Joint meeting of Clinical Development/Medical Affairs (CDMA) & Pharmacovigilance (PV) Working Groups (WG) – 6 & 7 June 2022, held in Geneva and by Zoom

Participants in person: Alexander Precioso (AP,Chair), Linda Nesbitt (LN), Richard Chawana (RC), Viska Iskandar (VI), Katharina Hartmann (KH), Bernadette Hendrickx (BH), Pieter Neels (PN), Varun Sharma (VS), Kerim Chitour (KC), Sivashen Cunden (SC), Aila Marini (AM), Sonia Pagliusi (SP) and Rebecca Chandier (ReC, Observer). Participants Virtually: Ravindra Mittal (RM), Lei Zhang (LZ), Hongde Xie (HX), Long Xu(LX), Phan Hoa (PH), Beatriz Luchesi (BL), Rajinder Suri (RS), Wang Ming (WM), Devi Sahoo (DS), Michael Ming (MM), Huiqin Zhu (HZ), Li Dong Xue (LDX), Wencheng Fan (WF), Sisi Li (SL), Danilela Lazzarini (DL).

AP welcomed all participants, who briefly introduced themselves. AP shared the list of the CDMA WG members with all (cf. https://www.dcvmn.org/Members-list-724) and summarized the outcomes of their 1st meeting, held on 22 March 2022: The purpose of the CDMAWG is to identify specific needs to foster and strengthen members' Clinical Development and Medical Affairs related practices, with the goal of identifying and assessing the members' capacity to develop a benefit-risk approach for Clinical and Medical activities. The specific objectives set were: 1) discuss the relevance of Benefit-Risk (B-R) approach within the conduct of clinical trials; 2) understand how the medical affairs activities are linked to the clinical development; 3) foster interactions among clinical development, medical affairs, and pharmacovigilance activities, mostly through training. The expected outcome of this meeting was: 1) to define a list of minimum "must-have" SOPs for clinical activities (both pre and post licensure) and 2) define ICH-GCP training needs.

PN provided an overview of the rationale for systematic B-R assessment for public health management, exemplified by historical examples of smallpox, polio and rotavirus vaccines, that led to the agreed approach on the methodology for B-R assessment with the publication of ICH E2C[1], in 1996. He added that during the rollout of vaccines the B-R analysis, based on some adverse events of new vaccines, helped to judge the practical deployment of certain vaccines across different age groups, in an effort to optimize coverage to achieve herd immunity. He mentioned the BRAVATO (Benefit Risk Assessment of VAccines by TechnOlogy) of Brighton Collaboration, supported by CEPI and acknowledged by WHO, that led to developed templates for COVID vaccines B-R assessment based on five vaccine technology platforms[2]. The B-R assessment within regulatory agencies started mainly after ICH E2E (10-15 years ago) and industry introduced a number of activities (discussed e.g. in the PV PSUR training slides in March 2020[3]). The use of these templates is not mandatory by any regulatory agency; however, they are helpful as checklist when doing RMP and B-R assessment activities. In addition, the concept of phase 4 studies based on "real-world experience" towards emergency use authorization has been discussed by CEPI, and could accelerate access, while decreasing time and costs related to large phase 3 studies. PN concluded that B-R assessment is a complex dynamic analysis involving disease pathophysiology and risks of probability of related harm, rather than only a mathematical formula. Thus, clinical benefits of vaccines can be assessed, rather than calculated, as illustrated by the HPV vaccine, of vaccinating large populations to prevent cancer in a subset of the population.

LN presented an outline of the B-R assessment and safety management in clinical trials, from the viewpoint of the pharmacovigilance working group. She shared the PV WG aims, according to a

[1] https://database.ich.org/sites/default/files/E2C_R2_Guideline.pdf

[2] • Nucleic Acid (RNA/ vaccines Kim D et al, https://doi.org/10.1016/j.vaccine.2020.06.017 • Inactivated viral vaccines Kochhar S et al, https://doi.org/10.1016/j.vaccine.2020.07.028 • Protein vaccines Kochhar S et al, https://doi.org/10.1016/j.vaccine.2020.06.044 • Viral vector vaccines Condit RS et al, https://doi.org/10.1016/j.vaccine.2020.08.009 • Live attenuated viral vaccines Gurwith M et al, https://doi.org/10.1016/j.vaccine.2020.09.042

[3] https://www.dcvmn.org/E-workshop-on-Vaccine-Safety-monitoring-and-Pharmacovigilance-tools

survey and as agreed in 2019, to 1) engage DCVMN members on priority global health issues, understanding the broader landscape in safety monitoring; 2) establish systematic and proactive dialogue with international bodies to shape the thinking on high priorities for DCVMs; 3) Equip DCVMN member companies with up-to date knowledge to implement best practices and formal training according to state-of-the art pharmacovigilance, aligned with WHO and relevant national regulatory requirements. She noted that over 2020-21 the group developed training materials and capacity building via the e-learning platforms, provided templates (audit checklist, SOPs) for members reference[4], and coordinated the Risk Management Plan interactive project, to support manufacturers in their compilation of such plans[5]. Most recently the group discussed active surveillance safety systems, and communication with NRAs, MoHs, healthcare personnel and patients, and importantly, communication and interaction between the pharmacovigilance and product quality department to tackle product shortcomings. Development of critical PV processes, including safety governance within company with an active vaccine safety committee/board could help strengthen safety monitoring. She highlighted that the RMP project achieved two major outcomes/deliverables: 1) sharing knowledge of a robust RMP meeting EU standards, and 2) initiate the establishment of a multidisciplinary team for Risk Management within 9 companies. B-R assessments and training appear slightly different from a pure pharmacovigilance safety perspective, and in fac different countries have different needs and measures of benefits and risks, leading to heterogeneity in needs of member companies as well. In practice, signals of adverse medical events detected locally may be different from those detected/reported globally. Quality data is needed for pharmacovigilance and safety assessments and she suggested to focus training on how to collect and share such information. LN concluded by sharing suggestions of collaborations with the CDMA WG, in three main areas: Safety assessment in Clinical Trials (CTs), CT Documentation tools and systems, and Safety reporting requirements and processes in CTs. She elaborated on each of these areas and opened as basis for discussions at this meeting discussions.

Discussions: AP stressed the importance of industry communication, both internal among departments and external with NRAs, and the public in general, as during the COVID-19 pandemic it was important to have clear safety messages to accelerate vaccine introduction and coverage, to mitigate harm of pandemic. BH agreed that during the pandemic, rapid data collection was achieved while communication could be improved. Also, good structured tools are needed to deal with media. AP agreed that both science and cultural aspects are key in good communication. He also agreed that collection of safety data during CTs can advance and facilitate understanding of potential safety matters. PN added that still data collection is a major issue in some regions, and the "top-down" approach "boosts" data collection efforts, while data need to be communicated "bottom up". Previously, safety was dissociated from efficacy data, and B-R assessments integrates these two areas already at clinical trial period. KH added that top-down approach, means that NRAs need to have a good understanding of safety (signals) to be able to support such approaches.

AP questioned if there would be lack of data in some regions, or rather lack of accurate/systematic collection and analysis of baseline epidemiologic data. RC added that while training healthcare professionals, it is valuable to sensitize them to collect and keep records of AEs data of populations, which could help early "signal detection", which is implemented in other countries, e.g. Japan. In addition to foster corporate communication and collaboration with immunization services, there is a

[4] https://www.dcvmn.org/Other-materials-and-templates-484
[5] https://www.dcvmn.org/IMG/pdf/rmp_project_proposal.pdf

need to analyse and integrate data already collected, added AP. Regarding communication of AEs to patients, on labels/package inserts, the B-R is communicated differently by private and public sectors, as to individual risks average risks. Progress has been made by EMA in analysing AE risks and became more prominent and widely discussed due to the high awareness during COVID-19 vaccination rollout (e.g. Thrombosis with thrombocytopenia syndrome) at subgroup/age group/gender levels and depending on infection rates, in a dynamic manner. RM mentioned that LMICs do not have infrastructure, experts and resources to do this: In phase 1-2 CTs there are active surveillance systems, but once a vaccine is on the market only passive surveillance is in place. AP added that safety and signal detection is a pre-marketing responsibility, as illustrated by the dengue vaccine case[6]. PN suggested exploring ways of improving collection and validation of real-world data, both pre and post marketing, with high performance quality management electronic systems.

KH provided an overview of the PV WG activities for 2022. While seeking to foster a systematic approach to safety, the WG posted master lists of SOPs that are relevant for both pre- and post-marketing periods, and apply globally. She commented that collection of data is an ongoing process during the whole product lifecycle. She added that the Safety Management Team (SMT) charter defines how the safety team works together, may vary depending how companies are organized, and how many tasks are done internally or outsourced. DSMB neither approves nor reviews PV documents - they review the safety and efficacy data from a specific trial at predefined time points during the conduct of the CT and can be approached in case of a specific safety question coming up in the specific trial. Based on their review of the data recommendations are made, if needed. Usually, RMPs and PASS (post-authorisation safety study) are prepared at the pre-registration stage, though RMP is a requirement for PQ, when vaccines are already licensed in countries where RMPs are not a requirement. Safety teams (SMTs) should include experts in epidemiology, statistics, clinical, medical and logistics and such teams have the responsibility and empowered to implement actions; the team is also responsible to implement the DSMB recommendations. RC added that CEPI has an initiative to create a pool of experts to help manufacturers to find independent experts for DSMBs.

Discussions: AP mentioned that the heterogeneity of vaccine manufacturers from developing countries needs to be recognized, depending on the number of vaccines they deal with, and if they engage in antigen manufacturing, or filling or labelling and distribution, in different areas, and safety monitoring might be under Clinical Department or under QA department. It was mentioned that many large multinationals have created mentoring programmes to train professionals in developing countries, to increase knowledge and expertise. RM reported that Safety Reporting Centers have been set up in India, however collected data and analysis are limited. LN mentioned that data collection in SA is also limited by availability of personnel and expertise. AP mentioned that in Brazil issues with cold chain are communicated to government and cascaded down to companies, but not issues with safety. VS agreed that it appears that safety data access and exchange between governmental organizations and companies is very limited, despite data collection and efforts to share more data in the COVID period. Another issue is that some companies would not have the infrastructure and systems to analyse and process data. AP suggested to build a joint agenda on B-R for both WG to follow up on. PN mentioned that the EMA guidance on R-B assessment is quite clear and provides a common ground for learning, thus could be circulated to DCVMs and a webinar can

[6] https://www.who.int/groups/global-advisory-committee-on-vaccine-safety/topics/dengue-vaccines/safety-update

be held by PN to discuss and clarify the assessment template together with DCVMs audience. PN added that the B-R assessment report is based on data and evidence already collected, and part of module 2 of CTD submission dossiers in ICH-member countries, thus differs from RMP that considers future risks and is a separate document, part of CTD section 2.5.6. Upon discussions, the participants agreed that a list of SOPs for CTs (Phases 1/2/3/4) needs to be setup and be available to all members, as basis for exchange and generating a common understanding of clinical development and medical affairs, with safety monitoring as a denominator.

RM mentioned that SOPs are critical for CTs phase 1-2-3 (pre-marketing), and mentioned that over the past 25 years the clinical operations evolved from a few SOPs to over 40 SOPs. through dialogue with NRAs, updates on GCP, and conducting clinical studies. LN and BL stressed that to be responsible for CTs people with experience is clinical operations are preferred. Some single SOPs for SAEs management have been more recently split into 3 SOPs, in order to improve granularity and accuracy on data collection. He suggested that a list of SOPs related to phases 1-2-3 be provided by the CDMA WG, and phase 4 studies (post-marketing) could be shared by the PV WG, for inputs from all. This way the WGs keep their focus on areas of expertise while enriching each other, through discussions. BH reiterated the need to implement SOPs in the practice, not only have a list of them, and reminded that manufacturers from different countries are at different levels of maturity in clinical operations, and in the experience of how to apply SOPs. BL added that training on SOPs is also critical for manufacturers to succeed. It was agreed that the WGs should keep the SOPs to a minimum, and keep general explanatory notes, as the details should be company and product specific. It was noted that, marketing authorization holders also need to keep track of SOPs and follow PV regulations in order to enable PV data exchange, as part of many licensing agreements. AP added that it is an important role of NRAs to clearly establish such responsibilities as requirements to licenses holders.

RM shared his view and experience with a list of 45 SOPs related to CTs phase 1-2-3, excluding phase 4 and post marketing activities, as these SOPs are already listed by the PV WG (cf. https://www.dcvmn.org/IMG/pdf/pv_sop_masterlist_draft.pdf). It was also clarified that any organization involved in clinical trials may be inspected by NRAs, but in the practice audits/inspections are carried out differently by different NRAs. The participants expressed some SOPs to be added to the list, e.g. indemnification, CT site selection, Ethics Committee, CROs selection, validation of software systems for CT data collection. It was agreed to circulate the list of SOPs as suggested by RM to all CDMA WG members for comments, and then share with the PV WG before posting on the webpage as a resource for manufacturers from developing countries.

KH reviewed the PV SOPs list available on the above link, and elaborated on the content of each of them, and committed to update the list to include such explanatory notes, for manufacturers to understand what is "behind" each SOP. This would be helpful for annual training and onboarding training of employees. She highlighted the importance of crisis management training, based on recent events such as dengue and COVID vaccines (S)AEs where manufacturers need to respond rapidly and clearly to the media (or not). It was agreed for DCVMN to coordinate a Crisis management and communication training workshop with the intervention of experienced consultants and journalists. She mentioned the need to involve professionals from Quality Assurance departments in such CT and PV discussions, and the participants agreed to integrate professionals from QA into future discussions.

Conclusions: AP reminded that over the discussions the main agreed points of action included:

1. Keep a common agenda on B-R assessments by having a follow up joint meeting in early July (tbd) and a pre-meeting among Chairs/expert consultants, as desired;
2. Circulate the EMA guidance documents to members, to serve as common ground for WG discussions (cf. https://www.ema.europa.eu/en/about-us/what-we-do/regulatory-science-research/benefit-risk-methodology) particularly the Benefit-Risk template for assessments to be discussed at a virtual workshop, to "walk through" for manufacturers to know how to proceed, if desired;
3. Compile the list of over 40 SOPs related to CTs (pre-marketing) suggested by RM on one document to be circulated to the CDMA WG members for comments, and thereafter to be shared with other relevant WGs and the members;
4. Update/complement the PV list of suggested SOPs (post-marketing) with explanatory notes to each item, for members to know the purpose and content;
5. organize a training workshop on Crisis management and communication, when suitable and convenient, acknowledging that an e-course on "Introduction to B-R assessments" based on slides presentations by expert consultant PN is already available to members on the Moodle page;
6. Keep quality standards as a common denominator to all SOPs, and engage with QA staff to join such discussions.

Rajinder Suri (RS), CEO-DCVMN who joined online at the end, and complimented all team members and encouraged to bring forward meaningful suggestions and joint action plan.

AP acknowledged all participants, co-chairs, consultants, donors and secretariat staff, and adjourned the meeting.

Notes drafted by S. Pagliusi

Acknowledged by CCDMA Chair

Alexander Precioso — 22 June, 2022

Dr. Alexander Precioso, Butantan — Location & Date

PS. The meeting agenda and presentations are available at https://www.dcvmn.org/2nd-Clinical-Medical-WG-PV-WG-meeting