KH0

PV SUMMARY OF PRESENT AND FUTURE PROJECTS

BENEFIT RISK ASSESSMENTS AND SAFETY MANAGEMENT IN CLINICAL TRIALS

JOINT DCVMN CLINICAL & MEDICAL AFFAIRS & PV WORKING GROUPS – JUNE 2022

Slide 1

KH0 Would not restrict the discussions to B/R assessment, but add also safety management in clinical trials

Katharina Hartmann, 2022-05-30T17:24:56.295

AIMS OF PHARMACOVIGILANCE WORKING GROUP – NOV 2019

Proactively engage DCVMN members on priority global health issues, understanding the broader landscape e.g. Safety monitoring

Establish more systematic and proactive dialogue with international bodies to shape the thinking on high priority DCVM issues.

Support and strengthening PV systems at corporate level to achieve global vaccine safety monitoring.

Equip DCVMN member companies with up-to date knowledge to implement best practices and formal training according to state-of-the art pharmacovigilance,

Align with WHO and relevant national regulatory requirements.

PROJECTS OF PHARMACOVIGILANCE WORKING GROUP – MAY 2020 – JULY 2021

Phase 1: In the short term (<6 months), development of material, content and provide Post-licensure training and capacity building via the DCVMN e-learning platform and virtual PV training workshops.

Phase 2: In the longer term (>6 months), development of tools and templates (forms, SOPs), and build capacity in more advanced PV areas including interactive projects with member engagement.

Address the other gaps identified in the 2019 DCVMN members' survey through a series of face-to-face interactive workshops.

Specificities of Vaccine PV & focus of vaccine safety surveillance

Continuous vaccine safety profile monitoring; Protection of vaccinated individuals & populations; Benefit-risk evaluation of registered medicines; acquaintance with health hazard evaluations;

Risk management systems - establishing, assessing and implementing; evaluating the effectiveness of risk minimisation;

ICSR Case Management

Reporting & processing of ICSRs from any source; Knowledge and command of Brighton case definitions; Familiarity and use of medical coding/ medical review of ICSR's; quality control of cases; causality assessments

Signal management; continuous Safety signal detection and evaluation;

Scheduling, review (including data evaluation and quality control), submission and assessment of DSUR/PSURs/PBRERS and availability of SOPs to do that;

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PVWG TRAINING LINKED TO PV BENEFIT-RISK ELEMENTS (2020 - 2021)

Slide 4

KH0 Would specifically mention the +/- high-level training / information on the B/R requirements in the PSURs - would propose to be more explicit

Katharina Hartmann, 2022-05-30T17:28:08.320

PVWG TRAINING LINKED TO& PV – BENEFIT-RISK ELEMENTS (2020-2021)

- Purpose and content of PBRERs/PSURs; reporting requirements; periodicity; additional analysis for vaccines; evaluation of B/R balance; concepts in RA; B/R assessment; Methodologies for assessment
- Communication about safety concerns between MAH & NRA, in particular notifying changes to the risk-benefit balance of medicines; meeting commitments and responding to requests from competent authorities;
- Communicating information to patients and HCPs about changes to the risk-benefit balance of products for the aim of safe and effective use of medicines; responding to safety crises; vaccine risk communication
- Keeping product information up-to-date with the current scientific knowledge; Implementation of safety variations to the SmPC and PIL
- Interaction between the pharmacovigilance and product quality defect systems;

PVWG TRAINING LINKED TO PV – BENEFIT-RISK ELEMENTS – FUTURE PROJECTS

KH1

- Development of critical PV processes, including safety governance within company with an active vaccine safety committee/board; KH0
- Identifying emerging safety concerns and any other information relating to the benefit-risk evaluation
- Awareness of ongoing or completed clinical trials and other studies that may be relevant to the safety of the medicinal products;
- Literature reviews

Slide 6

KH0 I don't think we were able to get these topics done - they are on our "wisj-list"
Katharina Hartmann, 2022-05-30T17:30:32.022

KH1 These trainings have been provided - they are still on the to do list" would propose to change the date (2020 onwards)
Katharina Hartmann, 2022-05-30T17:32:37.308

RISK MANAGEMENT PLAN PROJECT AND CONCLUSIONS (2021-2022)

- Cross-cutting initiative **The Risk Management Project [RMP]**
- ***Deliverables:***
- *1) A robust RMP meeting EU standards*
- *2) Establishment of **a** multidisciplinary team for RM (i.e., Safety Management)*

Timelines	Actions
March 2021	Project information and application
	e-learning training on the principles of the RMP as a pre-requisite for participation
	Proposal of a vaccine plus designated team, kickoff meeting & the roll out discussed and agreed
	Over 5 months development of RMP, guided and supported
Sept - Dec 2021	Completion and submission of 9 RMPs to 3 expert consultants for review and comment
Jan 2022	Individual 1:1 feedback by the experts
April 2022	Close out webinar
	After review of all submitted RMPs, the need for potential training on specific RMP elements may be considered
	Generic list of the observed issues prepared

COLLABORATION POINTS WITH CD/MA

Safety assessment in Clinical Trials (CTs) –

Systematic and comprehensive approach Evaluation of safety information/

Rapid detection of safety issues/

Risk assessments/

Causality assessment/

Look for evidence of other causes

CT Documentation (e.g., IB, synopsis, CT protocol, CRF, ICF, SAP, CSR). Safety/PV should be involved in all safety sections of the CT documents e.g., the IB is the RSI in Clinical development and is the basis for expectedness; standardisation of forms/definitions/methodology/data quality for meaningful analysis/data systems/how to approach amendments to safety documents e.g., IB/accessibility of data

Safety reporting requirements and processes in CTs/

Systematic approach to RM/ Criteria for expedited reporting/

Is aggregate or individual case reporting required?/

Country specific requirements/

Exercise regulatory agility based on sound scientific rational

COLLABORATION POINTS WITH CDMA

Critical Process Flows –

Need to understand both Clinical Development Plan/

Activities and Individual Clinical Study Plan/activities/

Project management/

Consider overall framework for PV processes

Identification of roles within a company/

Any shared responsibilities ?/ Interactions/

Coordination/

Communication

Design Considerations – systematic approach to RM/

Normally Safety/PV/

Pharmacoepidemiology is only included/

Responsible for study design in safety studies

COLLABORATION POINTS WITH CDMA

Trial goals - in Clinical development.

PV/Safety is only involved in safety endpoints –

this is different from safety studies

Final Clinical Study Reports
- will PV be involved here?
Transparency in availability of CT results

CLINICAL TRIAL PHASES AND SAFETY

- What level of risk attributed to the study?
- Are methods of intensity of safety monitoring commensurate with the risks, nature, size, and complexity of the trial?

- **Phase I Trials:** Principal purpose – evaluate the product's safety, toxicity and immunogenicity as well as determined how best to administer the vaccine to limit risks and maximise possible benefits/rigorous medical supervision KH0
- **Phase II Trials:** Principal Purpose – determine preliminary estimate of the clinical efficacy of the vaccine or the immunogenicity of the vaccine KH1

KH3

Phase I and II: some studies uncontrolled. AE assessment can be problematic.

Slide 11

KH0 Not sure what "uncontrolled AE assessment" means?
Katharina Hartmann, 2022-05-30T17:45:08.858

KH0 0 Phase 3 contains the pivotal trials for MAA and demonstrate safety and efficacy (effectiveness is post-licensure)
Katharina Hartmann, 2022-05-30T17:45:59.190

KH1 Not sure what "reagents" means?
Katharina Hartmann, 2022-05-30T17:46:28.310

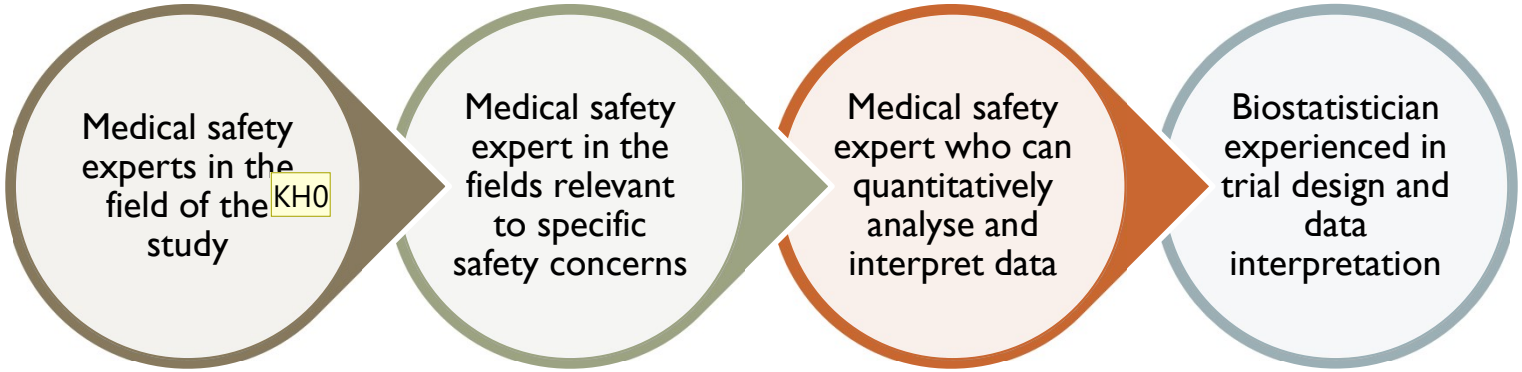
KH2 Severity scoring is often a subjective measurement, would rather use seriousness
Katharina Hartmann, 2022-05-30T17:48:29.283

KH3 Regulatory requirement for the size of the safety database at filing is 3'000 (detection of an AE with a frequency 1/1'000 which is considered already rare - Vaccine trials have meanwhile become rather large >30'000 subjects
Katharina Hartmann, 2022-05-30T17:50:49.644

CLINICAL TRIAL PHASES AND SAFETY

- **Phase III Trial** Principal purpose – pivotal for registration - demonstrate efficacy and safety
- Building tools for harmonised assessment of vaccines using standardised protocols is essential for efficacy and safety
- Safety assessments are based on evaluation of B/R using well defined case definitions/seriousness assessment

Prospective Randomised Trials for detection of AEs – designed for detection of common and acute AEs; Not usually designed to detect (uncommon (insufficient power)/ vague onset (hard to evaluate temporal association/delayed onset. Regulatory requirement for the size of the safety database at filing is 3'000 (detection of an AE with a frequency 1/1'000 which is considered already rare - Vaccine trials have meanwhile become rather large >30'000 subject



SAFETY EVALUATION IN CLINICAL TRIALS - MULTIDISCIPLINARY

Slide 13

KH0 Would not use the expressions "clinician" as this would allwys be considered an MD - would rather use "medical expert" how can be any "life-science expert"
In this context we usually use "medical safety experts"
Katharina Hartmann, 2022-05-30T17:53:25.064

IN CLOSING

- Opportunity for both WGs to fully unpack processes
- Clarify and identify CD/MA versus PV activities in pre-licensure safety trials
- What are the opportunities for synergy, to improve the effectiveness of the system and plans for clinical development
- Thank you for this opportunity