



Fifth meeting of the CIOMS Working Group on Severe Cutaneous Adverse Reactions of Drugs (SCARs)

13 December 2021

Meeting Minutes

Participants

Priya Bahri (EMA), Catherine Bates (CIOMS), David Brott (Takeda), Siew Eng Choon (Monash University), Chia-Yu Chu (National Taiwan University Hospital), Roni P. Dodiuk-Gad (Emek Medical Center), Leslie Dondey-Nouvel (Sanofi), Koji Hashimoto (Ehime Prefectural University of Health Science), Alexandre Kiazand (AstraZeneca), Gerd Kullak-Ublick (Novartis), Haur Yueh Lee (Singapore General Hospital), Sylvia Lesperance (Novartis), Ariel Porcalla (AbbVie), Lembit Rägo (CIOMS), Violeta Regnier Galvao (Eli Lilly), Melissa Reyes (FDA), Sarah Schlief (Bayer), Neil Shear (University of Toronto), Sabine Straus (MEB)

Regrets: Hervé le Louët (UMC/WHO), Filippa Nyberg (Karolinska University Hospital), Matt Doogue (IUPHAR/University of Otago/Christchurch)

The purpose of the meeting was to discuss the chapter outlines and agree next steps. Co-Chairs, Melissa and Chia-Yu reviewed the draft outlines. Chia-Yu started the discussion as he is the lead writer for the first four sections:

Intro/Conclusion

Alex asked if the impact of DISSI on patients, drug developers or the drug life cycle will be covered. Chia-Yu said the impact of different DISSI's would be covered in Chapter 1.

Roni asked if the criteria for diagnosis will be included somewhere. Chia-Yu said they too, will be covered in Chapter 1. She also asked if the paper from Japan on severity assessment will be included as a reference. Roni will email Catherine with any further references to be included.

Sylvia asked where the actual SCAR concept would be described vs DISSI, cutaneous ADRs? Because it is widely recognized terminology. Chia Yu responded that it will be included in Chapter 1 where each SCAR will be mentioned.

Chapter 1 - What is Drug-Induced Severe Skin Injury (DISSI)?

Chia-Yu read out Siew Eng's comments that the terms should be clearly explained, with the accepted SCAR and non-SCAR vs the new, proposed term DISSI. Chia-Yu would like to describe DISSI in Chapter 1, but include the detailed information of the different SCARS (SJS/TEN/EMM) in Chapter 2. Leslie wondered about including photos.

Roni expressed an interest in writing about long-term sequelae. Chia-Yu said they would be covered in subsequent chapters.

Chapter 2 - Diagnosing/Identifying DISSI cases

Siew Eng spoke to her comments and suggested moving the first three points of Chapter 2 to Chapter 1. 2.1.1, 2.1.2 and 2.2. Conversely, the details of each SCAR (Chapter 1) discussed above should be moved to Chapter 2.

Sections 2.1.1., 2.1.2 and 2.2 will be moved to subsequent chapters on pre/post marketing surveillance.

Melissa asked if CTCAE were used in a clinical setting given that it is generally used in pre-market assessments. Chia-Yu agreed and responded that it is mainly used in oncology clinical trials. This will be mentioned in the report.

- Mention CTCAE in both chapters (2 and 5).
- Change the heading from CTCAE to Severity Grading and under this heading, include CTCAE and more clinically-relevant severity assessment tools
- Section 2.3.1 to provide recommendations about the most appropriate severity scales.

Regarding photos, Leslie mentioned the value of photos for prescribers while acknowledging the difficulties in including them in the CIOMS report. Lembit referred to an [earlier WG](#) and suggested that maybe a few photos could be included as examples.

Chia-Yu stated that the importance of photos would be described in a general way in Chapter 1 and then again, in relation to each SCAR, in Chapter 2. To Alex's point about not including any photos in the report, Chia-Yu put forward that while it is not mandatory to have photos, including them is helpful for reporting purposes.

- The importance of photos should be stated in Chapter 1 and again, for each SCAR, in Chapter 2.
- There should be a note to explain the difficulties in including photos
- Reference clinical publications that have appropriate photos in the report if the WG cannot obtain its own photos.
- Add point on different phenotypes or severities of ADRs from targeted therapy (see Chapter 3.3)

Chapter 3 - Clinical Care

Violeta suggested that some of the topics under General Management could be deleted as they are already listed in Chapter 2 e.g. Biopsy, Imaging Studies

- Remove Biopsy, Imaging Studies from 3.1.1. General Management
- Remove Common DISIs from 3.1.2. Specific Treatment

Melissa raised the point Roni made earlier about long – term sequelae and suggested this might be covered as a separate point before 3.2. Special Populations of Interest and not included in this section.

Also, if the causative drug is an antibiotic, would one be talking about desensitization protocols that would happen for the patient long term? e.g. a child as it would potentially effect their life for

longer than that of an elderly individual. Chia-Yu mentioned the example of South Africa where they perform desensitization for tuberculosis drugs as TB treatments cannot be avoided.

Violeta mentioned that it makes sense to keep 3.4. “Guidance and Investigation post reaction” in particular 3.4.1 “General Guidance”, but move 3.4.2. Patch Test and genotyping to Chapter 2 as these relate to diagnosis.

- To recap Chia-Yu stated that under “General Guidance”, there could be two parts:
 - Long-term sequelae
 - Follow up/guidance on post reactions for each SCAR

Melissa raised two points:

- Distinguish between acute care and long-term/ chronic care as a way to organize this section?
- Address patients’ fear of future medication

Siew Eng asked about HLA/genotyping and if these were discussed earlier in the report. She also mentioned acute and chronic care and asked where these topics would be placed. Chia-Yu responded that HLA/genotyping would be described in Chapter 2 and in later chapters e.g. large clinical trials and surveillance. The group could discuss how it wants to structure the acute/chronic care section.

- Chia-Yu recommended describing acute care first and chronic care second.
- Chapter 3.3. “ADR Induced by Targeted Therapy”: Haur Yueh suggested adding a section in Chapter 2 to delineate the different phenotypes or severities of ADRs from targeted therapy.

Chapter 4 – New Skin Safety Biomarkers for DISSI

Melissa provided a brief overview of the chapter and opened the discussion for comments. Gerd mentioned that FDA has the best glossary. He suggested that assessing other kinds of biomarkers could be a useful undertaking for the group to consider in the future. Melissa concurred with Gerd’s point.

To Neil, safety would be the primary one because there's such a discrepancy across the world about areas where it's absolutely mandated before you get to therapy. In North America, product monographs are clearly not strong enough. They can put a lot of information in them, but they don't make [biomarkers] mandatory. Neil put forward that an opinion may be needed on this. He added that guidance to make the product monograph more useful could be considered.

Neil put a question to the group about having a section in the CIOMS report specifically related to biomarkers or would this be outside the group’s purview? Gerd agreed and followed up by suggesting that maybe there could be an initiative on qualifying new biomarkers or would this look at established lab values, only? He surmised that this initiative would be about exploratory, as yet unqualified markers which are not implemented in routine drug development to date. Would the objective be to propose new biomarkers to be implemented in drug development studies in the future and ultimately, qualifying them with regulators?

Or, rather, would it be to guide clinicians into including a biomarker when they deem it appropriate?

Gerd stated this would only make sense if it leads to binding recommendations for companies to implement biomarkers in the future. This applies for immuno-safety as well, which is even more confusing than other organ system biomarkers. There's a lot of work being conducted in terms of qualifying new biomarkers, e.g. safety, liver, kidney, pancreas, vascular. There is recognition of cutaneous adverse reactions so, maybe this is a good time to state the need for biomarkers.

Gerd suggested that maybe the group could work on this as a next step and make a case for the need for safety biomarkers in drug development on a much more regular basis. This would mean qualifying these biomarkers.

- Neil added that an encouraging word could be included so those who do the reporting to share the information

Melissa commented that the utility of biomarkers would be covered in Chapter 4, but it could also be included in later chapters on surveillance and post-market in connection with reporting structures.

- Sarah suggested creating a questionnaire as an appendix, which would include a question about biomarkers.
- Gerd stated that a CIOMS recommendation would enable the WG to take the messages to the [EU Innovative Healthcare Initiative \(IHI\)](#). So, the group would produce a summary and a section on future outlook. The topic on biomarkers could be added to the latter.
- Should the group consider following up systematically with bigger groups, consortia, multi-stakeholder groups (academia + industry) to see how useful these biomarkers could be?
- Sylvia suggested the chapter could focus on the different diseases. It could include a short summary of what is already available and establish a link with what should be collected for the different syndromes. She felt this would make the chapter more practical, but would need to be kept up to date.

As examples, Neil mentioned

- 1) The literature textbook that he edits every year, to which certain known HLAs, etc, were added, including descriptions. But, this section now comprises about eight pages of information. So, one has to look at which ones are appropriate for a given population and which ones can one actually get access to. Ultimately, one might have to direct people off the actual science report.
- 2) Bruce Carlton at the University of British Columbia who is bringing the costs of mass testing down to less than CAD 20 for a single unit.

Neil stated that testing will probably become more widespread and biomarkers will also become more important. Although this is probably beyond the scope of the CIOMS project, where the group could have an impact is to encourage physicians to include

biomarkers as part of their practice and urge people who report [events] to share information about e.g. genetic markers.

- Sylvia asked if Neil could share the information about Bruce Carlton's work with the group. She also referred to Sarah's idea of including a questionnaire and asked if Sarah could share some thoughts about this with the group.
- Sarah has an example of a questionnaire which she can share with the group and which could be updated according to the group's needs. It could be included as an appendix.

Chapter 5 - Pre-Marketing Surveillance for DISSI

Melissa went through the outline for the group and opened it up for discussion.

Lesley pointed out that in drug development, one doesn't have an approved risk management plan yet so what one has is a development risk management document. This distinction should be emphasized. It is also important to understand the approach a team should adopt if an event occurs.

- Should point 8 be worded as "risk management" or "development risk management"?

Ariel asked Melissa if there was another chapter solely focused on risk management. Melissa said there is, namely Chapter 7, which also covers this topic. Whereas there are some risk management aspects that are specific to drug development, rather than to the "big picture". The group can discuss if it makes sense to cover it in a dedicated chapter or touch on those things that are really just relevant to pre-market here.

Alex intervened to say that to him, points 8 and 9, were about the management of the risk, rather than risk management plans (RMP) or other regulatory documents. It was more about clinical management of the condition and the impact of DISSI on, e.g. the protocol, the Investigator Brochure (IB), the "Dear Investigator" letter, as opposed to the risk management plan that has specific chapters about populations not studied or important risks.

Ariel agreed with Alex's point, saying that point 8 should cover anything that pertains to a clinical trial. When a sponsor knows that the event is truly drug-related, then, one can infer that there is a definite risk for this product. And when you determine this, there is an impact on clinical regulatory documents, e.g. the IBS, ICF, clinical protocols, the exclusion, inclusion or monitoring.

- The point about "risk minimization" is probably part of the risk management RMP activity that can be covered in Chapter 7.

Sarah shared that there's an overlap with the post-marketing chapter and if one uses a targeted questionnaire, this could be used for clinical trial cases, but also for post-marketing cases. So there is some overlap. She wasn't sure how this could be addressed, maybe in both chapters.

Lesley agreed with Sarah. In development, when you do your monitoring, and make decisions about the impact on your program, you will define whether those risks have been

identified. This is important and should be stated, because there is process to adjudicate adverse events.

- Violeta suggested merging points 7, 8, 9 into one section which would cover the impacts for the investigator brochure, protocol, ICF, development, risk management strategies.

Alex remarked that this reminded him of the DILI report. The way we addressed it then was to write the chapters up. Once the draft was mature enough, we reconvened and went through it to determine if the different topics were in the right place and if the headers made sense. To him, these titles should be seen more as placeholders, than actual section headings to make sure all aspects are covered. The group can come back on the draft at a later stage and move sections around if needed.

Melissa agreed and emphasized, however, that there are topics that are specific to development programs that don't really apply to post-market, mainly, development risk management that would essentially close this program. Whereas, topics such as educating the patient or monitoring could fit under post-market. Regarding Violeta's point about merging 7,8,9, Melissa said this would be acceptable and makes sense.

Alex asked about adjudication and whether the group should provide recommendations on the composition of the Adjudication Committee, e.g. dermatologists versus non dermatologists, drug developers versus generalists. Ariel said this is sponsor- specific or product specific. So, this may be difficult.

- Maybe the report could state which specialties should be on the committee

According to Melissa, this is what was important about the CIOMS guidance was that we have all the experts in this group. Would it be useful for drug developers to have this? In case they hadn't thought about having a SCAR specialist on hand to adjudicate these events. At the very least, the report could provide which specialties might be involved, e.g. dermatologist, immunologist. Given how broad the group's audience is, it might be useful for individuals who don't deal with this regularly and therefore, might be less familiar with this topic.

Neil agreed with Melissa and shared his experience on data monitoring committees, but publications rarely mention them. So, it might be worthwhile to draw some attention to this topic. He was unsure as to which section it would go under. FDA issued some guidelines a few years ago.

Ariel suggested including a section in this chapter about data monitoring committees (DMC) and the composition. It's really important to know that one can receive input from the DMC. Ariel added a point about photographs which is helpful for regulators. Not just a description and characterization of the rash, but a photograph as well. That might be another guidance that we can include under clinical trials.

Neil warned about the challenges of including photos. The lighting is often sub-optimal and in skin of color, one needs side-lighting because most digital cameras do not capture dark skin. He also mentioned a committee in Canada that he and others created to improve textbooks about colored skin for trainees. Essentially, while it sounds nice to have pictures, sometimes, it's more complicated and not as fulfilling as one would hope.

- Ariel suggested that as the group is providing guidance, it could state the features that should be optimized when considering a photograph. So industry sponsors know what DMCs or regulators expect.

Regarding monitoring, Lesley added that investigators are expected to take pictures when there is a communication on how to document serious skin events. She didn't know if these pictures are good quality, but there are recommendations to provide them with respect to monitoring.

Melissa recapped the discussion about pictures and stated that they can be helpful, but the provider must ensure they are as useful as possible. The group could include references on how to take a good photo.

This topic is not specific to pre-market so the group can decide whether to include it in one of the earlier clinical chapters as well.

On the subject of DMCs and adjudication, Alex asked if this chapter should be broken down into two sections, one about the drugs that come with a skin risk, and then the drugs that do not have a known risk for skin reactions. A lot of the programs that Alex is familiar with, when they are up for approval, state that there is a skin risk, but there is a DMC and a dermatologist or skin reaction specialist is on this DMC. So, the sponsor is confident that risk mitigation measures are working. So, Alex reiterated the question, should the two categories be addressed separately or together?

Melissa asked if there were any comments. There weren't any so she shared her views with the group. Referring to programs where the rash is known. Everything is called either a grade I or II rash with relevant criteria. If it's a grade III or IV rash, the sponsor will have processes in place with the DMC. So, it's an important point to bring up because everything is skin focused and it will circle it back to those non-DISSI, cutaneous ADRs. She asked if Alex would like to have two separate parts or would it be enough to just highlight that this is a consideration in this chapter?

Alex replied that this could be tackled in two ways. Either we have enough data for two dedicated sections, or there are not enough differences and under each of these headers, we could cover each situation separately. As an example, point 3. Data Sources could include a paragraph on drugs with known skin effects, and then another paragraph on drugs without a known skin effect.

Neil's view is to focus on the whole DISSI idea and referred to the rashes trial subjects were presenting due to covid masks. These symptoms were disturbing, but not serious. Violeta stated that there might not be sufficient data to have two sections and would opt for covering it in a single section.

Maybe the group could consider specific examples for those drugs that are known to cause or belong to a family that that is known to cause disease, but she would not include two separate sections.

Neil mentioned aromatic sulphonamides that cause severe problems, but Celebrex and other sulphonamides, HydroDiuril don't do that. So if you announced that you're worried about sulfonamides, it's not enough. It has to be quite specific. On the FDA label for Bactrim, Septra, sulfamethoxazole, it still says that you should not take them if you're on Celebrex. You shouldn't take it if you've had a reaction to sulphonamides. That is incorrect, but it's there. Who is going to remove it? Neil cautioned, this was the kind of issue the group might get into, which may create more problems. So, Alex concluded that maybe the way forward was to leave it as is and tackle the issue if needed.

Neil followed up by saying that if there was a need in terms of feedback, what happens? The report goes out and then do we revisit it a year later? Two years later? I'm not sure what the CIOMS strategy is on that.

➤ [How do we receive feedback once the report is published?](#)

How do we update it? How do we deal with feedback and suggestions? How dynamic is this topic? There's a review cycle, but it'd be interesting to hear feedback because safety is so underserved. And I think all of these safety issues that CIOMS is championing are fantastic. It would be interesting to know how they resonate with prescribers, investigators, industry, etc.

Melissa agreed and stated that CIOMS has a procedure for collecting feedback and raised the possibility that the group could reconvene at a later stage. Going back to Alex's point, we should include that because Melissa mentioned drugs whose mechanism makes one think that there'd be more skin reactions. So that piece would be important to put into this chapter. There's probably not enough for separate chapters, but I do think a dedicated section would be useful.

Chapter 6 - Post-Marketing Surveillance for DISSI

Melissa summarized the main points in the outline and pointed out that the challenge of post-marketing is that regulators typically rely on spontaneous reporting. And based on that type of data, how do we identify the case? We're talking about MedDRA terms. How are we then able to confirm the diagnosis?

- [Lesley commented that as this chapter is about post-marketing, maybe it would be useful to outline its specificities and limitations. Melissa and Sarah concurred with this approach and suggested this could be placed at the beginning of the chapter.](#)
- [To point 6.4. "Risk Management Process and Strategies" David felt it could serve as an introduction to the next chapter. It should not necessarily go into any great depth, but just to highlight what is carried out post marketing and that it will be discussed more thoroughly in chapter 7.](#)

Ariel agreed with this approach. This is where the authors can introduce what they do, what they typically provide, e.g. risk management plan or PV plan. And the DISSI registries if the sponsor thinks there could be important risks that it wants to follow and, then, additional pharmacovigilance activities. This is more European, but just some agreed surveillance activities for these risks could be included here, when we're transitioning from pre market to post market.

To Alex, there are two things that he would refer to in this section to understand what what he is supposed to do [as a clinician reading the report]. The first thing is how to detect DISSI and SCAR and second, how to assess the severity of that DISSI.

Based on that, the chapter covers the first part in terms of detection, the need for a registry, and once we get an event, how to evaluate, etc. However, Alex was not sure if the severity aspect was covered in a satisfactory manner as that's what will drive the actions he needs to take when dealing with these cases. He didn't know how realistic it was to cover the second point.

In terms of spontaneous reports, for post marketing, Ariel stated that the lack of information is always a challenge, especially for DISSI cases because the reports come from outside and don't provide sufficient information.

➤ Should the group provide guidance on this beyond describing what it is? How does a sponsor or regulator confirm that it's DISSI? Do we want to include criteria to determine that it's DISSI?

The reports come mostly from clinicians. Melissa asked how one can encourage clinicians who see these cases first hand to report back either to regulatory authorities or the drug manufacturer. We can refer to these data points in the questionnaire.

Priya referred to section 6.4 as a bridge between pre and post marketing and regulators and other stakeholders. She felt chapter 6 should only cover pharmacovigilance activities and cover risk minimization in chapter 7. We can cross-refer between the two.

Should the bridging between pre and post and different stakeholders be stated as an introduction to chapter 6? We could bring it up before all the methods are explained rather than at the end. Melissa and Ariel agreed with Priya.

Regarding Alex's point about severity of this association of DISSI and a given drug, Melissa suggested covering this piece in Chapter 7. Alex confirmed this was fine as long as one can refer to this guidance at some point to understand the severity. Alex wanted to know what regulators look for when deciding to leave a drug on the market or not. The key is that this should be covered somewhere in the document.

Melissa added that this piece will go in Chapter 7. She recapped that the important point in chapter 6 was the transition from pre to post marketing, how it changes, about pharmacovigilance (PV) in post-marketing and everything that goes with it, e.g. case detection, causality. The transition for the last paragraph is about how to deal with what you just found and Chapter 7 will be about risk mitigation.

Ariel mentioned surveillance activities, or PV activities and suggested that the registries could probably be included in along with these activities, because if you're monitoring for that [DISSI cases], these can only be monitored through registries or post-marketing observational studies that are going to be very long in duration.

Ariel proposed to wait and see if the report is lacking in terms of surveillance activities, e.g. Post-Marketing Requirements (PMR). If these are required, they can be added as part of additional surveillance activities.

Melissa stated that the challenge as a regulator is that DISSI is so uncommon, it's very difficult to justify any type of post-marketing requirements study.

- However, the group could give guidance about what other types of studies could capture safety information about DISSI.

Chapter 7 - DISSI Risk Management and Communication

Melissa presented the outline, saying that based on the previous discussion on pharmacovigilance, the focus of Chapter 7 is to describe what to do with that information.

Violeta spoke about oncology adding that the group could include

- A specific sub-topic on oncology patients as the benefit-risk assessment might be different
- Other special populations e.g. tuberculosis treatment

In addition, Priya mentioned women of child-bearing potential, pregnant women, breast-feeding as special populations.

Regarding 7.1., Priya would like to start with the benefit-risk assessment, because very often, it's the risk minimization that tips the benefit risk balance towards a positive outcome.

- Risk management plan could go in the introduction in Chapter 6.

Melissa agreed with Priya's recommendation. To Ariel, it could go in either chapter. As long as it's a major section of the report.

CIOMS has already published a report on [risk minimization](#) measures.

- Priya suggested referencing the tools described in the CIOMS report and use the definitions.

This would help to avoid additional explanations and instead, the group could focus on the wording the authors would like to see. Melissa liked Priya's suggestion to refer to the CIOMS report and agreed with the suggestion to

- Provide example language under point 7.2. "Label/Package Leaflet"

Melissa felt that

- "Terminology" did not belong here and should be placed in Chapter 6.

Priya, Ariel and David agreed.

Regarding additional risk minimization activities, educational materials and programs, healthcare communications are about how we communicate risk and we can expand on those.

Point 7.3 is really important and might be the place where we can put our opinion forward about choosing the better drug and how this would happen. Melissa asked if the group agreed to include it here or should it be considered as part of the conclusion?

➤ Sarah stated it fits better in the conclusion because it is an overarching point.

Melissa agreed.

Regarding 7.3, Ariel asked if the group had discussed pharmacogenomics and genetic testing earlier? If it did, he agreed, it would fit better in the conclusion. Ariel added that it would be useful to provide details about what is meant by pharmacogenomics and genetic testing.

Sarah asked if this was covered in the chapter on diagnosis. Chia-Yu said it was, but that the roles are different. For diagnostics, we use pre-confirmed genetics, but here, maybe the group could include some which are under investigation.

Melissa added that the piece that could fit in here is on labelling so that there's different guidance about when that language makes it into regulatory labeling compared to when it is put into practice clinically.

Conclusion

Chia-Yu asked Neil to provide some comments as a conclusion.

A conclusion is this is a science of its own. Safety has always been a “second or third cousin”. Neil believed the purpose of the CIOMS report is to “shine a light in a dark place”, and give people confidence that their perspectives, whether it's on the industry side, early development or regulatory, are relevant. The hope is that this document will help support that and make their job easier. Also, it should state that the Working Group is open to feedback.

The call to action would be that this group could spread the message, and contribute. Neil said he would like to hear from the group what they would like to take back to their constituencies.

➤ Violeta thought that the group could pick up the main idea from the seven chapters, and write up a brief statement on each. Chia-yu added that future aspects could be included as well.

Next Steps

Chia-Yu asked for volunteers to lead the drafting process for each chapter. The leads/co-leads (see table below) will call a meeting with their respective chapter group and discuss the best way forward. Suggested deadline for a first draft: Monday, February 28th 2022.

Intro/conclusion	Chapter 1	Chapter 2	Chapter 3	Chapter 4	Chapter 5	Chapter 6	Chapter 7
David	Siew Eng	Roni	Haur Yueh	Sylvia	Violeta /Alex	Alex	Ariel/Priya/Sabine