

Some Partners (such as the WB, PEPFAR) may even be interested in supporting additional countries to participate in Phase 1. The European Union expressed its interest in supporting PV and is already engaged in some joint activities with WHO, and we will build on this promising alliance.

The Gates foundations may decide to join this initiative, as synergies could be defined and relevant joint actions taken.

The GF Secretariat will also look for defining joint activities with partners such as MMV, that has a privileged role of interfacing with the manufacturers.

The manufacturers will be engaged so they can contribute in this effort and participate in it, understanding that the GF and its Partners will work at building the regulatory capacities in countries to enable the manufacturers to meet their PV obligations (may these be post marketing studies, control trials...). The strategy will consider and mitigate the risk of conflict of interest of all parties.

Finally, additional technical Partners will be invited to participate in the initiative.

The following table illustrates what could be the role of different potential Partners during this project, understanding that a mapping of Partners and of their interest will be obtained during the preparation phase.

Partner	Category	Example of core activities
Countries	Drug regulatory authorities, Policy makers and Implementers	To provide inputs in strategy, to review proposed tools and processes, to implement Phase 1, to share lessons learned...
Patients and clients alliances	Main beneficiaries	To participate in selected PV activities
The GF	Financing entity	To co-define with WHO the strategy, to stimulate the partnership on PV, to fund the 'situation analysis', to facilitate dissemination of PV guidelines, to sponsor in-country PV activities within the major GF supported programmes...
WHO	Normative and lead technical agency	To define the minimum PV requirements with Partners (esp. countries), to define the PV toolkit, to coordinate technical support to 10-20 countries...
Green Light Committee	Technical agency	To participate in the definition of norms, to deliver technical assistance...
UNITAID	Financing entity	To review proposed concept note, proposing upgrades, and join the effort (co-funding some specific activities) as a joint WHO/GF/UNITAID initiative
PEPFAR	Financing entity	To review proposed concept note, proposing upgrades, and join the effort (co-funding activities) as a joint WHO/GF/UNITAID/PEPFAR initiative, including additional PEPFAR supported countries in Phase 1 To facilitate the delivery of technical assistance by its implementing partners...

Partner	Category	Example of core activities
Gates Foundation	Financing entity	To join the initiative, ensuring advocacy at high level and to potentially sponsor some global level activities
The WB	Financing entity	To review proposed concept note, proposing upgrades, and join the effort (co-funding activities) as a joint WHO/GF/UNITAID/PEPFAR/WB initiative, including additional WB-supported countries in Phase 1 To use its advocacy power and bring the debate at the highest level, to facilitate delivery of technical assistance, to perform fund leveraging....
EU	Financing entity	To review proposed concept note, proposing upgrades, and fund additional global activities (regional CEM...) To facilitate delivery of technical assistance
MMV	Technical agency interfacing with academic institutions and pharmaceutical companies	To facilitate the setting-up of active surveillance processes (e.g. CEM) in some countries in collaboration with Manufacturers
GAVI	Financing entity (sister organization to the GF)	GAVI is already engaged in PV: GF could learn from GAVI experience in PV, and the two organizations could in general synergize their PV activities
AFSSAPS	Technical agency	To accompany (mentoring) selected francophone countries as part of Phase 1
CHAI	Technical agency interfacing with different stakeholders	To fund and/or co-organize and/or participate in regional workshops for phase 1 countries
MSF	Technical agency, with financing and direct implementation activities	To review proposed concept note, proposing upgrades; to provide specific support to some countries...
MSH (under USAID/SPS program)	Technical agency	To accompany (mentoring) selected English-speaking countries as part of Phase 1 To propose (and potentially, to test) innovative methods of notification To share its PV tools, to co-sponsor/co-organize the PV stakeholder workshop...
Universities and scientists	Technical experts and organizations	To accompany (mentoring) selected countries as part of Phase 1
Manufacturers	Funder, Technical support	To provide inputs in strategy, to review proposed tools and processes, to provide financial and/or technical resources and/or technical advice to conduct special activities (roll-out of risk management plan in few selected countries)

Technical expertise:

The GF and WHO will build on the Advisory Committee on Safety of Medicinal Products (ACSoMP) to obtain sound technical advice and expertise on PV.

Management of the project:

The GF and WHO are setting up a core **steering group** with clear terms of reference, to manage the project. In addition to the two organizations, representative of other GHI willing to join the initiative will be invited (e.g. UNITAID, WB...).

5- Proposed Operational plan

The strategy will be defined and operationalized following a **phased approach**:

A- The **preparation phase** (2009 until Oct 2010) will aim at defining the overall concept of this initiative and preparing tools and processes for launching Phase 1. The key deliverables expected during this phase are: draft GF strategy on PV (with inputs from Partners), PV minimum requirements, PV toolkit, Situation Analysis, PV plans for Phase 1 countries.

B- **Phase 1** (from Oct 2010 to June 2012) will implement the draft strategy on PV, using different approached in 10-20 countries. The key deliverables expected during this phase are: strengthened PV systems in 10-20 countries; analysis of the different approaches that were used to support countries in strengthening their PV systems; guidelines to the GF; guidelines to countries, and as the key deliverable based on lessons learned during Phase 1: the GF strategy on PV, to be shared with the Board in Nov 2012.

C- **The roll-out phase** (from 2013 and onward) will aim at implementing on a wide scale (i.e. across the whole GF portfolio) the GF strategy on PV. The key deliverables expected during this phase are: rooted within all GF grants, plans to strengthened PV systems in all countries, to meet as a minimum WHO requirements on PV.

A Gantt-Chart proposes a graphical overview of this initiative, with key milestones (Annex 2).

5.1 Preparation phase (2009 until Oct 2010): GF and Partners will mature the PV concept for GF, countries and Partners, including the supportive tools and processes.

In particular, the GF and WHO will run between Dec 2009 – June 2010 a **'Situation analysis study'**²⁵ to

- I. To review and analysis of GF portfolio to assess the status of PV in GF grants (R4 to R9): the aim is to categorize the different countries receiving GF resources in term of pharmacovigilance status, in regards to the HS and public health programmes (HIV, TB, Malaria) and answer the question: *out of 140 countries supported by the GF, how many meet the minimum requirement on pharmacovigilance as defined by WHO?*
- II. To map-out pharmacovigilance tools, methodologies and supporting processes; to propose any relevant update of these
- III. To propose the structure and content of the 'pharmacovigilance toolkit', in close collaboration with WHO: the toolkit is expected to be a set of

²⁵ See Annex 3 for more details

tools (e.g. standard form for passive surveillance, communication flowchart, standard protocol for cohort event monitoring, standard course in pharmacovigilance...) and supporting processes with description of required resources (e.g. resources for implementing pharmacovigilance activities, list of technical assistance providers in pharmacovigilance, description of required activities so pharmacovigilance would be included and implemented in GF grants...). The main target audience of the toolkit will be the countries. The toolkit shall also come with an identification of the level of capacity required for implementing these tools and methods

- IV. To propose a list of eligible countries to be accompanied in 2010-2011 (Phase 1 of the pharmacovigilance project) to be based on well defined and agreed upon selection criteria)
- V. In collaboration with the GF and WHO, map-out Partners (including manufacturers). Identify their expectations, respective skills, capacity, comparative advantages and resources to be dedicated to such project

This situation analysis will issue recommendations to ensure the success of phase 1.

The **operational plan** will be the following, for the **preparation phase**:

- Sept-Nov 2009: GF and WHO will draft a concept of a global PV strategy for the GF
 - Definition of this concept note on PV (GF and WHO²⁶)
 - Initiation by WHO of the specification of the 'minimum standards for PV', and setting up a consultation with countries as needed using GF resources
 - WHO will seek for consultants to ensure the situation analysis; GF will make resources available and manage these consultants
- From Nov 2009: initiation of the interaction with key Partners with interest in joint PV activities (among which the Countries, World Bank, PEPFAR, UNITAID, the EU, AFSSAPS, CHAI...); GF will share this concept note for inputs
- Nov 2009: Setting-up of the Steering Group
- Jan 2010: Workshop with countries experts to define minimum PV requirements
- Dec 2009 – June 2010: Situation analysis study run by the consultants managed by WHO and sponsored by the GF (see summary above and details in Annex 3)
- September 2010: Based on outcome of situation analysis study: workshop probably organized by the GF and hosted by WHO, gathering key Partners to refine the setting-up of partnerships, tools, and supporting processes before the launching of Phase 1. The major outcome of this workshop will be a **draft strategy on PV** to be issued from this concept note and taking into consideration the situation analysis and comments from Partners
- From July 2010: Sensitization/Capacity building on PV

²⁶ Focal points are:

WHO-EMP: Shanthi PAL (coordinating WHO inputs, -Mary COUPER has retired in Dec09); WHO-Malaria -TBD;
 WHO-HIV: Chris DUNCOMBE (Micheline DIEPART has retired in March10); WHO-TB: Dennis FALZON.
 The Global Fund: Serge XUEREF.

- At country level: sensitization from Partners (such as WHO and the WB) directed at the countries invited to participate in Phase 1
- Within GF (responsibility of the GF): capacity building especially targeted towards the FPM in charge of the proposed countries; review of grant budgets to review amount of resources available for PV and/or to define potential additional sources of resources
- Nov-Dec 2010: PV Workshop with proposed Phase 1 countries (to be supported by Partners with focus on PV such as UNITAID and/or CHAI?)
 - Overall goal will be to clarify the initiative for the countries, seeking their approval for participating in Phase 1, and define subsequent PV plan of action
- Nov - Dec 2010: Finalization of PV plans by countries and launching of activities, including PV strengthening workshops at country level

5.2 Phase 1 (from October 2010 to June 2012): GF and Partners will work with (10-20) invited countries to review lessons from the past, to test the defined approach and implement PV plans using PV toolkit. Lessons about the first wave will be identified between July and Oct 2012.

A strong link will be ensured with the AMFm: some AMFm eligible would be part of Phase 1, and lessons learned will be drawn from the 8 countries participating in the AMFm (specifically for ACTs).

The **expected outcomes of phase 1** will be:

- a. **Strengthened PV systems** in the participating countries, with concrete evidence of progresses towards patient safety and value for money of GF investments. Success stories on update of treatment guidelines and/or treatment practices and health service quality, optimal use of PV to highlight resistance, counterfeiting...
- b. **Analysis of the different approaches that were used** to support countries in strengthening their PV systems. Lessons will be learned
 1. From the past (i.e. before 2010): what has been working and what has not been working, and why?
 2. From Phase 1, with an analysis of the effectiveness of the PV toolkit and innovative PV techniques.

Inclusion of special studies could be considered, including operational research to assess the value of different approaches;

- c. **Guidelines to the GF** (Board, relevant Committees, TRP, Secretariat, LFA...) to ensure that PV is included in grant proposal, successfully implemented at country level and adequately managed by the Secretariat (through a light reporting mechanism);
- d. **Guidelines to countries** (CCM, PR, Governments, NDA...) so they can design and implement PV system (including operational package with description of tools and processes, with governance structures...)

Then, as the **major outcome of Phase 1, the final GF strategy on PV** will be defined and proposed to the Board for approval in November 2012.

5.3 Roll-out phase: From 2013, it is expected that the GF and Partners will implement on a wide scale (i.e. across the whole GF portfolio) the GF strategy on PV.

According to the operational plan that would accompany such final GF strategy on PV, it is foreseen that the PV toolkit will be proposed to **all** countries applying for subsequent rounds (and maybe to those that are still on-going²⁷):

The key deliverables expected during this roll-out phase would be:

- Rooted within all GF grants, plans to strengthened PV systems in all countries, to meet WHO minimal requirements on PV
- As a consequence, **strengthened PV systems** in countries, with concrete evidence of progresses towards patient safety and value for money of GF investments. Success stories on update of treatment guidelines and/or treatment practices and health service quality, optimal use of PV to prevent resistance, to participate in the assurance of use of quality medicines....

6- Monitoring and Evaluation (M&E)

The whole project shall be monitored and evaluated with a well pre-defined simple and effective **M&E plan**. Such plan will be defined once this concept note would have been cleared by GF management.

Still, the following information can be shared:

The M&E plan will consist in two interrelated pieces:

(i): Each Phase (especially phase 1 and roll-out phase) will be **monitored though specific indicators**. As much as possible, each indicator will be precisely defined, according to the information provided in the following table:

Name	Rational	Definition of indicator			Measurement			Baseline	Targets	
		Numerator	Denominator	Disaggregation	Source	Frequency	Responsibility			

The quality of each indicator will be assured by defined data quality mechanisms.

(ii): Phase 1 and roll-out phase will also be evaluated according to a simple but effective **evaluation plan**. The evaluation plan will be based on evaluation questions that will query whether the initiative met its objectives. To answer the evaluation questions, information will be obtained through the indicators, complemented with additional data (from special reviews....), using quantitative and/or qualitative information, so the major output/outcome/impact of each phase can be precisely assessed when confronted to its objectives.

7- Budget

A detailed **operational budget** will also be specified, once this concept note would have been cleared by GF management.

²⁷ To be defined in the final strategy

Still, the following considerations can already be expressed:

- In general, and as for any initiative, GF resources are the ones that are channeled and available through the country grants: the support of implementation of PV activities at country level will be ensured by technical Partners, as requested (and funded) by GF Principal Recipients (PR) using in-country GF resources.
- Still, the GF would be able to engage few additional resources for few specific activities (such as the situation analysis). But it is expected that the required additional resources for international workshops, regional TA...will be obtained from other sources (potentially: UNITAID and/or CHAI for a workshop on PV, EU, GAVI...). The GF commits to work with WHO at engaging these other Partners (see section 'Partnerships')
- For each Phase, a specific budget will be defined, with a clear definition of the source of funding
- For the Preparatory phase, country grants resources will not be leveraged, and the required resources will come from the global level. The GF will support the cost linked to the situation analysis and the March 2010 workshop. Additional source of funding (from Partners) need to be found for the May-June 2010 workshop with countries.
An illustrative summary table can be shared and will be refined, once this concept note is approved.

Phase	Activity	Main responsible	Timeframe	Expected Costs (USD)	Source of funding
Preparatory phase	Initial agreement on the concept	GF/WHO	Sept-Nov09	Staff	/
	Situation analysis	WHO/GF	Dec09-June10	75,000	GF
	Consultation with Partners	GF/WHO with Consultants	From Nov 09	Staff	/
	Consultation with stakeholders (esp. countries) to define PV minimum requirements	WHO	Jan 10	75,000	GF
	PV stakeholder workshop	GF/WHO/UNITAID?	September 10	150,000	GF
	Sensitization at country level	WHO	July-Oct10	Staff	/
	Sensitization at GF level	GF	Sept-Oct10	Staff	/
	Regional workshop(s) with countries	Volunteer Partners and WHO/GF	Oct10	200,000	volunteer Partner(s): UNITAID? CHAI?

	In-country assessment workshops	PV	WHO with technical Partners and GF	Oct-Nov10	20 countries x 15,000 = 300,000	GF grant + other sources
	Participation meetings, conferences (IAS...)	in	GF, WHO, Technical Partners	All along the project	TBD	Part of agency operational budget
Phase 1	Technical assistance		WHO with technical Partners	Oct10-June12	As appropriate	GF grant + other sources
	Regional workshop?					

ANNEX 1: GF vision, mission and founding principles

The GF vision is to “make a sustainable and significant contribution to the reduction of infection, illness, and death, thereby mitigating the impact caused by HIV/AIDS, tuberculosis and malaria in countries in need, and contributing to poverty reduction as part of the Millennium Development Goals”.

The GF mission is “to attract, manage, and disburse additional resources,” and its means, “through a new public-private partnership.”

The founding principles (below) are guiding the GF in the conduct of its business.

Founding Principles of the Global Fund (Global Fund Framework Document)

- A** The Global Fund is a financial instrument, not an implementing agency.
- B** The Global Fund will make available and leverage additional financial resources to combat HIV/AIDS, Tuberculosis and Malaria.
- C** The Global Fund will base its work on programs that reflect national ownership and respect country-led formulation and implementation processes.
- D** The Global Fund will seek to operate in a balanced manner in terms of different regions, diseases, and interventions.
- E** The Global Fund will pursue an integrated and balanced approach covering prevention, treatment, and care and support in dealing with the three diseases.
- F** The Global Fund will evaluate proposals through independent review processes based on the most appropriate scientific and technical standards that take into account local realities and priorities.
- G** The Global Fund will seek to establish a simplified, rapid, innovative process with efficient and effective disbursement mechanisms, minimizing transaction costs and operating in a transparent and accountable manner based on clearly defined responsibilities. The Global Fund should make use of existing international mechanisms and health plans.
- H** In making its funding decisions, The Global Fund will support proposals which:
- Focus on best practices by funding interventions that work and can be scaled up to reach people affected by HIV/AIDS, tuberculosis, and malaria.
 - Strengthen and reflect high-level, sustained political involvement and commitment in making allocations of its resources.
 - Support the substantial scaling up and increased coverage of proven and effective interventions, which strengthen systems for working: within the health sector; across government departments; and with communities.
 - Build on, complement, and coordinate with existing regional and national programs (including governments, public/private partnerships, NGOs, and civil society initiatives) in support of national policies, priorities and partnerships, including Poverty Reduction Strategies and sector-wide approaches.
 - Focus on performance by linking resources to the achievement of clear, measurable and sustainable results.
 - Focus on the creation, development and expansion of government/private/NGO partnerships.
 - Strengthen the participation of communities and people, particularly those infected and directly affected by the three diseases, in the development of proposals.
 - Are consistent with international law and agreements, respect intellectual property rights, such as TRIPS, and encourage efforts to make quality drugs and products available at the lowest possible prices to those in need.
 - Give due priority to the most affected countries and communities, and to those countries most at risk.
 - Aim to eliminate stigmatization of and discrimination against those infected and affected by HIV/AIDS, especially for women, children and vulnerable groups.

ANNEX 3: Terms of Reference, Situation Analysis

The Global Fund Secretariat requests technical assistance from the World Health Organization (WHO) to provide guidance and assistance on the design of its strategy on pharmacovigilance.

Objective:

The objective of the agreement is to ensure sufficient technical support is provided for the design of the Global Fund strategy on pharmacovigilance.

Activities:

To achieve the objective of this agreement, a situation analysis will be undertaken by the QSM/WHO team:

The overall goal of the situation analysis is to prepare tools, processes and perform activities to ensure the success of phase 1 as documented in the document 'Towards a strategy on pharmacovigilance': an inception report will be shared in 2009 and the final report of this situation analysis by end of February 2010.

The specific objectives of this situation analysis are:

- To review and analysis of GF portfolio to assess the status of PV in GF grants (R4 to R9): the aim is to categorize the different countries receiving GF resources in term of pharmacovigilance status, in regards to the HS and public health programmes (HIV, TB, Malaria) and answer the question: *out of 140 countries supported by the GF, how many meet the minimum requirement on pharmacovigilance as defined by WHO?*
- To map-out pharmacovigilance tools, methodologies and supporting processes; propose any relevant update of these
- To propose the structure and content of the 'pharmacovigilance toolkit', in close collaboration with WHO: the toolkit is expected to be a set of tools (e.g. standard form for passive surveillance, communication flowchart, standard protocol for cohort event monitoring, standard course in pharmacovigilance...) and supporting processes with description of required resources (e.g. resources for implementing pharmacovigilance activities, list of technical assistance providers in pharmacovigilance, description of required activities so pharmacovigilance would be included and implemented in GF grants...). The main target audience of the toolkit will be the countries. The toolkit shall also come with an identification of the level of capacity required for implementing these tools and methods
- To propose a list of eligible countries to be accompanied in 2010-2011 (Phase 1 of the pharmacovigilance project) to be based on well defined and agreed upon selection criteria)
- In collaboration with the GF and WHO, map-out Partners (including manufacturers). Identify their expectations, respective skills, capacity, comparative advantages and resources to be dedicated to such project

Two consultants to be hired by WHO will be required to perform this work, to start no later than 1st December 2009.

Deliverables:

2009:

Inception report, including:

- 1- a sound description of activities to be ensured to fulfill the five parts of the situation analysis;
- 2- identification of key potential bottlenecks in the project and WHO-proposed options to overcome them;
- 3- curriculum vitae of consultants, detailed workplan for consultants;
- 4- initial report on Analysis of GF portfolio on pharmacovigilance;
- 5- proposed criteria for the selection of countries to be accompanied in Phase 1 of the pharmacovigilance project;
- 6- proposed structure of the pharmacovigilance toolkit;
- 7- proposed list of Partners in pharmacovigilance to be interviewed and initial report of completed interviews.

2010:

Final report, comprised of five sub-deliverables:

- 1- Analysis of GF portfolio on pharmacovigilance;
- 2- mapping-out of pharmacovigilance tools, methodologies and supporting processes with propositions for any relevant update of these;
- 3- the pharmacovigilance toolkit;
- 4- list of eligible countries to be accompanied in Phase 1 of the pharmacovigilance project;
- 5- mapping-out of Partners in pharmacovigilance.

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