



**First meeting of CIOMS Working Group XI:
Patient involvement in the development and safe use of medicines
19-20 April 2018, Geneva**

Minutes (web)

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Introduction

The Secretary-General of CIOMS, Lembit Rägo, opened the meeting of the CIOMS WG XI and welcomed the participants. He informed members that participants from emerging economies may also join the WG in future and/or receive minutes of the discussions. Lembit highlighted the fact that at initiation of the WG there are limited patient groups being represented at face-to-face meetings, however CIOMS and the WG should seek additional patient input through various methods. These could include surveys of stakeholders and patient groups and, if feasible, to arrange a face-to-face conference or meeting to gather more patient feedback as the WG progresses; optimal timing for this to be determined.

Participant perspectives

Short interventions from participants were presented.

World Health Organization (WHO) perspective – Shanthi Pal

Shanthi presented the WHO perspective including that of UMC. Historical perspectives started in the 1960s when only healthcare professionals (HCPs) were deemed appropriate to report ADRs; over time there has been a shift towards including other HCPs and more recently patients; potential advantages of consumer reporting were mentioned such as faster identification of safety issues; better characterisation of risks; more detail on ADRs including effects on patients' quality of life; also, better coverage of certain types of products (OTCs, herbals)

The new EU legislation in 2012 included patient reporting of ADRs across all EU countries and was a key development in that region. WHO and UMC have introduced guidelines and web tools for patient reporting that are proving a success and the overall reporting of ADRs has increased in volume and,

importantly, has led to identification of new serious ADRs and safety signals. Other areas where consumer reporting may be useful include detection of counterfeit drugs and ADRs 'difficult' to discuss with HCP. Finally, WHO supports bringing patients on board early-on in the product development process and that this could perhaps improve the learning curve, especially regarding dosage forms, dosing frequency, packaging & labelling.

Patients perspective – Kaisa Immonen (EPF)

Kaisa presented on the need for patient engagement as partners in the drug development and innovation to meet medical needs. Such patient involvement could have wide applicability in the healthcare system. Kaisa presented the barriers to meaningful patient involvement. It was mentioned that resources and funding are important considerations when addressing patient involvement. Kaisa then informed the WG that patient representatives can, and do, wear many "hats", but there is increasing professionalism and maturity in patient movement in the last years in terms of codes of ethics, principles for conduct & collaboration, transparency as well as diversification of funding, good financial management & governance. An important consideration is that individual patient experts should be treated like other experts. Another key area is transparency and, in this context, the EPF transparency guidelines for patient organisations (2018) could be a useful reference. Finally, initiatives where EPF is involved were briefly described and these included the IMI PARADIGM project on patient involvement in pharmaceutical R&D.

Note: There was Q&A on the above topics and an intervention by Marilyn Metcalf proposing use of 'patient experts' and not 'expert patients'.

Patients perspective – Nikos Dedes (EATG)

The stakeholders of relevance to patients are not limited to regulators and industry but also include healthcare professionals, academia and HTA bodies. EATG supports the inclusion of patients in safe use of medicines in the CIOMS XI concept paper but this paper should also highlight their 'optimal' use to support health of patients and public health. The concept paper does not mention helping the health system towards better outcomes and better use of resources. Patient input is important to support the benefit-risk evaluation and decision. With regards to the role of social media it should be recognised that this source of information is not limited to PV. In drug development there is a need for designing better PROs for evaluation and approval of medicinal products. In the EU there is patient involvement in regulatory committees, however, the CHMP does not yet include patient representation in the review and decision-making process and this is seen as a gap. There are also issues of confidentiality as demonstrated by industry not usually sharing clinical trial protocols with patients (e.g. during phase II). There are good examples of some companies, however, who have engaged patients in the medicines lifecycle and feedback including practical examples that should be obtained for CIOMS XI.

Patients perspective - Kerry Leeson-Beevers (Alström Syndrome UK)

Kerry gave an introduction regarding Alström Syndrome and ASUK which is the patient organisation providing advocacy and consultation in a patient-led service for this ultra-rare condition. ASUK contracts with pharmaceutical companies to support clinical trials with confidentiality agreements in place. Kerry went on to describe her experience with other organisations such as EURORDIS as well as regulatory advisory committees including the Paediatric Committee (PDCO) of the EMA as patient representative.

Regarding scope for the WG, one area where patients have a role is the PV area where they can share adverse event experiences with patient organisations when they don't want to bother the

investigators. Regarding the CIOMS XI topic, Kerry raised the opportunity to describe terms of engagement for patients and the need for guidelines on how patients and patient organisations can interact with key stakeholders including pharma. Other areas for consideration by the WG include training needs, access to information, communication between the stakeholders, research priority setting, use of social media and other technologies. Patient organisations can be co-applicants in research grant applications and can contribute to studies assessing quality of life (QoL) measures.

Note: There was an intervention from Judy recommending use of examples of patient interactions/engagement to be included in CIOMS XI which was endorsed by the WG. Francois gave a brief description of one such example where a small patient group was actively involved in developing a medicine. As with other CIOMS, an Appendix of CIOMS XI may include practical examples of patient engagement during development and lifecycle of medicines.

CIOMS Comment: WG members are requested to propose practical examples of patient engagement during the lifecycle of medicines to be included as an Appendix to the main CIOMS XI report. These examples should be considered irrespective of the outcome being positive or not.

Industry perspective – Stephen Heaton (Bayer)

Stephen had previously participated in CIOMS IX which covered risk minimisation and where patient perspectives were briefly discussed within a wider discussion on stakeholders. He started with a short update on regulatory initiatives regarding patient perspectives and preferences in both US and EU which are also touching upon benefit-risk. Stephen supported the view that PV is a key stakeholder in patient engagement initiatives from early development through launch and lifecycle. The interaction with patients in PV and risk management during collection of safety information and risk minimisation activities provides unique opportunities for engagement. In addition, Stephen urged CIOMS to include HCP representation in this WG.

The concepts of patient perspectives, preferences and patient reported outcomes (PROs) were then briefly covered. Patient perspective and preference methodologies can be applied during benefit-risk assessment and risk minimization tool design. Patients are best placed to ensure such tools are used in the least burdensome and most effective manner. This can potentially save substantial time and cost, especially if performed during development. Providing results of patient input to regulatory authorities may also increase benefit-risk acceptability and support decision-making. Finally, Stephen stressed the importance of communication between stakeholders including the use of plain language to communicate more effectively.

Industry perspective – Mary O’Hare (Roche)

Mary provided additional industry perspective by commenting on the broad scope of the CIOMS concept paper saying that it should be targeted on a few key areas to have an impact. Despite patients being previously under-represented in this area, the proposed patient-centric approach fits very well with development of the personalised healthcare concepts. Industry is supportive of patient involvement in drug development, pharmacovigilance, risk management and use of digital technologies and social media as sources of safety information. In drug development, patients and patient groups that may contribute should be identified and training/education given including adverse event reporting separately from HCPs to identify what matters to the patients.

Patients/groups should be involved in PV and risk management, providing input to inform on acceptable risk-benefit balance also mitigating some of the current problems with data privacy. The use of digital technologies and social media for identifying safety signals is not established and there are concerns regarding various aspects including data quality and data privacy issues. Mary highlighted

potential priorities for the WG: improving the effectiveness of risk mitigation activities; increasing understanding of and adherence to labelling requirements; encouraging participation in data collection via organised schemes (e.g. registries), and; increasing understanding of the utility of unstructured social media type data in PV. Some concerns were also expressed regarding the heterogeneity of patients/groups, as well as the exponential rise in volumes of safety data and data that are less robust in quality. Industry is very supportive of the CIOMS XI initiative but is concerned to ensure that changes really add value and expectations are managed (i.e. cannot address all needs / priorities for each individual patient).

Regulator's perspective – Judy Zander (US FDA)

Judy presented the FDA perspective suggesting narrowing the scope of the WG to safety and within that to identify gaps and avoid duplication with ongoing initiatives. FDA believes that the scope should not include processes that are governed by national or regional legislation. Judy described a range of current initiatives at FDA involving patient input, from Advisory Committees during pre-marketing to post-marketing consumer reporting of adverse events via paper as well as electronic media. There is also a 'Voice of the Patient: Patient Focused Drug Development Initiative' that collected patient perspectives on drug development in a wide range of therapeutic areas under PDUFA V through a series of public meetings.

Judy presented several possible gaps for further consideration by the WG. In drug development, these gaps included the planning and conduct of clinical trials as regards safety communication with participants; approaches to safety data reporting from CT participants and ethical aspects for interactions and human protection. In risk management, knowledge is lacking on what risk management burdens are acceptable to patients, as previously identified in CIOMS IX where these concepts could be further developed. In pharmacovigilance, gaps include the methods for signal detection and evaluation from patient reported data, PSPs and registries and value of social media as a source of PV information. Judy also suggested future research on the best way to bring the patient perspective rather than individual patients perspective from a diverse community for regulatory consideration.

Regulator's perspective – Isabelle Moulon (EMA)

Isabelle provided EMA's perspective on patient involvement in a range of Agency activities. EMA has established for some years a framework for interacting with patients, consumers and their associations. This framework encompasses several principles including legitimacy, accountability and transparency. Interaction involves patients as representatives or experts. The representatives are not involved in product-specific activities but more on policy and guidelines. The experts are involved in the medicinal products in the same way as all other experts (e.g. clinical; scientific). Representatives must be transparent regarding funding and experts complete declarations of interest to avoid conflicts and sign confidentiality agreements. Patients and HCPs are currently involved in most of the key activities, committees and expert advisory groups pre- and post-approval at the level of EMA, including Scientific Advice, orphan drugs, paediatrics, human medicines, advanced therapies and at the Pharmacovigilance Risk Assessment Committee (PRAC).

The range of involvement includes face-to-face meetings, written consultation, committee meetings surveys and public hearings (as of September 2017). In addition to patients and patient organisations, civil society representatives and the general public may be involved.

The EMA advocates several principles for patient engagement: Keep your word and deliver; develop trust; seek mutual benefit and build on mutual respect. There are also challenges: funding and

remuneration; managing conflicts of interest; training and capturing patient's input from drug development to post-marketing.

Academia perspective – Sten Olsson (ISOP)

Sten provided the academia perspective starting with harm from medicines and accompanying burden to society. He went on to say that medicine-related harm cannot be determined without direct patient contribution and there are a number of reasons for that: very little is known about the burden in the community; several factors complicate the assessment: self-medication, internet sales, traditional meds, illicit drugs etc. There are also QoL consequences of medicine exposure; also old medicines will be new – patient reports, therefore, reflect burden better.

Regarding the profile of harm there can be additional perspectives from patients who are not inhibited by lack of explanation regarding side-effects. Patients may not be forthcoming in relation to HCPs when the harm involves sexual function, mental problems, abuse etc. or when they are not adhering to treatment. However patients are happy to tell their stories if encouraged. There is currently mounting scientific evidence for the value of patient reporting of adverse events even though it is not known how representative the results are.

From an academic perspective, needs exist in the following areas: Methodological development to adapt to use of soft data and vague information; literacy; communication challenges such as local languages, terminology that can be understood by patients and cultural considerations. There are also technological developments to consider such as social media screening, apps etc. as well as the need for collaborations, particularly with consumer organizations.

Mapping other initiatives relevant to the Working Group initiatives

Members of the WG exchanged knowledge on ongoing initiatives that could potentially be relevant to the patient topics under discussion in CIOMS XI and these initiatives are listed below, together with names of WG members (initials within brackets) that could provide feedback on progress, as appropriate.

- TRANSCCELERATE: Reporting from patient support programmes (CC),
- EFPIA initiative: EFPIA code of practice on relationship between pharmaceutical industry and patient organisations (CC)
- EUPATI: Patient education (KI)
- IMI PARADIGM: Patient engagement, expected to complete 2019 (KI)
- IMI PREFER: Patient perspectives and preferences, expected to complete 2021 (MSm, SH, LR)
- ADAPT SMART, completed (KI)
- WEB-RADR Part II electronic records, expected to complete in 18 months/Q4 2019 (MF)
- CTTI (Clinical Trials transformation Initiative): Framework of CTTI/FDA patient engagement collaborative (MSm, CC)
- PFMD: Patient Engagement Quality Guidance(MM)
- SCOPE: PV patient reporting (MF)
- Good Participation Practice for CTs (ND)
- ASTERIX project: Patient engagement in CTs (KLB)
- PCORI (Patient Centered Outcome Research Institute : Patient engagement standards (LR)
- ICMRA (International Coalition of Medicines Regulatory Authorities): (WG Member TBD)
- Summer School for patient advocates (FH)
- Vigil: contact person for pharmacovigilance in patient organisations (FH)

- Eurocab: community advocacy board, patient representatives for development of CTs and products in rare diseases (FH)
- BIO PHARM (MSm)
- PDUFA draft guidance (JZ)
- EMA guidance (IM)
- NHC: Patient representation in CTs
- Medical Device Innovation Consortium (MDIC) (PT)
- MRCT: Health literacy in CTs (CC)
- Patient groups @ DIA: (ND)
- DIA patient process/engagement (MSm)
- Universal patient language (MR)
- Dutch Pharmacist Association (KNMP) (WG Member TBD)
- PRINS (WG Member TBD)

The WG also discussed the need for other stakeholders who could contribute and add to the thoroughness of the membership. Lembit noted that he can contact the World Medical Association to look into the possibility of having a clinician representative join the WG. It was also highlighted that in general, this WG must strive to take a truly global approach and that may mean recruiting members from global regions not currently represented. In addition, the possibility of having an ethicist join was discussed. The concept of “patients’ rights” was also brought up (<http://www.aapsonline.org/patients/billrts.htm>).

Reflections on participants’ presentations and general discussion

The WG had discussions regarding the topics raised in the presentations and reviewed these in the context of the key elements of the CIOMS concept paper. In these discussions it was acknowledged that many initiatives in the area of patient involvement were ongoing and it was not the intention of the WG and CIOMS to duplicate any of these initiatives but to define where CIOMS would provide most value based on its consensus approach. For instance, the IMI PREFER project was tackling methodologies for eliciting patient perspectives and preferences in the benefit-risk assessment of medicines throughout their lifecycle. The CIOMS XI WG would not include the same scope within this WG, however, it could report the current state of knowledge arising from PREFER in CIOMS XI as members of this WG are also involved in PREFER. A similar situation would apply to several other initiatives and it would enrich the output from CIOMS XI to be able to provide an all-round status in the CIOMS XI book from many of these initiatives through the WG membership. As far as the WG was concerned there is no single reference document or group that covers the whole ‘universe’ of patient involvement with medicines and that CIOMS XI could provide such a reference document.

It was agreed that the views of the patient representatives on the scope of the WG were critical and therefore there was a breakout session involving the patient representatives. The high-level output from the patient breakout session was as follows:

- The scope should include the development of key principles and recommendations for patient involvement in the medicines lifecycle.
- The WG should gather examples of existing best practices but also examples of new thinking.
- The WG should consider patient involvement as a concept beyond medicines.
- Patient and community input should be obtained.

- The output of the WG should pull together all existing guidelines and processes from companies and regulators.
- The output should be reviewed by patients and feedback taken into consideration.
- The scope should include product information and PV communication.
- Patients do have practical examples regarding their involvement and these could be shared.
- Feedback from industry regarding their experience with patient involvement should also be obtained.

Areas for further work

The WG considered the following areas for further elaboration regarding its scope:

Key principles for patient involvement

The following could be considered (non-exhaustive list) under this topic:

- Rules of engagement
- Ethical considerations
- Informed consent in clinical trials
- Use of expert patient input in medicines development

Patient involvement in pharmacovigilance and risk management

The following could be considered (non-exhaustive list) under this topic:

- Reporting of ADRs by patients;
- Sources of reporting such as patient support programs (PSPs);
- Social media (open and closed, some concerns expressed by WG members);
- Technical developments (digital and mobile technologies);
- Risk management, communication and risk minimisation;
- Consider guides for patients: ADR reporting; risk management.

Communication (discuss in both of the above)

- Communication and feedback: From and to patients.
- Means and mode of communication
- Language considerations
- Survey of patient representatives and groups
- Development of a glossary

Note: Under the communication topic it was mentioned that ISOP are actively involved with risk communication initiatives and that interactions with persons leading such initiatives could be made.

Subgroups

The WG agreed to form 2 subgroups that then proceeded to have break-out sessions for the rest of the meeting. Membership of the 2 groups was agreed. Some highlights of the discussions on scope of the WG are detailed below.

Group 1: Principles of patient involvement

Output

The following are the highlights as presented to the plenary session at the end of Day 2:

- Proposed vision for the whole CIOMS XI WG: Developing medicines in partnership with patients.
- Scope for the group includes:
 - Guiding Principles for patient engagement
 - Rules of engagement
 - Review of background documentation
 - Review of best practices
 - Legal perspectives

The above in addition to other discussion topics are summarised below:

Landscape

Objective: Understanding the patient landscape around the world.

- Definitions for patients, carers, advocates etc. should be included in the CIOMS XI Glossary. EUPATI mapping for where patients could be engaged, timelines should be considered.
- Methodologies for patient engagement: patient groups; individuals; surveys.
- Why should patients be involved and what's in it for all stakeholders?
- Case studies should be sought that show the partnership is working.
- Need to manage the expectations of patients and patient groups and to prioritise.
- Pre-approval access e.g. accelerated approval (ICF needed?).
- Transparency: This is a topic that also applies to Group 2. It was agreed that Panos would join at least some of the TC discussions of group 2 to obtain feedback and avoid duplication.
- Ethics of patient involvement: Identified as a possible gap. Initially to be explored with CIOMS who have access to ethics expertise in their network. In this context it is important to come up with clear questions to be answered.

Five overlapping sub-teams were formed within Subgroup 1 to address the various topics on the work-plan: S1 – Landscape; S2 – Regulatory (How to engage patients and patient groups); S3 – Guidance from Industry; S4 – Literature on patient engagement across the lifecycle(ethics/environmental scan); and S5 – Surveys of patient engagement.

Other topics:

Action points on the following were added to the Subgroup's work plan:

- Glossary (in collaboration with Subgroup 2)
- Methods for engaging patients: Library of methods; How to engage?; Literacy considerations
- Communication (the involvement of a communications expert is being considered)
- EMA/PRAC and EU guidance on patient engagement
- Ethics and funding considerations
- Vulnerable populations including children and adolescents.
- Industry use of registries.
- Ethics: Funding; data privacy; disclosure; industry-patient collaboration; transparency.
- EU Legislation regarding prohibition of direct-to-patient promotion.

As many WG members have not participated in previous CIOMS WGs, a recent CIOMS book such as CIOMS IX will be made available to the WG members so that they could familiarise themselves with the final output from a CIOMS WG in terms of typical content and presentation.

The guidance to be produced by CIOMS Working Group XI will be written in plain language to be understandable to a wide audience including patients.

Group 2: Patient involvement in pharmacovigilance and risk management

Output

Vision for CIOMS XI: Effective participation of patients in the development and safe use of medicines.

Vision for Group 2: Effective participation of patients in pharmacovigilance and therapeutic decision making.

Outline of topics:

Group 2 further divided itself up into sub-teams on the following topics:

1. Guiding principles for patient involvement in the content and formatting of labeling
2. Guiding principles for patient participation in the design, implementation and evaluation of additional risk minimization measures
3. Guiding principles for patient participation in the generation of safety data
4. Guiding principles for patient participation in developing crisis communications regarding medicinal products
5. Guiding principles for patient participation in therapeutic decision-making

The work plans for Group 1 and Group 2 will be posted in the WG XI members' area of the CIOMS website for all WG members to view.

Concluding plenary discussions

Several topics were discussed by the WG members as follows:

- The 2 subgroups should continue to work through teleconferences (TCs). CIOMS will assist in organising these TCs as required.
- The 2 subgroups can form sub-teams to work on the various topics agreed in their work plans. Members can participate in several sub-teams according to their interests, expertise and availability.
Post meeting note from CIOMS: It would be possible to have members participate in sub-teams of both group 1 and group 2; expressions of interest can be made directly to group co-leads keeping CIOMS informed.
- Draft outputs from sub-teams of Group 1 and 2 should be prepared and circulated to members by the next meeting. They may include summary points (e.g. bullet points) of the key elements and/or more developed detailed text where appropriate.
- Mapping of existing projects in the patient engagement space: Updates on their progress will be provided via the CIOMS website.

Date of next meeting

The next meeting will take place in Berlin on 23–24 October 2018.

Participants

CIOMS	Lembit Rägo Panos Tsintis	Secretary-General Advisor
WHO	Shanthi Pal	Safety and Vigilance Team (SAV)
Patient representatives	Nikos Dedes Francois Houÿez Kaisa Immonen Kerry Leeson-Beevers	European AIDS Treatment Group (EATG) European Organisation for Rare Diseases (EURORDIS) European Patients' Forum (EPF) Alström Syndrome UK
Regulators	Ton De Boer Mick Foy Liz Anne Gillham-Eisen Isabelle Moulon Tsunehiro Oi Martina Schäublin Judy Zander	Medicines Evaluation Board (MEB), the Netherlands – Day 2 only MHRA, United Kingdom Health Canada* European Medicines Agency (EMA) Ministry of Health, Labour & Welfare (MHLW), Japan Swissmedic U.S. FDA
Academia / Pharmacovigilance	Linda Härmark Marie Lindquist Sten Olsson	Netherlands Pharmacovigilance Centre Lareb Uppsala Monitoring Centre (UMC) International Society of Pharmacovigilance (ISOP)
Industry	Matthias Boedding Cathryn Clary Beverly Harrison Stephen Heaton Marilyn Metcalf Mary O'Hare Ravi Patel Laura Peppers Michael Richardson Leo Russo Meredith Smith	Merck Novartis Janssen Bayer GSK Roche United Therapeutics Takeda Bristol-Myers Squibb Pfizer Amgen Inc.

Apologies

Patient representatives	Kawaldip Sehmi	International Alliance of Patients' Organizations (IAPO)
Regulators	Almath Spooner	HPRA Ireland

* Post-meeting note: Denis **Arsenault** subsequently replaced Liz Anne Gillham-Eisen as the representative for Health Canada.
