



**Second meeting of CIOMS Working Group (WG) XI:
Patient involvement in the development and safe use of medicines
23-24 October 2018, Berlin, Germany**

Minutes

As at 22 November 2018

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Opening

LR welcomed the participants and mentioned the added value that the CIOMS guidance can have to help promote principles of patient involvement as described in various documents.

Dr Michael Levy, Head of Pharmacovigilance, Bayer AG, added his welcoming words, pointing out the importance of pragmatic guidance on patient input all along the life cycle of medicines, from development to retirement from the market. He appreciated the impact that the CIOMS working group with its members from across a range of sectors can have to ensure that a patient-centric approach is taken in considering the risks and benefits of medicines.

Stephen Heaton and Panos Tsintis, assisted by Monika Zwegarth, were selected as rapporteurs for the meeting. Nikos Dedes and Kerry Leeson-Beevers, assisted by Kaisa Immonen, were selected as Chairs. The participants then introduced themselves. New group members briefly described their expertise and type of input they can bring to the Working Group. A list of participants is shown in **Annex 1**.

Agenda, approval of previous meeting minutes

The participants adopted the meeting agenda. The minutes of the 1st WG meeting, held in Geneva on 19-20 April 2018, were adopted at the end of Day 1, with one clarification: The perspective of ISOP is wider than “academic” to include all stakeholders. (*Post-meeting note: The minutes of the 1st Meeting have been amended.*)

Experience from FDA initiative on patient-focused drug development

Theresa Mullin gave some background about the FDA's initiative to develop FDA guidance on patient-focused drug development. The revision of the first guidance in a series of four¹ was informed by extensive user feedback and lessons learned. This has resulted in a much clearer guidance that has been well received by stakeholders across all sectors. A public workshop was held on 15-16 October 2018 to inform the development of two additional texts.²

The meeting participants appreciated the feedback on this initiative, in which some of them have been involved. The EMA's patient engagement cluster has been in ongoing information exchange with the FDA about this initiative, and the European Patients' Forum (EPF) had submitted a draft reflection paper. The experience from this initiative will be considered by the WG in producing its report.

General and procedural remarks on WGXI report

Added value

There are numerous existing materials on patient involvement initiatives undertaken by different organizations. The added value of the CIOMS report will be to: (1) bring this information together in one place; (2) provide a global perspective, and (3) fill gaps in existing guidance, notably in the post-marketing phase of medicines.

Audience

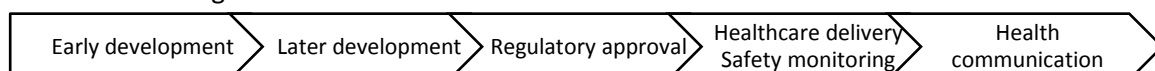
The audience of the report will be the stakeholder groups represented in the WG. In addition, strategic direction will be provided to national policy-makers. As the CIOMS recommendations are not mandatory, the report can make some bold, aspirational statements. Some call-out boxes could be included throughout the chapters, listing what would be needed in the wider environment ("ecosystem") to enable full implementation of the recommendations.

Language and format

For maximum impact the report should convey clear messages in an easy-to-read, appealing format. Theo Raynor gave some guidance on how to achieve this:

- Use clear (not necessarily simple) language, aim for a conversational tone
- Break down the text by using subheadings and bullet points.
- Include brief, illustrative case studies in the chapters.
- Start each chapter with a short summary and/or 5-9 key messages in bullet points. Taken together, these short sections could form a brief, easy-to-read version of the CIOMS WGXI report.
- Ensure easy navigation of chapters and sections.

It was suggested to use a graphical representation of decision-making stages throughout the report for easy navigation. An example was proposed by Group 1 (see below), along with a table of contributions that patients, health care professionals, pharmaceutical companies and regulators can make at each stage.



¹ Patient-Focused Drug Development: Collecting Comprehensive and Representative Input. June 2018/ <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM610442.pdf>

² Meeting materials available at: <https://www.fda.gov/Drugs/NewsEvents/ucm607276.htm>

Once the report is more mature, the WG will consider the inclusion of visuals, including good quality infographics.

CIOMS will consider whether the final report could be made available as an e-book with electronic links (in addition to PDF and hard copy).

Input by patient representatives

Patient representatives in the WG will provide input to all chapters of the WG report.

Need for surveys

Participants agreed that surveys should only be conducted to answer any burning questions. Focus group discussion could be an alternative to collect information on certain topics. The sub-teams will collect questions in the lead-up to the 3rd WG meeting. The open pre-meeting to be held ahead of the 3rd WG meeting (see page 7) may also present opportunities to identify any new questions or find answers to existing ones.

Additional experts

The WG members felt that more input is needed from patient representatives and health professionals, and in specific areas such as bioethics. To keep the WG to a manageable size, this input will be sought from “ad hoc members” who will participate in teleconferences and have access to working documents, but will not attend face-to-face meetings. Their contributions will be listed in the acknowledgements section of the report.

Progress with WGXI report drafting

Draft table of contents

Panos presented the current working version of the table of contents for the WG XI report (see **Annex 2**), together with WG members’ comments received. This had formed the basis for groups and sub-teams to draft specific sections as shown below.

The sub-teams then presented outlines of their sections for discussion by the full Working Group.

Glossary

Definitions world-wide are evolving, and CIOMS can possibly contribute to alignment. One way of achieving this is to compile a cumulative glossary of past and current definitions from CIOMS reports to be maintained as a live document on the web. An illustrative draft was presented at the meeting. Participants agreed that a cumulative record of evolving CIOMS definitions over time would be a useful resource. All definitions must be referenced.

For the WGXI report, new terms to be defined include (list not exhaustive): “Risk tolerance”, “Patient-centric”, “Unmet medical need” and “Patient involvement”. The report should also clarify the roles of patients versus that of care-givers and family, and define or explain what is understood by “meaningful” patient input³.

The subteam in charge of the Glossary will review the report for consistent use of terms across chapters.

³ Post-meeting note: Elisabeth flagged the ongoing work by ISPOR’s Patient-Centered Special Interest Group; see <http://press.ispor.org/index.php/defining-patient-centeredness-in-healthcare/>

Chapters 1-4 (Group 1)

1. Introduction

This section will:

- Set the scene, i.e.: State “why” the topic of patient engagement is so important throughout the medicines lifecycle, give historical context, explain why there is a compelling need for this book now, and set out some fundamental definitions and concepts.
- Give examples of how patient engagement will add value, and will discuss:
 - The perspective of patients, carers/caregivers and patient organizations (with a special section here or elsewhere on characteristics of reputable patient organizations)
 - Special populations: children, the vulnerable such as cognitively impaired, rare diseases
- Give an overview of the topics covered in the report. It will mention that access to marketed medicines is out of the scope of this guidance, noting that one way to improve access to needed products is to consider patient input early in development.

The group endorsed the proposed outline and suggested to include some language on the patient role in e-health and the importance of engagement with HTAs.

2. Landscape of patient engagement, patients involved in regulatory initiatives

This section will provide an overview of regulatory and non-regulatory patient engagement initiatives globally. It will:

- Describe how and when in the medicines life cycle patients can be involved in decision-making (using a life cycle graphic);
- describe common challenges such as: conflicts of interest, managing expectations, need for technical harmonization, need for capacity-building, and compensation issues; and
- make recommendations, based on lessons learned and experience made in different jurisdictions to date.

The section will provide more details and references in an appendix; this could show the historical evolution of patient involvement over time.

3. Patient Involvement in Advancing Treatments for their Disease

This section will:

- Introduce the scope of patient engagement in development, noting that it goes beyond specific product development programmes;
- outline how stakeholders can work together at all stages of development, from expression of interest through early and late development to regulatory assessment and value assessment; and
- show how stakeholders can communicate about these efforts to the broader patient/disease community and to the public.

4. Guiding principles for engagement

This section will cover:

- The principles of transparency, communication and reciprocity, and other relevant ethical concepts to be identified with the help of a bioethicist;
- points to consider in building patient-centric drug development organizations, i.e. how to promote a patient-centered mindset and ensure that all partners have the capability and resources to engage with each other efficiently and sustainably;
- best practices for selecting partners, implementing training and education, and managing legal and patient right issues (contracts, conflicts of interest, compensation, fair market value and health literacy), giving some examples;

- measures of success, and their use for continuous improvement; and
- future directions.

It was suggested to consider the upcoming revision of the ICH Good Clinical Practices guideline (ICH E6R3), as well as examine ISO 27500 about human-centered organizations as an applicable standard.

Chapter 5: Patient involvement in pharmacovigilance (Group 2)

5.1: Patient involvement in the content and formatting of labeling

This section will cover the following topics:

- The unique value of patient engagement in product labeling
- Landscape:
 - Countries world-wide providing patient-targeted labeling
 - Types, formats of patient-targeted labeling provided
 - Rules and regulations in place on patient-targeted labeling, and what they say about the need for involving patients
- Historical overview of initiatives to improve patient-targeted labeling; examples
- Gaps/needs
- Recommendations and proposed future steps

It was suggested to add a consideration of differences between patient populations and subgroups. The report should also mention the need for specially designed practical instructions on how to take medicines and suggest that regulators could require such materials in addition to the routine labeling/SPC, as piloted in the Netherlands. The role of medical associations, pharmacists and other trusted gatekeepers in disseminating practical instructions should be highlighted. Furthermore, the report could include examples of the impact of patient-centric labeling.

The need for a survey to inform this section will be reconsidered after the 3rd WG meeting (see also page 3).

5.2: Patient involvement in the design, implementation and evaluation of additional risk minimization measures

This section will describe:

- How patients can provide input to the design of risk minimization tools (e.g. labeling, consent), and
- how patient perspective and/or preference in benefit-risk acceptability can change if risks are reduced, considering
 - which risks are important to patients
 - how risk reduction affects adherence to treatment, and
 - what factors may impact the benefit-risk acceptability including ethical considerations.

It was suggested to add information on digital technologies, and on how measures and communication of uncertainty (as a statistical concept) affect patients' perception of the benefit-risk trade-off. Stephen mentioned the App previously considered (but not taken further) by CIOMS IX that could be shown in this WG in order to further discuss if it could be further explored.

5.3: Patient involvement in the generation of safety data

This section will describe the following:

- Current environment: Setting and context (various types of studies, social media, legal actions, crisis management), communication channels between stakeholders, rules and criteria for engagement, methods of communicating data
- The patient's perspective

- Gaps, needs and untapped opportunities for open access to patient benefit-risk data
- Challenges (e.g. linked to legal requirements, large volumes of real-world data, social media, training, and vulnerable populations)
- Future directions, conclusions (with a case study on lessons learned).

It was noted that data affecting the benefit/risk trade-off include real world data from the post-marketing setting on both safety and effectiveness.

5.4: Patient involvement in developing crisis/time-bound communications

This section will cover:

- Basic concepts: What is meant by urgent and/or time-bound communication, in what situations is this needed, and what it aims to achieve, namely: to make sure that relevant, clear, actionable communications reach the patient.
- Scope: medicines and devices needed to deliver them, e.g. inhalers.
- Patient involvement: What is the patient population to be addressed; why involve patients in designing urgent communications; developing ideas and degrees of urgency for various communications; adaptation based on patient feedback; what do patients consider a crisis, and what should be communicated how and when.
- Communications: Types (e.g. clarification, additional communication, educational); contact for questions; links for communication, role of patient organizations; how to ensure vulnerable patients are reached.
- Delivery of messages: Clear language; template development; review process; details to include in a “crisis communication”; how to ensure a prompt response to the issue at hand.
- Considerations for specific types of medicines: Investigational versus marketed products; generics (e.g. how to make it clear which generic products are concerned)
- Distribution: in print, online, via apps; future trends: social media, YouTube etc.; links to formal regulatory messages; and how to ensure that the target population is reached.

Patient representatives had provided their input to the subteam’s work, highlighting the importance of:

- Clear communication on who is impacted, how they are impacted, and what they should do (putting the most urgent actions first).
- Timelines: Ensure the urgency is understood by the patient; use of SMS or e-mail where possible, and/or direct communication by patient organizations to the people concerned
- Identifying the most common channel linking the medication and the patient (e.g. pharmacist, health care professional, online pharmacy carer, etc.)
- Follow up: Consider metrics for assessment of effectiveness. Has the communication reached patients, have they understood the message, and were they able to act appropriately in response?

In the discussion participants mentioned that communication channels may differ depending on the setting, and that the terminology for urgent communications can be prepared and tested in advance.

5.5 Patient involvement in therapeutic decision-making

This section will essentially reference existing recommendations on patient involvement in treatment guideline design. The report should document the current trend towards more patient involvement in treatment guidelines, and how this has added value. It could also flag areas where patients are still not sufficiently involved.

The topic will be discussed with WMA experts. It was agreed that drafting of this section does not require a separate sub-team.

Gaps and cross-cutting topics

The participants identified gaps in the sections as outlined above and allocated the topics to Groups (see **Annex 2**).

The following cross-cutting topics were identified:

- Communication about uncertainty; trust issues; feedback to patients
- Access to information
- Vulnerable populations (e.g. children, pregnant women, incarcerated)
- Generating and sharing patient data – rationale and impact (detail to be provided in Chapter 5; principles to be referenced in Chapters 1-4)
- Impact of patient sharing their experiences
- Donating data for further scientific understanding (e.g. data on medicines that do not progress to market; placebo data)
- Preventative versus treatment, and how to communicate about each
- Methods of gathering patient data, methods of analysis (references to existing work)
- Societal pressures to speed up access through ‘right to try’ and expanded access programmes

The report will not address the following topics:

- Media, role of journalists
- Access to medical products: pricing, intellectual property etc.

Group work and report-back

Groups 1 and 2 worked separately to consider the outlines and suggestions made for additions, and briefly reported back in plenary session at the end of Day 2. The Groups will work by teleconference on their allocated sections in the time until the next face-to-face meeting.

Date of next meeting

The 3rd Working Group meeting will be held on 1-2 May 2019 in Geneva.

Open pre-meeting

The 3rd Working Group meeting will be preceded by an open pre-meeting, to be held on 30 April 2019 in Geneva. This will help to raise awareness on the work of the CIOMS WG on patient involvement and to obtain input from patient organizations and other stakeholders.

2019 marks the year of the 70th anniversary of CIOMS. A press event and a webcast can be organized to give wider publicity to the Council and its current work on patient involvement.

CIOMS will explore possibilities to offer financial support for participants from patient organizations to attend the pre-meeting.

A programme committee for the pre-meeting was established, consisting of: Cheryl Renz, Elizabeth Oehrlein, Kerry Leeson-Beevers, Regina Kamoga, Judy Zander and Leo Russo. The committee will meet by teleconference and circulate its proposals to the full WG for input. Judy will link with DIA and facilitate a CIOMS presentation at the DIA annual meeting to be held in San Diego in June 2019.

Closure

In closing the meeting Lembit Rāgo thanked the participants for their commitment and passion in producing this timely and needed guidance. He extended special thanks to Bayer AG for hosting the meeting. Bernd Düsing was thanked for his excellent organization of the logistical details.

Annex 1: Participants

* = new member

CIOMS	Lembit Rägo Panos Tsintis *Monika Zweygarth	Secretary-General Senior Advisor Technical writer
WHO	Shanthi Pal	Safety and Vigilance Team (SAV)
Patient representatives	Nikos Dedes Kaisa Immonen *Regina Kamoga Kerry Leeson-Beevers *Elisabeth Oehrlein	European AIDS Treatment Group (EATG) European Patients' Forum (EPF) International Alliance of Patients' Organizations (IAPO)/Community Health and Information Network (CHAIN) Alström Syndrome UK National Health Council, U.S. (alternate for *Marc Boutin)
Regulators	*Denis Arsenault Ton De Boer Isabelle Moulon Theresa Mullin Judy Zander	Health Canada (replacing Liz Anne Gillham-Eisen) Medicines Evaluation Board (MEB), the Netherlands – Day 1 only (alternate for Sabine Straus) European Medicines Agency (EMA) U.S. FDA U.S. FDA
All stakeholders / Pharmacovigilance	Brian Edwards Linda Härmark Theo Raynor	International Society of Pharmacovigilance (ISOP) (alternate for Sten Olsson) Netherlands Pharmacovigilance Centre Lareb Leeds University, U.K. (retired)
Industry	*Olatayo Apara *Stella Blackburn Matthias Boedding Cathryn Clary Beverly Harrison Stephen Heaton Marilyn Metcalf Mary O'Hare Ravi Patel Cheryl Renz Michael Richardson Leo Russo Meredith Smith	Takeda (replacing Laura Peppers) IQVIA Merck Novartis Janssen Bayer AG GSK Roche United Therapeutics Abbvie Bristol-Myers Squibb Pfizer Amgen Inc.

Apologies

Patient representatives	Francois Houÿez	European Organisation for Rare Diseases (EURORDIS)
Regulators	Mick Foy Daisaku Sato / Tsunehiro Oi Almath Spooner Martina Schäublin	MHRA, United Kingdom PMDA, Japan HPRA Ireland Swissmedic
Academia / Pharmacovigilance	Marie Lindquist / Christina Star	Uppsala Monitoring Centre (UMC)
Health care professionals	*Christian Thomeczek	World Medical Association
Industry	*Rebecca Noel	Abbvie

Annex 2: Report structure, and additional topics identified for Groups 1 and 2

Section	Gaps / additional topics identified; (Comments)
<p>To be drafted by Group 1:</p> <p>1. Introduction</p> <p>2. Landscape of patient involvement initiatives</p> <p>3. Rules of engagement</p> <p>4. Patient involvement during drug development</p>	<ul style="list-style-type: none"> • Regulator perspectives outside US/EU, differences in regulatory approaches • Added value of patient involvement • Genetic testing/samples, in the context of data protection: ethical guiding principles • Communication, health literacy, design of materials • Health literacy: key principles (reference) • Patient involvement in trial design, ongoing feedback • Patient engagement individually versus through organization • Access to medicines, different mechanisms for • Principles of patient engagement, transparency • How to engage in a systematic way • Who is the audience of the report • Bioethics (also in an appendix - need expert) • Role of caregivers/partners (also in glossary) • Consumers versus patients (also in glossary)
<p>To be drafted by Group 2:</p> <p>5. Patient involvement in pharmacovigilance</p> <p>5.1 Guiding principles for patient involvement in the content and formatting of labeling (Sub-team 1)</p> <p>5.2 Guiding principles for patient participation in design, implementation and evaluation of additional risk minimization measures (Sub-team 2)</p> <p>5.3 Guiding principles for patient input in the generation of benefit-risk data throughout the life cycle of a medicinal product (Sub-team 3)</p> <p>5.4 Guiding principles for patient input in developing safety issue communications regarding medicinal products (Sub-team 4)</p> <p>5.5 Guiding principles for patient participation in therapeutic decision-making</p>	<ul style="list-style-type: none"> • Safe use of medicines • Digital, including educational tools • Advanced therapies, individualized therapies, hospital-only medicines, vaccines: communication; leaflets? • Metrics of success / impact (avoid over-quantifying) • Human factor testing – methods, labeling etc. • Confidentiality, GCPs, guidance; data privacy (note the upcoming revision of ICH GCP: ICH E6 R3) • Reimbursement (generating meaningful data for) • How to develop registries, natural history studies etc., practical guidance • Individual data protection, ownership of data
<p>To be drafted at a later stage:</p> <p>6. Patient involvement in benefit-risk</p> <p>7. Key stakeholders</p> <p>8. Future directions</p> <p>9. Conclusions and recommendations</p>	<p>(WG member comment: A standalone chapter on patient perspectives on medicines may be written by the patient representatives participating in the WG to appeal to a patient audience that may find other parts of the book not so relevant to them.)</p> <p>(WG member comment: This could be included in each chapter above, as relevant)</p>
APPENDICES:	
<ul style="list-style-type: none"> • Glossary 	(To be drafted by the Glossary subteam)
<ul style="list-style-type: none"> • Ethical considerations 	(WG member comment: Bioethicist needed)
<ul style="list-style-type: none"> • Stakeholder feedback (meetings and surveys): Patient organizations; healthcare professional organizations; pharmaceutical companies 	(This will show experiences and benefits of patient involvement as perceived by each type of stakeholder. It could be linked to the introduction and landscape of patient initiatives.)
<ul style="list-style-type: none"> • Practical examples of patient involvement in the medicines' lifecycle 	Examples should be used throughout the main body of the report. Where more detail would be useful to the reader, detailed examples can be presented in the Appendix.
