Summary and recommendations from the third joint meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) and WHO Global Advisory Committee on Vaccine Safety (GACVS).
13-15 November 2023

The third joint meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP¹) and WHO Global Advisory Committee on Vaccine Safety (GACVS²) occurred between the 13 to 15 November 2023 at WHO Headquarters in Geneva, Switzerland. The two advisory Committees meet twice a year, in May (independently) and in November (jointly). A summary of the discussions and recommendations from the medicines-specific sessions and from sessions of common interest for the pharmacovigilance of both medicines and vaccines is provided below. The medicines-specific sessions were chaired by Dr Gerald Dal Pan from the United States Food and Drug Administration (US FDA) and sessions common to both vaccines and medicines were co-chaired by Dr Dure Samin Akram from the Health, Education and Literacy Program in Pakistan, Dr Rita Helfand, Centre of Disease Control (CDC), United States and Dr Gerald Dal Pan.

Update on Cohort Event Monitoring (CEM) project and implementation in pandemic response

Active surveillance for COVID-19 therapeutics (molnupiravir and nirmatrelvir-ritonavir) has been discussed in previous ACSoMP meetings³,⁴,⁵. The objective of the session was to update the Committees on work done to leverage lessons learned with CEM to better prepare for future pandemics. The committees were updated on progress of the WHO-coordinated CEM study for COVID-19 therapeutics. Two of the four countries that expressed interest are currently collecting data. The number of patients recruited is limited due to the drop in usage. The plan to conduct a survey for lessons learned was shared. The objective is to understand the challenges and successes, identify gaps in infrastructure, processes and capacity needed to perform active surveillance, and use findings to develop recommendations for preparedness. The Ghana FDA also shared their experience of conducting active surveillance which was used during the COVID-19 pandemic to compliment existing spontaneous reporting systems. Key lessons learned for success included collaboration with the expanded programme of immunization (EPI), involvement of regional level at planning stages, involvement of National

¹ https://cdn.who.int/media/docs/default-source/pvg/acsomp/acsomp-composition.pdf?sfvrsn=7c4030da_2 (accessed January 2024)
³ ACSoMP recommendations May 2023 https://cdn.who.int/media/docs/default-source/pvg/2023-may-acsomp-recommendations.pdf?sfvrsn=5d138433_1&download=true (accessed January 2024)
⁴ ACSoMP recommendations December 2022 https://www.who.int/publications/m/item/2022-december-acsomp-recommendations (accessed January 2024)
⁵ ACSoMP recommendations June 2022 https://www.who.int/publications/m/item/2022-acsomp-recommendations (accessed January 2024)
Service staff as the study team members, and making participants feel cared for through the follow up process leading to more willingness to share information.

**Discussion and Recommendations:**
The Committees welcomed the concept of the study and the aspiration to implement CEM and asked to be kept informed of progress and results.

**Safety issues due to administration errors of medicines and vaccines**
The objective of the session was to provide updates on safety issues related to medication and immunization errors. The WHO Collaborating Centre for International Drug Monitoring, Uppsala Monitoring Centre (UMC) provided an overview of reports of medication errors in VigiBase (the WHO global database of Individual Case Safety Reports). Using “medication error” as the search term (October 2023), there were more than 1.5 million cases of medication errors reported in VigiBase, with 78% medicines and 22% vaccines. General characteristics such as top reporting countries, reporters, products with the most frequent reports, proportion of reports in males and females, and different age groups were described.

The Committees were briefed on the third WHO Global Patient Challenge- Medication Without Harm, which began in 2017. WHO commissioned a meta-analysis to investigate the preventable burden of medication-related harm. A draft report has been developed, and initial findings show that one in 20 patients is impacted by an avoidable medication-related harm. Globally, the pooled prevalence is around 5%, (7% in lower- and middle-income countries, and 4% in high-income countries). Approximately, 25% of these are life-threatening. The aim of the Challenge is to reduce severe avoidable harm related to medications by 50% globally.

**Discussion and Recommendations**
The Committees recognized that the opportunity should be taken to conduct further analysis of reports in VigiBase to determine the magnitude of adverse events. An in-depth analysis of each medication error report would be required to fully understand how the error occurred. The Committee welcomed the initiative of the third WHO Patient Safety Challenge, “Medication Without Harm”, and discussed the overlap of nomenclature between drug-related problems, preventable adverse drug reactions, and medication errors. It is important that there is more clarity around definitions to ease reporting.

**ADR Reporting**
The objective of the session was to share updated core variables and present WHO standard form for suspected ADR Reporting and solicit feedback. The core variables comprise of 35 variables, divided into six sections: record identifier, patient identification, suspected adverse drug reaction(s)/details, drug(s)/details, past medical history and any other relevant information, reporter’s information. The Scope of the core variables is primarily for signal detection, where further investigation of individual case causality assessment is needed. The
main aim of the core variables is to support standardization of the information transmitted to
the WHO global database of Individual Case Safety Reports, VigiBase and to improve causality
assessment, assessment of seriousness and preventability.

Discussion and Recommendations:

ACSoMP acknowledged the benefit gained through updating the 35 core variables. The
potential of their incorporation into national reporting systems means increasing universality of
data acquired through the use of Vigi-tools and aligning the data being sought in VigiFlow and
VigiBase with the data being captured at point of care. The Committee mentioned that there
needs to be a balance between thoroughness and the time needed to complete a report.
Additionally, narratives are very important and help with the analytical tools. Consideration
must be given to clearly communicate and explain the updated core variables, its intent and
purpose at the time of the rollout.

Update on Miltefosine and WHO procedure for addressing signals
The object of the session was to provide updates on actions taken to minimize risk of ocular
adverse events with the use of miltefosine. This topic has been discussed in previous ACSoMP
meetings. In December 2022, ACSoMP supported the conclusions of the multidisciplinary
technical group (MTG) which were published by WHO together with further documents to
minimize the risks. In May 2023, ACSoMP discussed lessons-learned and reviewed a patient
information brochure, which has since been finalized. A public assessment report is being
finalized and a publication of a peer review article is planned. An update of new cases was
presented by UMC. It was not known whether the recommended risk minimization measures
were implemented in the cases that occurred after the publication of ACSoMP’s
recommendations in December 2022. An outline of a WHO procedure for addressing future
signals was presented to the Committee.

Discussion and recommendations
The Committee discussed the process of managing new signals and how the decision to engage
ACSoMP is made. A standard operating procedure for addressing signals is essential and will
ensure a timely response to identified signals. The use of follow up forms to obtain further
information on cases to aid signal detections was suggested. The importance of access to the
narrative in reports for signal detection was highlighted, and challenges of sharing of
information such as the narrative globally, was suggested as an agenda item in future ACSoMP
meetings.

6 WHO Measures to minimize the risk of ocular adverse events with miltefosine [website]. (https://www.who.int/news/item/12-04-2023-acomp-miltefosine accessed January 2024)
Update on Safety monitoring of Dolutegravir and Cabotegravir
The object of the meeting to provide an update on WHO guidelines and safety monitoring of Cabotegravir (CAB LA) and Dolutegravir (DTG).

Information from a number of relevant randomized control trials were shared. The data, continues to show that DTG is highly effective and safe in pregnant women. Moreover, adverse pregnancy outcomes are not higher with preconception administration of DTG. This suggests that the neural tube defects signal on the relatively small number of exposures was erroneous and corrected with increased number of exposures. Regarding CAB LA, initial studies show the drug as being well-tolerated and there are 34 implementation studies, of which one is complete, 10 are ongoing, and 23 are planned.

The Committees were briefed on a novel collaborative approach to monitoring safety of antiretrovirals in pregnancy, including surveillance. The process involves developing key principles drawing on lessons learned from past practices. There is a recognition that no one region will have enough numbers of pregnancy outcomes to answer the full scope of the safety outcomes. Work on monitoring the CAB LA studies is ongoing and WHO will continue to inform ACSoMP. The Committees were also informed of ongoing joint assessment activities involving several WHO units that aim to promote collaboration amongst national authorities for facilitated registration of quality assured products.

Discussion and recommendations
The Committees recognized the importance of international collaboration in pregnancy related research, and the Dolutegravir story is a good example of how careful follow up can clarify a signal in a beneficial way.

The Committee welcomes the new approach to the study of HIV and pregnancy, and acknowledges the opportunity for WHO HIV, Pharmacovigilance (PVG) and Facilitated Product Introduction (FPI) teams to work together on this issue.

Sodium valproate safety updates
The objective of the session was to provide updates on actions taken since the previous ACSoMP meeting. The Committee was informed of the release date (20 November 2023) of the 3rd edition of the WHO Mental Health GAP Action (updated mhGAP) guideline. The updated guideline includes recommendations on the use of sodium valproate in the treatment of epilepsy and bipolar disorder. This is available on the WHO website.

The dissemination of information on the third edition of the mhGAP guideline is occurring through various platforms and channels, including an article in Lancet Psychiatry, WHO websites, press briefings, and social media.

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7 Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders https://www.who.int/publications/i/item/9789240084278 (accessed January 2024)
8 Reducing the uses of valproate: a controversial decision; The Lancet Neurology (February 2024) DOI: https://doi.org/10.1016/S1474-4422(23)00507-0
Furthermore, the Committee was briefed on a post-authorization study on outcomes of paternal exposure to sodium valproate required by the Pharmacovigilance Risk Assessment Committee (PRAC) of the EMA. The study is designed as a retrospective, non-interventional longitudinal population-based cohort with secondary data derived from multiple registry databases.

**Discussions and recommendations**

The Committees welcomed the work done to support the drafting of a new WHO guideline regarding the use of Valproic acid, and it awaits the result of the assessment by the European Medicine Agency currently ongoing.

**Upcoming ACSoMP meetings**

The next ACSoMP meeting is planned to be a virtual meeting in May 2024, with a joint ACSoMP/GACVS in-person/hybrid meeting in November 2024.