2nd meeting of the CIOMS Working Group WG XIV on Artificial Intelligence in Pharmacovigilance

10-11 October 2022, Geneva, Switzerland, hybrid meeting

Meeting Minutes

Overview:

Summary and action points 1
Minutes of discussion 1
1. Opening and welcome 1
2. Subgroups presentations of their draft Tables of Contents 2
3. Involving vendors 9
4. Forming writing teams 10
5. Way of working 11
6. Next steps / next meeting 11
7. Closing remarks 11
8. Annex 1: List of participants 12
9. Annex 2: Writing teams 13
10. Annex 3: Merged Table of Contents (Draft) 13

Summary

The CIOMS Working Group XIV on Artificial Intelligence in Pharmacovigilance held its 2nd meeting with participants attending both in-person and virtually on 10-11 October 2022.

The WG discussed the Table of Contents of the future report. Two subgroups presented the independently drafted table of contents of the future report, which were merged during the WG 2nd meeting. Chapter teams were formed to start drafting.

Minutes of discussion

Day 1

1. Opening and welcome

Hervé le Louët, CIOMS President, welcomed the members to the 2nd CIOMS Working Group XIV on Artificial Intelligence (AI) in Pharmacovigilance (PV) and wished all a fruitful meeting.

Lembit Rägo, CIOMS Secretary General, added his words of welcome and opened the meeting as Chairman for the two days (for a list of participants see **Annex 1**)

CIOMS has recently published:

- Patient Involvement in the development, regulation and safe use of medicines report of the CIOMS Working Group XI.
- CIOMS Cumulative Glossary with a focus on Pharmacovigilance (Version 2.0). This is a living document and terms form the CIOMS WG XIV report glossary will be added in time.
- Glossary of ICH terms and definitions.

WG XII Benefit-risk balance for medicinal products and WG XIII Real-world data and real-world evidence in regulatory decision making are both expected to be finalised next year. There are several CIOMS WGs continuing their work with information available at the CIOMS website.

The meeting was held in a hybrid form with several members joining via Zoom.
Tour de Table: all participants introduced themselves.
The meeting agenda was adopted.

2. Subgroups presentations of their draft Tables of Contents

- Walter gave the Subgroup 1 team's presentation and Arvind gave Subgroup 2's. The following represents the discussion points raised after both presentations.
- We can use the currently available sources to ensure the validity of some of the existing AI capabilities. This is an area for further discussion and guidance from regulators will be valuable.
- Regarding the section on the audience and the statement that HTA should take the lead - is there an overarching goal for how the discussion should proceed? The general approach is to recognise that there are many similarities but also some clear differences in the needs of different stakeholders.
- In terms of implications for the workforce, the goal is to use the machine to help people prioritise and focus on other activities that improve patient safety.
- The aspect of trust towards the new technology should be addressed. There needs to be clarity about the methods to ensure the validity of the results.

On human gold-standard

- We should address the expectations regarding the 'human gold standard' and note that humans are not perfect. Perhaps we should describe the kind of studies that could be done to define the actual overlap of expert decisions so that we have a benchmark against which to measure AI.
- Human performance should be the baseline. The minimum performance of the machine must either be equal to or better than human performance.
- Would the section on setting expectations focus on the positive aspects of AI in terms of continuous improvement, e.g. improving data quality, or on the challenges of AI?
- It is difficult to set expectations and claim that AI's decision-making will be equal to or better than human decision-making because AI is supposed to learn from its own decisions. We should set some initial thresholds and convey that the system will evolve to be as reliable as human decision-making or even better.
- We should address the expectations and perhaps the hopes of different stakeholders about AI. Some consensus or set of principles will be useful.

- One of the most important points in the report would be to agree on what is considered acceptable when introducing AI technologies. Comparing AI to human performance is perhaps the most obvious option, but we should bear in mind that even if algorithms do not perform as well as humans, they can analyse large amounts of data much faster than humans.
- AI and ML technologies only provide us with the tools for decision-making, not fundamental truths.
- Standards would be a beneficial addition to all aspects of the future report. The questions raised are:
    - Are we all compliant with a particular standard?
    - Are our data structured similarly across different institutions?
    - When we evaluate whether a system works, do we have the same set of principles?
- It is among the responsibilities of regulators to conduct inspections to ensure that PV systems meet standards, and every PV group in the industry must also ensure that they meet these standards. There may be some challenges, e.g. if different standards are applied by different regulators, this would create some uncertainty within a company, which in turn discourages the adoption of a new technology.
- If a human is asked to confirm the AI's findings, the knowledge that the information came from an AI may change the outcome. Human verification is therefore best done independently of the AI results.
- There is a widespread belief that human decision-making is the gold standard, although, in clinical situations, including in PV, people make mistakes and do not always agree. The quality system approach aims to ensure that there are multiple ways to ensure that the machines' contribution to the system leads to the correct answer, similar to how a fully human system must have multiple ways of assuring that the answer is correct.
- AI and ML are efficient tools. They will always have false-positive and false-negative testing characteristics, which need to be taken into account.
- From an industry perspective, we need some governance and best practices or guidelines for dealing with this technical component that now also produces false positives or false negatives that did not exist in the past.
- The expectation that new technologies will increase efficiency and effectiveness and generally perform better than humans should be addressed. Vendors promote AI as a solution that will improve a given organisation's effectiveness. Discussions need to carefully balance the fact that while technology is evolving, it is not always 100% flawless.
- We need to be careful when comparing the quality of an AI or ML algorithm to the performance of a human. From the perspective of a PV system, we are concerned with the quality of the overall performance of the system, not just the quality of the components used in that system.
- There is a certain caution, perhaps unique to AI and ML, about the potential transferability of algorithms from one data source to another, even if they have been validated to a gold standard.
- A clear gold standard facilitates the inspectorate to decide whether the assessment of the algorithm is correct. The WG will hopefully provide recommendations on the discussions about when AI and ML will be successful. If human judgement is considered the gold standard, it should be human assessment in realistic conditions.
- In academia, the term 'reference standard' is used instead of the gold standard because humans make mistakes. We need to consider whether we expect AI tools to support decision-making

with humans actively involved in the final decision, or whether we expect more automation and more final decisions from these tools.

Including use cases

- The WG needs to discuss how use cases will be handled.
- Setting expectations for regular use cases will be a big challenge, e.g. setting the threshold for signal detection. Several factors affect whether AI is appropriate for certain use cases.
- Certain tasks are the same in all use cases, e.g. processing free text and converting it into structured data, which is required at all stages of the PV lifecycle. We could have a language processing system that converts the free text data into a structured format that is acceptable for all use cases.
- The aim of this WG is also to identify specific use cases and this kind of technology, innovation can assist the whole industry as everyone is facing the same data issues when it comes to processing a large amount of data
- Should the role of the WG not only be to inform but also to help accelerate innovation? We should rather discuss where AI tools can be used, and which aspects of PV AI could improve.
- Examples with illustrations of AI implementation or what has already been applied would encourage stakeholders to follow suit.
- The WG should aim to develop a set of general principles that would encourage future openness to developments. Appendices of the report can be used to illustrate the trends and provide examples.
- Use cases could be added as appendices and discussed in terms of their application to some of the core concepts. Over time, we could add more use cases to keep the document up to date without major changes to the core concepts.
- Finding appropriate use cases could be a challenge, as the organisations which have identified them may not wish to discuss them in detail. We should maintain a dynamic approach to the use of use cases as there are advantages to both attaching them as appendixes and distributing them throughout the document.
- More significant use cases may emerge in the future, but recognising the characteristics of particular use cases would provide information on the technical aspects to be evaluated in the development of AI tools. This in turn provides the basis for defining the requirements for future use cases. Therefore, we should consider including the description of use cases in the main document.

Glossary and language

- Precise terminology will be crucial. 'ML and processing' versus 'ML and decision-making' are different things. The definitions should be kept separate to some extent and may converge at some point.
- The WG discussed including a section on terminology at the beginning of the report explaining the relevant terms, including the distinction between artificial intelligence and augmented intelligence.
- The term AI should be defined as very specific to PV itself.
- The creation of a glossary and the use of synonyms aid in establishing common definitions.
- Should the terms and definitions in the glossary be for experts or laypeople?

- When compiling the glossary we must consider the main audience of the report, which for CIOMS documents are regulators, industry, and academia. An executive summary will include information on all chapters and will be written in language that involves the wider audience.
- It was agreed to include a lay summary of all chapters as this would appeal to the widest readership.
- The aim is to focus on the PV, although the issues concerning the use of AI are extremely broad.
- Several documents on definitions have been shared with the WG and uploaded to the WG member area. We should not be too constrained by these definitions as the field is constantly evolving.
- The CIOMS Cumulative Pharmacovigilance Glossary 2.0 is available on the CIOMS website and compiles terms and definitions from published CIOMS PV reports. The WG is welcome to consult it as a resource when considering its terms, definitions, and sources.
- It is encouraged to use existing definitions, but new definitions may be created, or existing definitions modified as needed.
- Chapter leads will collect and suggest terms during the drafting process, which will then be discussed with the WG and added to the glossary.

Including initiatives

- Kirsten shared a link to the EU inspectorate working group (Suggested criteria for using AI/ML algorithms in GxP). The project is based on healthcare data from Denmark registries and from health practitioners which include relevant examples.
- Kirsten will also share the Draft of Questions for critical GxP AI-ML application.
- WG members involved in or aware of initiatives discussing AI are invited to inform the members in order to share knowledge and avoid possible overlap between the work of parallel groups.
- It would be beneficial to conduct a gap analysis to identify some of the areas of consensus and some of the outstanding issues that have not been addressed by current initiatives.
- A comprehensive examination of the literature would help identify the missing areas in related documents.
- Articles on AI have already been published which also discuss the gaps in the regulatory agency that AI might support. The WG members involved are invited to share the relevant articles.

Including examples

- A list of general PV life cycle process steps would provide examples for all areas to make the document more attractive to the audience. Examples to illustrate the general principles are still needed.
- We should only use real examples where the contribution of AI and ML to PV is visible.
- The U.S. FDA Sentinel is a valuable example of how multiple partners contribute different data that adhere to the same model and support the model in development.

Inspections

- We should have a common understanding of what the expectations are for a successful inspection.
- The purpose of inspection of AI and ML is to ensure that we can maintain quality.

- The inspection of systems that use ML and NLP is firstly to ensure quality and human oversight, and secondly to ensure that the company is properly monitoring the systems in use. We would like the regulators to go further in their questions because this will also challenge the industry.
- It is important to be transparent and maintain open communication with stakeholders because even if the tool created is not 100% accurate, it will be accepted with less resolution. Otherwise, the process of adapting the new tool will fail.
- Are there risks to the core of safety surveillance in any of the process steps we want to automate? The models used are trained on past data, so is there a risk that new associations will not be recognised? How can we integrate this into the agenda?
- Lembit suggested the WG consider adding an appendix to the future report that provides more high-level information on the key points about AI and ML in PV.
- How should we seek input from inspectors? Should we approach the members from regulatory bodies or should CIOMS try to identify and approach the relevant authorities? AI will become a part of PV activities and consequently remain under the inspection radar.
- The industry's willingness to participate more actively in the application of AI and ML in PV depends on a clear understanding of the regulatory landscape and inspection expectations. The value of a CIOMS guidance document lies in providing a set of principles that facilitate a common understanding, which in turn can be used to develop a harmonised set of expectations to advance the field.
- Instead of data science and other technical aspects, the inspectorate will focus more on the overall quality aspects.
- The future report should aim to define the approach to inspection, because, e.g. from the FDA's perspective, the regulatory framework is already in place. It is a matter of translating new technology into the practical steps of conducting inspections.
- For members of the regulatory body to contribute more fully, they need to be familiar with the systems in place, which may not always be the industry's preferred approach. We need a safe space to share ideas and perhaps this is an area where CIOMS WG can contribute, but it does not necessarily require inspectors to participate in WG.
- We should be cautious about setting requirements at this stage as inspectors, by producing final guidance, may restrict some of the research and development that companies and regulators may wish to undertake.
- The WG agreed that the inclusion of a set of overarching principles for the report would be beneficial and members of the WG will seek input from agencies and inspectors at the appropriate stage of drafting the report.
- Benny offered to share information on the work of the Pharmaceutical Inspection Co-operation Scheme (PIC /S) working group, which is specifically looking at developing training materials for inspectors to inspect AI systems. Communication between the two working groups would be beneficial.
- Members of the (PIC /S) WG as well as other relevant initiatives could be invited to the meetings of CIOMS WG (in person or virtually) to give a presentation and thus promote interaction for mutual benefit.
- Discussions on inspections and audits deserve a separate section. Ethical issues should be addressed, whether they are straightforward or different from those in other areas of biomedical research. It is worth discussing data protection and social equity.

- The document should provide mostly high-level principles for audits and inspections and not make precise regulations.
- There are two sides to the issue of inspections and audits, one is the development of software and AI used in pharmacovigilance, and how inspectors and auditors will look at these tools. Secondly, there is a tool that can be used by regulators or inspectors, and perhaps internally in audits, to use AI to determine how healthy a PV system is. This introduces an ethical aspect, as these tools will become very important in inspections in the future.

Data privacy and social equity

- There are major privacy and equality concerns in the application of AI. From a privacy perspective, much research data is not subject to oversight under U.S. Department of Health & Human Services regulations because it is exempt from regulations under the older regulations without direct identifiers. When using Big Data, you cannot be sure of the limits of the datasets and the conclusions. How AI tools will affect industry and data protection depends on what exactly they are used for and at what stage they are applied.
- When developing AI tools in the diagnostic field, e.g. X-ray or MRI imaging, the regulatory agency may require the assessment of two human experts to review the programme or machine evaluation. The training data set is based on the company's existing data. If the adjudicator comes to a different conclusion, does this affect the existing data and would it need to be amended? Currently, there are no regulations or guidelines in this area.
- The standard approach would be to apply a tiebreaker to the situation and the outcome would be the result. There is a lack of examples of industry concerns about inspections, so this is an example we can discuss once we have developed the principles to address the issue.
- We should not reinvent the existing principles of the quality management system. In any controlled system where a problem is found with the data or algorithms, the impact would be assessed to find a solution. We do not need to deviate too much from this kind of approach.
- There are AI tools that have been developed by regulators, including algorithm impact assessment tools that we should consider.
- We should try to focus on the ethics of using AI in PV, and even more specifically on the ethical issues of using AI and ML in healthcare.

Scope

- As the CIOMS WG includes representatives of the three main stakeholder groups, it is up to the WG to decide and agree on the scope of the future report. Public consultations in the final phase will be an opportunity to receive additional input. It will again depend on the group's decision on how to take the feedback received into account.
- The WG agreed that discussions on future development areas should be held among the stakeholders involved in the WG.

Involving other CIOMS WGs

- The WG discussed addressing benefit-risk assessment (BRA) in the context of the future report. Would the report focus on the evaluation of the individual cases and the potential change in BR?
- The WG agreed to approach two CIOMS WGs, WG XII Benefit-risk balance for medicinal products and WG XIII Real-world data and real-world evidence in regulatory decision making with a

request to share their draft reports for the WG XIV to be able to familiarise themselves with the work underway in both groups. The language of the three WGs should be consistent when addressing the same areas.

- Emerging technologies, e.g. publications on causality inference detection, may have a direct impact on the work of the WG XII. We should consider addressing the issue in this particular report or within the BR report as one of the potential use cases that could impact BR in the future.
- The WG agreed to acknowledge existing guidance and publications from industry, regulators and academia as beneficial references and will aim to fill in the gaps that exist in various initiatives. This could be included in the background section of the future report.

Structuring the report

- One of the approaches was to start with use cases and then move on to the issues of definitions and aspects of the scope. If one starts with the principles before discussing the use cases, there is a risk that the report will leave out valuable aspects, whereas it is always possible to generalise from the use cases.
- Suggestions for a comprehensive approach to the use of AI in PV were expressed. The report should be structured according to the specific interest of the experts at WG in specific areas of PV and the impact of AI on the specific areas, and then address specific applications.
- Specific recommendations could be used as a basis for the report and it would be beneficial if WG agreed on this at an early stage.
- We should also include the broad coverage of the field of PV and discuss the possible roles of AI and ML in the different stages of the product life cycle. One possibility is to use the concept of the PV lifecycle and break it down into a specific component we wish to discuss, and then the use cases can fall into that area. Beyond structured data, we will also discuss social media data and multiple insight generation, which also fall into the PV domain, but are more patient-centred.

Data

- To realise the full potential of AI, the focus must also be on external data, not just the data available to a company. If AI can be used to analyse this information and predict signals, behaviours and outcomes that can help patients, then that is the true benefit of AI.
- Electronic health records (EHRs) have certain quality issues, but at the same time hold enormous potential. AI could be used to benefit from EHRs. Using EHRs for PV could change the information contained in EHRs.
- Do we need the standardisation of data to make use of it? The discussion could be included in the document under future perspectives or considerations.
- If the application were to collect information on medications taken and treatments beforehand, this information would be extremely valuable for PV, but still challenging to obtain. We should include comprehensive discussions. The discussion is about data access as a whole.
- The report should be forward-looking because there are opportunities that are currently underutilised that could benefit PV more.
- We need to consider the loss of precision that occurs when using standardisation and common data models. When we discuss this in a future report, we should include our recommendations.

- Most of the common data model models cannot support different use cases in PV. CIOMS WG can provide certain suggestions. This does not mean that we must propose our own common data model, but we should at least discuss it.
- A good example of how common data models can support biomedicine can be found in the fields of precision medicine and precision oncology, where very detailed data representations are being developed using common data models.
- The real power of AI and ML lies in the possibility that the new technology can help save lives, as a diagnosis confirmed by AI can lead to earlier treatment
- AI and ML can drive the development of data models.

Hervé and Lembit concluded the meeting and thanked all for their participation and discussions.

DAY 2

Hervé welcomed the WG and thanked all for the fruitful discussion the previous day. The aim for the second day is to focus the discussions towards creating a merged TOC which would facilitate future work.

Lembit summarised the Day 1 discussions and opened the Day 2 discussions.

Based on the discussions on the previous day, Arvind compiled a draft TOC as a starting point for the discussions. The team members were invited to review and feedback on the TOC.

3. Involving vendors

WG had agreed to include vendors not as core members but in the form of an advisory group. A group of volunteers (Andrew, Dieter, Elizabeth, Jesper, Justyna, Luisa, Nicolas, and Phil) drafted the Terms of Reference to facilitate transparent interaction with the Advisory Group. This was forwarded to the WG for review during the 2nd meeting.

- The very title of the Advisory Group suggests that their advice will be taken into account, but the final decision rests with the WG.
- Lembit suggested that the draft TOC be shared with the Advisory Group and their input sought for the next WG meeting. The Advisory Group would be invited to join for a period of time during the next meeting.
- Vendors, who have used AI and ML in healthcare have an experience that would be of great benefit to WG, but involving vendors from other areas of healthcare should also be considered.
- The Advisory Group is urged to participate in discussions within their group to obtain more consolidated views. Vendor interoperability could be a key point for future discussions in this area.
- We should not ignore the possibility that vendors may want to gain a commercial benefit from participating in the Advisory Group. Their benefit will be to the industry as a whole, e.g. by reducing manual work and labour costs. Forced interoperability among vendors may not lead to the expected outcome.
- In addition to joint sessions with the WG and the Advisory Group, chapter leads may contact the Advisory Group as needed, but are expected to communicate this with the WG in advance. The

process must be transparent and the vendor's contribution to the discussions must be documented.

- Should we also include generic pharmaceutical companies?
- The perspective of a small pharmaceutical company would be helpful. We should consider the whole industry and not just the big companies.
- Vendors will not participate fully in the WG meetings but will work independently and in parallel with the WG and attend the WG meetings for an agreed time. Nevertheless, it should be ensured that the two groups move in the same direction.
- The CIOMS Secretariat has already received some recommendations on which members to invite to the Advisory Group, and further suggestions are welcome.
- The list of proposed vendors will be made available to the WG. CIOMS will send invitations to the selected vendors to join the Advisory Group on behalf of the WG. The final decision on the inclusion of vendors will remain with CIOMS.
- Information on the process of involving members in the Advisory Group will be made available on the CIOMS website along with the Terms of Reference to ensure transparency for all interested parties.
- The Terms of Reference need to be revised to transform them into more general, overarching principles. Remove the section that states that there will be a public call for the Advisory Group members.
- The Advisory Group will not be involved in the drafting of the WG report. The expected group will consist of up to 10 members.
- They will not participate fully in the WG meeting but will work independently and in parallel with the WG and will attend the meetings of WG at an agreed time.

Forming writing teams

Lembit called for volunteers to form writing teams and for team leads and co-leads to nominate themselves. (Please see Annex 3 for the draft Table of Contents).

- The draft TOC is derived from the TOCs proposed by subgroups 1 and 2. As chapter teams begin to draft their sections, they are welcome to update the chapter outline and suggest changes to the TOC.
- We should aim for a balanced representation of stakeholders in each writing team. WG members are welcome to participate in more than one writing team.
- Lengthy discussions before drafting do not necessarily add value to the draft itself, so it is best to start the process now. Chapter leads and teams can suggest and contribute ideas that would otherwise have gone unnoticed in the collective discussions.
- Lembit urged the chapter teams to communicate and work together. If teams find overlaps between chapters, meetings with other chapter leads and teams are encouraged.
- To balance and strengthen the WG, all are invited to suggest additional members from academia. Suggestions should be sent via email to Lembit.
- Members who were unable to attend the meeting were contacted after the meeting and invited to join the drafting teams.

- Begin drafting. Each chapter team will decide how they prefer to organise their work. CIOMS Secretariat can assist in organising the meetings of the chapter teams.

4. Way of working

- CIOMS reports in the past have been quite unique and of varying lengths. They range from 100 to 200 pages in A5 booklet format. The length depends on the writing style, appendices, and editing.
- The AI in PV WG aims for a 100-page document that can be developed further as technology changes, as decided by WG. The length of the report will often be extended by appendices that can be created and added for reference by the WG or other initiatives.
- The addition of possible visualisations will extend the document.
- All CIOMS reports contain references. Some working groups have chosen to add references after each chapter, for some reports all references are at the end of the report.
- CIOMS reports are usually finalised by an editorial team consisting of five to six members from the WG. A near-final draft is presented to the whole WG during the final meeting.
- CIOMS has an Editorial guideline document that will be circulated to the group.
- A public consultation will be held upon the decision of WG in the final stage of finalising the report. The consultation period will be approximately six weeks and will provide an opportunity to gather additional feedback. The editorial committee will decide on the inclusion of comments received.
- The CIOMS Secretariat will assist in organising Zoom meetings, taking minutes and general communication.
- Virtual meetings are an opportunity to discuss progress and address possible challenges according to the needs of the WG. Chapter leads are invited to present the current draft and WG is welcome to provide feedback.

5. Next steps / next meeting

- The next full WG meeting will be held virtually in January 2023. Chapter teams will report on progress and discuss any questions on draft chapters. CIOMS Secretariat will assist with scheduling the meeting.
- The CIOMS Secretariat will circulate the list of participants and editorial guidelines.
- Dates will be researched for the next WG full in-person meeting in May. Dieter has kindly expressed the possibility of Genetech hosting the meeting in the United States, California. Discussions on the organisation of the meeting will follow.

6. Closing remarks

Hervé and Lembit thanked the WG members for joining and for the productive discussions.

7. Annex 1: List of participants

Attending in person

Arvind Bellur (Sanofi), Taxiarchis Botsis (Johns Hopkins University School of Medicine, US), Piero Francesco Franco (Pfizer), Thomas Henn * (Unither), Alexander Horst (Swissmedic), Kirsten Egebjerg Juul* (Danish Medicines Agency), Vijay Kara* (GlaxoSmithKline), Dieter Kempf (Genentech, Roche), Denny Lorenz (Bayer), Hervé Le Louët (CIOMS), Niklas Norén (World Health Organization / Uppsala Monitoring Centre), Ravi Patel (Unither), Kateriina Rannula (CIOMS), Lembit Rägo (CIOMS), and Walter Straus (Moderna).

Attending virtually

Justyna Amelio (AbbVie), Robert Ball (US FDA), Adrian Berridge (Takeda), Hua Carroll (Biogen), Flávia Moreira Cruz (ANVISA, Brazil), Kendal Harrison* (The Medicines and Healthcare Products Regulatory Agency, UK), Stephen Heaton* (CIOMS), Benny Ling (Health Canada), Dirk Mentzer (Paul-Ehrlich Institute), Stephen Rosenfeld (North Star Review Board), Hans-Jörg Römming (Merck Group), Elizabeth Savage (Johnson & Johnson), Phil Tregunno (The Medicines and Healthcare Products Regulatory Agency, UK), Panos Tsintis (CIOMS Senior Adviser), and Manuela Messelhäußer* (PEI).

*Alternate

Apologies
Russ Altman (Stanford University, US), Luisa Barrios (Merck Sharp & Dohme), Andrew Bate (GlaxoSmithKline), Jesper Kjær (Danish Medicines Agency), Roli Mathur (India Council Medical Research), Yusuke Matsunuga (Pharmaceuticals and Medical Devices Agency, Japan), Richard McAteer* (Health Canada), Yuki Kikuchi* (Pharmaceuticals and Medical Devices Agency, Japan), Nicolas Perez * (Swissmedic), and John Reinhard Pietzsch* (Bayer).

8. Annex 2: Writing teams

Chapter number(s)	Title	Team lead(s)	Members
1,2,3	1. Introduction 2. Landscape 3. Scope	Walter	Walter Straus, Stephen Rosenfeld, Flávia Cruz, Piero Francesco Franco, Justyna Amelio, Benny Ling, Hua Carroll, Niklas Norén
4	Guiding Principles	Elizabeth	Stephen Rosenfeld, Vijay Kara, Elizabeth Savage, Niklas Norén, Phil Tregunno, Justyna Amelio, Benny Ling, Manuela Messenhaeusser, Dirk Mentzer, Alexander Horst, Jesper Kjær, Kirsten Egebjerg Juul
5	Validation and qualification considerations	Hans-Jörg	Hans-Jörg Römming, Adrian Berridge, Hua Carroll, Manuela Messelhäußer, Dirk Mentzer, Dieter Kempf, Luisa Barrios
6,7	6. Consideration of AI 7. Implementation and maintenance lifecycle aspects	Taxiarchis and Arvind	Taxiarchis Botsis, Dieter Kempf, Arvind Bellur, Bob Ball, Elizabeth Savage, Phil Tregunno, Justyna Amelio, Thomas Henn, Hans-Jörg Römming, Luisa Barrios, Jesper Kjær, Kirsten Egebjerg Juul
8	Future vision	Ravi and Denny	Ravi Patel, Denny Lorenz, Piero Francesco Franco, Andrew Bates, Vijay Kara, Thomas Henn

9. Annex 3: Merged Table of Contents (Draft)

This is a high-level draft TOC derived from the Subgroup 1 and Subgroup 2 discussions. Chapter leads are welcome to further discuss specific sections and accordingly update the TOC.

Timeframe – Jan 2023 (initial drafts)

1. Introduction
   - 1.1. Terminology (definitions)
   - 1.2. Background (Background and current state of ML in PV)
     - 1.2.1. Exponential growth of data and data analytic capabilities (use of AI in other industries)
     - 1.2.2. Alignment with stakeholders
     - 1.2.3. Outstanding need for guidance
     - 1.2.4. Intended audience

2. Landscape
   - 2.1. Opportunities for AI in PV (Value areas or opportunities in PV lifecycle)
     - 2.1.1. Problem statement – industry/regulators/academia

- 2.2. Practical application / Use cases
- 2.3. Review of existing AI in PV literature/guidance/references (current state of ML in PV)
  - 2.3.1. Transcelerate
  - 2.3.2. Guidances

3. Scope
   - 3.1. In Scope
     - 3.1.1. Detection, assessments, and analysis of AEs
     - 3.1.2. Benefit-Risk application
   - 3.2. Out of scope
     - 3.2.1. Exhaustive review of methods and technologies
     - 3.2.2. General aspects of AI/ML
     - 3.2.3. Use of AI for generating and analysing RWE data

4. Guiding Principles (General best practice) (could be part of 6/7)
   - 4.1. Quality and conformance with standards
   - 4.2. Data reliability
   - 4.3. Data bias (social equity)
   - 4.4. Explainability
   - 4.5. Transparency/data access
   - 4.6. Data protection/privacy
   - 4.7. Ethics

5. Validation and qualification considerations

6. Considerations of AI (Expectation settings, limitation)
   - 6.1. Expectation/change management
   - 6.2. Current limitations
   - 6.3. Audit trail
   - 6.4. Quality checks
   - 6.5. Retrospective oversight of Machine recommendations
   - 6.6. Continuous Monitoring and Automated Alerts

7. Implementation and maintenance lifecycle aspects (implement and maintain ML along the lifecycle)
   - 7.1. Data models
   - 7.2. Data strategy for model training
   - 7.3. Model design, training, validation, and deployment
   - 7.4. Performance Monitoring (Metrics/dashboard)
   - 7.5. Governance
   - 7.6. Quality management system
   - 7.7. Validity of the system
   - 7.8. Performance monitoring
   - 7.9. Inspections and audits (regulatory framework)
   - 7.10. Case study Implementation of specific components (could be appendix)

8. Future vision