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The Global Vaccine Safety Initiative

Aligning forces to strengthen vaccine pharmacovigilance systems in low and medium income countries

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THE GLOBAL VACCINE SAFETY INITIATIVE

ALIGNING FORCES TO STRENGTHEN VACCINE PHARMACOVIGILANCE SYSTEMS IN LOW AND MEDIUM INCOME COUNTRIES

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Abstract

The Global Vaccine Safety Initiative (GVSI) was launched under the auspices of the World Health Organization in March 2012. It is based on the Global Vaccine Safety Blueprint, the safety strategy of the Global Vaccine Safety Action Plan (GVAP). The GVSI vision is to establish effective vaccine pharmacovigilance systems in all countries by 2020. It focuses on improving monitoring and response to vaccine safety concerns in low- and middle-income countries.

The work of the GVSI is attracting an increasing number of countries and organizations involved in drug and vaccine safety monitoring and research. This has led to the rapid development of the GVSI work plan. Its implementation is calling for clear delineation of work processes and rules of engagement. This article describes the operational structure of the GVSI with focus on its steering group (the Planning Group), its portfolio of activities (the GVSI Portfolio) and how stakeholders can be involved.

BACKGROUND

The Global Vaccine Safety Initiative (GVSI) addresses the need of building capacity for better monitoring and response to vaccine safety concerns in low- and middle-income countries (LMIC). While many technical solutions for enhancing vaccine pharmacovigilance are available, the awareness and use of those established solutions as well as solutions enhancing international, regional, and global interaction remain limited in many parts of the world.

GVSI participants work together to support LMIC in improving current vaccine safety monitoring. The strategic plan of the GVSI is the Global Vaccine Safety Blueprint, a document that was developed by the World Health Organization (WHO) together with technical consultants (Collaborative Group)[i] . The Blueprint is rooted in a detailed landscape analysis and surveys of various stakeholders including experts in vaccine pharmacovigilance coming from public health organizations, regulatory agencies, professional organizations, patient care, and vaccine manufacturers[ii]. The Blueprint vision was endorsed by the WHO's Strategic Advisory Group of Experts (SAGE)[iii] at its November 2011 meeting[iv]. The Blueprint was subsequently identified as the vaccine safety strategy of the Global Vaccine Action Plan (GVAP)[v]. The vision and mission were previously described in detail[vi]. In brief, the mission of the Blueprint is to optimize the safety of vaccines through effective use of pharmacovigilance principles and methods. The three strategic goals are: first, to assist low and middle income countries (LMIC) to have at least minimal capacity for vaccine safety activities; second, to enhance capacity for vaccine safety assessment in countries that introduce newly-developed vaccines, that introduce vaccines in settings with novel characteristics, or that both manufacture and use prequalified vaccines; and third, to establish a global vaccine safety support structure.

The Blueprint proposes eight complementary strategic objectives. Four of these aim to improve the technical aspects of spontaneous reporting, active surveillance, risk communication, and

harmonized methods and tools. These are complemented by four objectives promoting establishment of effective managerial principles to facilitate international collaboration and information exchange. Capacity building through national development planning and access to external support when required are broadly recognized approaches. They need to be further developed to ensure that the use of effective vaccines is accompanied by adequate safety monitoring everywhere. Implementing the Blueprint is a task that requires coordinated participation of vaccine safety stakeholders worldwide. To that effect, the WHO launched the Global Vaccine Safety Initiative (GVSI). In this paper, we describe the operational structure of the GVSI and how different groups of participants may interact to achieve the vision of establishing effective vaccine pharmacovigilance systems in all countries by 2020.

OPERATIONAL STRUCTURE AND PROCESSES OF THE GVSI

The GVSI is neither a legal entity, nor a partnership[vii]. It is a WHO mechanism for enhancing vaccine safety by providing a framework for WHO to convene its member states and partners for the implementation of the Global Vaccine Safety Blueprint. As a forum for collaboration between vaccine safety stakeholders, it highlights existing tools and resources, creates synergies, and prevents duplication of efforts and wasted resources towards the achievement of its mission. The work of the GVSI is supported by the WHO GVSI Secretariat.

Participants in the GVSI

GVSI participants include: governmental institutions (in particular immunization programmes, pharmacovigilance centers and agencies involved in regulatory activities); intergovernmental organizations (including World Health Organization), international non-governmental organizations and academic institutions; international industry associations/umbrella organizations that have a demonstrated interest and experience; and WHO Collaborating Centers. In addition,

observers such as organizations, agencies or institutions who do not meet the criteria for participation, but are involved in activities which are relevant to all or part of the mandate of the GVSI, may be invited to attend all or certain designated meetings of the Initiative. Organizations interested in participating are invited to submit an application to the WHO Secretariat. All applications are reviewed with WHO's GVSI advisory body, the GVSI Planning Group. Participating organizations accede to the GVSI network by agreeing to the GVSI terms of reference[vii].

At the strategic level, a Planning Group that includes 5 to 9 external experts complementing WHO staff from headquarters and the six regional offices is appointed. The chair of the Planning Group is designated by WHO from among the external experts. External experts participate in their individual capacity. Their institutional background serves relating the GVSI work to the actual needs of LMIC for improved vaccine pharmacovigilance. All members sign a confidentiality agreement in order to protect proprietary or otherwise confidential information of WHO, its member states, and all other GVSI participants. Each member also provides individual disclosure of interest. The Planning Group operates by consensus. Currently, it meets regularly through telephone conferences and twice a year, through a mid-term retreat and on the occasion of the annual GVSI Meeting. The Planning Group provides overall direction for the Initiative. Its main tasks include: providing suggestions and advice on the implementation of the Blueprint, guidance on the work of the Initiative, and input on the Initiative's strategic and financing plans. It also oversees the review of the main strategic products, the Initiative's work plan and budget, activity reports and other outputs of the Initiative. Further, it reviews applications for participation in the GVSI and advises WHO accordingly.

At the operational level, activities and resources are coordinated by the WHO GVSI Secretariat to facilitate project-based collaborations. The core management tool is the GVSI portfolio. It is a dynamic listing, characterization and classification of activities proposed by GVSI participants and identified as priorities by the Planning Group for implementing the Blueprint. Each activity is listed with a summary of its purpose, relevance, description of work, deliverables, indicators for progress

monitoring, budget, and level of priority (Table 1). Prioritization is based on the criteria listed in Table 2 and specifies priority 1 for key activities for which funding is immediately needed, priority 2 for important activities for which funding is recommended, and priority 3 for desirable activities that should be part of a full GSVI work plan (Figure 1).

Activities submitted to the portfolio are not necessarily WHO activities but rather those that have been identified by the Planning Group as valuable contributions towards the shared mission of the Blueprint. Submission of activities to the GVSI portfolio is primarily for information purposes to assist WHO in coordinating global activities. WHO is neither responsible nor accountable for activities implemented by GVSI participants outside specific project agreements. WHO aims at bringing together donors and participants and coordinates interaction between them.

The current edition of the GVSI portfolio includes activities prioritized by the GVSI Planning Group in November 2013, some of which are expected to extend up to 2020 in line with the duration of the Decade of Vaccine and its strategic Plan, the Global Vaccine Action Plan endorsed by the World Health Assembly[v]. A public version of the portfolio, reviewed at each Planning Group face-to-face meeting is available on the GVSI website[viii].

FUNDING OF GVSI ACTIVITIES

The GVSI is not a funding entity. According to its terms of reference, each participant and observer is responsible for meeting its own expenses in relation to the GVSI. On the basis of the portfolio of activities, WHO actively raises funds from other sources to support the work of the GVSI, in accordance with WHO's established rules, policies, administrative practices and financial rules and regulations[ix]. These financial contributions are also administered in accordance with the aforesaid financial rules and regulations, and administrative procedures and practices. Subject to the availability of funds, the GVSI Secretariat may, in consultation and agreement with the GVSI Chairperson, decide to support

the participation of representatives from certain developing country organizations, agencies and institutions. The secretarial support and related day-to-day operation of the GVSI is financed by grants to WHO for the implementation of the Blueprint and voluntary contributions from each participant. WHO provides the participating organizations, agencies and institutions with an annual financial report, including information on contributions received to support the GVSI Secretariat and related day-to-day operation of the GVSI, explaining how these funds have been used.

While WHO actively raises funds for its part of GVSI activities, participants are encouraged to conduct their own fund raising. Through the portfolio coordination mechanisms, efforts are made to ensure that there is little or no competition among participants during fund raising and that opportunities for collaborations on relevant projects are identified as early as possible. As ex-officio member of the GVSI, WHO readily advocates for financial support of all activities prioritized through the portfolio. For participant's individual funding efforts this provides added value of having projects listed in the portfolio.

INTELLECTUAL PROPERTY OF PARTICIPANTS

The WHO GVSI Secretariat is responsible for protecting the intellectual property of each GVSI participant. This is accomplished through registration of GVSI participants, acknowledgement of existing infrastructures, resources, expertise or IP utilized for GVSI activities, protection of proposal content submitted to the GVSI, and definition of author, copy and use rights related to outputs generated as part of the GVSI. In addition, acknowledgement of authors, donors and other contributors is given for all submissions to the GVSI portfolio. The confidentiality agreement of Planning Group members specifically aims to protect participants not currently in the Planning Group.

CONFLICTS OF INTEREST

Each contributor to the GVSI faces potential conflicts of interest that reflect their own stakes in the success of effective vaccine safety work. There is only a limited number of vaccine safety experts globally. As a result, participants provide expertise to several groups of stakeholders at the same time and also compete for limited funding in order to support their activities. This can be a source of actual, potential or perceived conflict of interest.

To address this, the Initiative adheres to a strict conflict of interest policy consistent with current WHO practices, using a declaration of interest form that is required for every expert that serves in an advisory role to the organization[x]. All experts serving in an advisory role must disclose any circumstances that could represent a potential or actual conflict of interest (i.e., any interest that may affect, or may reasonably be perceived to affect, the expert's objectivity and independence). This includes all GVSI participants and consultants and specifically the members of the Planning Group and participants in strategic GVSI meetings. The Secretariat is responsible for reviewing each declaration of interest to determine whether there is a conflict of interest relevant for the GVSI. It does, in particular take into account the circumstances such as nature and magnitude of the interest, timeframe and duration of the interest. Based on those elements, the Secretariat may conclude that no potential conflict exists or that the interest is irrelevant or insignificant. In the case that a declared interest is determined to be potentially or clearly significant, various measures may be applied from allowing full participation, with public disclosure of the interest, mandating partial exclusion (i.e. from that portion of the meeting or work related to the declared interest and from the corresponding decision making process), or mandating total exclusion. All potentially significant interests are disclosed to the other participants at the start of each project or meeting. A summary of all declarations and actions taken to manage any declared interests

are published in all resulting reports and work products.

Furthermore, if the objectivity of the work or meeting in which a participant has been involved is subsequently questioned, the contents of their declarations is confidential but the Secretariat must make public disclosure of that interest to meeting participants as well as in the final report, relevant publication or work product emanating from such meeting or activity. In discussions related to the prioritization of GVSI Portfolio activities, Planning Group members recuse themselves from discussions that relate to proposals originating from institutions or organizations that they are affiliated with. Likewise WHO Secretariat members recuse themselves from decisions related to activities led by WHO headquarters or regional offices.

PUBLIC-PRIVATE INTERACTION

As specified in the GVSI terms of reference, umbrella organizations of vaccine manufacturers can apply as participants to the Initiative. Individual vaccine manufacturing companies are not eligible, but can request to become observers or be invited to serve as consultants to meetings. In order to optimize public-private dialogue, the Blueprint specified a strategic objective to establish mechanisms for appropriate interaction between national governments, multilateral agencies and manufacturers at national, regional and international levels. Such dialogue is pivotal, as vaccine manufacturers are accountable for the safety and efficacy of the products receiving marketing authorization. Thus, the possibilities offered by improved vaccine pharmacovigilance in low- and middle-income countries should also allow better product specific monitoring of adverse events administered in LMIC.

The Blueprint proposes that safe use of vaccines can be improved with well-structured information exchange mechanisms between regulatory

authorities, procurement agencies and industry. To that effect, the Council for International Organizations of Medical Sciences (CIOMS) re-assembled a Working Group on Vaccine Pharmacovigilance following an initial effort that had allowed harmonizing a number of definitions in the field[xi]. It aims to serve as a key platform for well-described and regulated public private interaction related to review and implementation of harmonized methods and tools.

FIRST TWO YEARS OF OPERATION AND NEXT STEPS

The GVSI is an ambitious WHO mechanism proposed to utilize the broad global experience in conducting vaccine pharmacovigilance and implementing the most efficient activities to ensure adequate vaccine safety monitoring in LMIC. During its first two years of operation the Initiative has completed several activities such as the development of core variables for AEFI monitoring and a new classification scheme for causality assessment of serious AEFI, updating benchmarks for national vaccine pharmacovigilance systems, establishing a global training resource center with e-learning material on vaccine safety, establishing regional expert groups, publishing a regional reference manual for AEFI surveillance and enhancing capacity building in several countries[xii].

Current strengths of the GVSI include the broad acceptance of the Initiative, the high level endorsement of the vision by key global immunization stakeholders, the engagement of well-recognized authoritative vaccine safety experts and the rapid development of its activity portfolio. As the Blueprint is more broadly adopted, many more vaccine stakeholders need to be approached in order to achieve the shared aim of furthering global vaccine pharmacovigilance. To that effect, participation in the Initiative as described here needs to be more actively formalized. A clear definition of roles and responsibilities, proper acknowledgement of respective contributions and contributors, transparency in the management process

and effective implementation of the principles described in this paper need to be promptly demonstrated. Finally, resource mobilization in order to fully implement the Blueprint strategies remains insufficient and to date, several portfolio activities, even those identified as the most urgent are not or only partially funded. Identification of the required resources and active fund raising are critical to attaining the shared vision.

In summary, increased attention to the safety of vaccines is a direct result of the successful implementation of global immunization programs. More effective disease control strategies and new vaccine introductions require important improvements in vaccine safety practices. The GVSI assists WHO to meet these needs in LMIC. Interested parties are encouraged to join the GVSI as participants, consultants, or observers. The GVSI is a WHO mechanism for structured efforts into enhancing vaccine safety globally. Investments are directed to ensure that all vaccine recipients benefit from immunization with similar standards of safety monitoring and response. This is to minimize any untoward effect and to avoid unnecessary disruptions of valuable protection against an increasing number of infectious diseases causing death or devastating health outcomes.

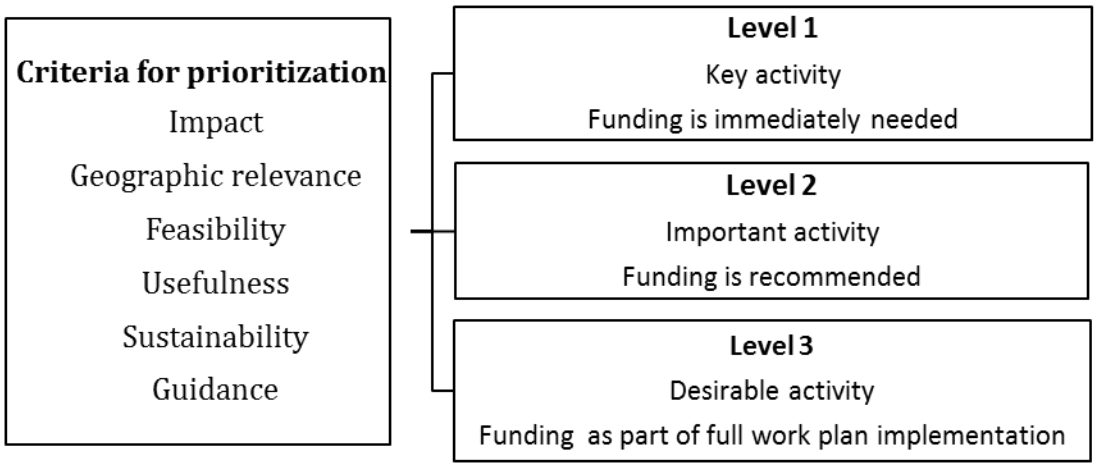
Table 1: GVSI Blueprint main portfolio variables

Activity identification	**Prioritization**
• Activity title • Activity description • Expected end product(s) • Activity duration • Contribution to the Blueprint Objectives • Activity contact	• Impact • Geographical relevance • Feasibility • Usefulness • Sustainability Guidance
Progress monitoring	**Financial aspects**
• Activity status • Expected date of completion • Milestone(s)	• Funding status • Available funds • Source of funding or funding sources approached • Cost in the next phase

Table 2: Criteria for prioritization of GVSI portfolio activities to implement the global vaccine safety Blueprint

Criterion	Description
Impact	Activity's measurable improvement of vaccine pharmacovigilance and its tangible contribution to attaining the goal and objectives of the Blueprint.
Geographic relevance	National relevance: single country involvement.. Regional relevance: more than one country in single WHO region involved. Global relevance: more than one WHO region involved. Reproducibility in another countries or regions increases geographic relevance of projects primarily implemented with geographically limited implementation.
Feasibility	Ability to measure accomplishment of activity targets according pre-set parameters.
Usefulness	Practical worth or applicability evaluated by anticipated frequency, and scope of use.
Sustainability	Capacity to endure according to metrics predicting the ability to maintain established infrastructures and processes with available local and global resources and efforts.
Guidance	Recommendations from advisory groups, governing bodies or national committees (e.g., GACVS, SAGE, ITAG).

Figure 1: GVSI prioritization scheme



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