Council for International Organizations of Medical Sciences

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

9 May 2022

Meeting Minutes

Participants

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Secretariat: Lembit Rago, Catherine Bates

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

Action items:

See “Comments table”

Chapter leads were asked to provide a brief overview of their respective sections for the group.

Introduction

The group discussed whether to use DISI, DISSI or SCAR. Priya felt that the guiding principle should be to choose the term that is clearest and well-established and stated that clinicians generally use the term SCAR. However, if the group feels DISSI is better term and clinicians can be convinced to adopt it, then DISSI is fine. Priya reminded the group that DISSI has “drug induced” in it and the report refers to drugs as small molecules, whereas it also covers large molecules. This needs to be addressed.

The group needs to come to a decision. In some circles, SCAR is more widely-used. If a new term is used, we need to think of what the uptake would be. Another option might be to use the “old” term, but state a recommendation in the report to use the new one in the future. It depends on the opinion of the experts in this group. What would be the most pragmatic way forward?

Start with broad concept of DISI followed by more widely-used SCAR

For effective pharmacovigilance and benefit risk management, it’s more important to track drug-induced SCAR which is why want to introduce the term “drug induced severe skin injury”. Choon mentioned the CIOMS definition for drug-induced ADRs which refers to at least a reasonable possibility of causality by the culprit drug. Could this terminology be taken up by the group?

Alex asked if it would be acceptable to start with the concept of “drug induced skin injury”, which is a very broad concept, and then switch to SCAR, which is widely used across the board, rather than introducing yet another concept of drug induced severe or serious skin injury as this may lead to confusion among readers. So, his suggestion is to start with DISI with just one “s”, and then spend the rest of the document on SCAR, which implies a drug relationship. Violeta agreed with Alex’s proposal. The group would begin with DISI with one “s” which is a broader concept and includes reactions that are less severe so exanthema, urticarial lesions and then focus on SCAR as the most severe subtypes of DISI with one “s”.

Choon supported this approach. Moreover, this would also account for discussions about where lupus, erythrocytosis and bullous pemphigoid which are also serious conditions would fall into. To Priya, this would be an acceptable approach, but there was an earlier comment that not all SCAR are drug-induced. Whereas, “AR” in SCAR means adverse reactions and is therefore, by definition a response to a medicinal product. Do occupational or environmental health professionals also use the term for other types of exposure, e.g. chemicals? Choon agreed with Priya’s comment. One cannot say all SCAR are drug-induced which is why we, as a group, should use this term.

A comment from Ariel was that it was the other way around, namely that a drug is involved. In any case, SCAR is more well-known and Ariel felt using DISI might lead to confusion. Choon agreed and said that what we want to do now is monitor SCAR that are induced by medicine. Chia-Yu stated that the problem is that most dermatological terms are named by the morphology, e.g. erythema multiforme. And today, we understand the causes of the reactions and the culprit drug than in the past so, now we believe that most reactions are caused by drugs whereas they might not be. The morphological term is still used and leads to confusion. We agree that SCAR is used to describe AGEP, GBFDE or DRESS or Stevens-Johnson Syndrome and Choon already put a lot of effort to describe the differences between SCAR, DISI and DISSI. So, perhaps the group could look at the introduction and explain why it will use SCAR and DISI in parallel and make it clear for readers.

Keep SCAR as the title of the report

Neil pointed out sir, that to him, the historical background was that the group started following drug-induced liver injury that is where DISI first appeared. This was disturbing as Neil felt the group should have its own disease and not copy the report on the liver. SCAR does that and separates it from DILII. DISSI with two "ss" came up because of severity and to differentiate it from DILLI, but SCAR does that as well and there could be a discussion about this in the introduction. Ultimately, if the group agreed on SCAR as the name of the WG, Neil would support this title. One will always have nuances e.g. SCAR from vaccines and the group will be able to manage this. And SCAR is simple. Neil would support using SCAR.

Choon and Leslie both concurred with Neil's point of view. Getting the buy-in from audiences for a new concept always takes a lot of time.

SCAR and not DISI/DISSI

Alternatively, the concepts could be used together. Given the terms appear to be used interchangeably in the draft report, Lembit suggested that it is important to explain them clearly in the introduction. Because SCAR is more widely-used today, it will be used in the CIOMS report, but DISI will be used in the future. Priya conducted a Google search and she was unable to find the term SCAR in the context of occupational exposure. So, therefore, it always refers to adverse reactions due to medicines and as a result, she felt, the group did not need the term "drug-induced-scar". The group can opt for SCAR. At the time, SCAR was defined as sever cutaneous adverse reactions, but it is also mentioned that they are life-threatening and thus, are serious. The group could advocate for renaming SCAR as an acronym for "Serious Cutaneous Adverse Reaction" which address our concerns. We might not need DISI or DISSI in the end.

Melissa pointed out that the group could use DISSI and SCAR as a way to introduce the seriousness aspect. Clinicians could provide feedback on this. Another option would be to refer to the "severity" of SCAR which comprise "serious" adverse reactions. This could be acceptable for the group and clinicians as well. Ariel's perspective was that some clinicians would not grasp the "seriousness" concept as this is pharmaceutical/regulatory terminology. Clinicians might not be aware of the difference between serious and severe. So, he would favour to keep it simple. "Severe cutaneous adverse reactions where we have "severe" which also alludes to the seriousness of the condition and AR refers to adverse reaction. SCAR is more inclusive in scope where it's not just about the drugs, but that's how clinicians think when they see an adverse reaction, namely in terms of the etiology of the condition and the report tells them it is about drug-induced severe skin reactions. Chapter teams can provide some context e.g. risk minimization to help readers better understand the "seriousness" concept.

A compromise solution: DISI and SCAR

Could the group make a compromise and use DISI and SCAR together because if one googles occupational SCAR, nothing comes up, but historically, in SJS, there are many reports that describe occupational or chemical exposure. AGEP as well has been seen to be induced by amino acids. So, Chia-Yu's suggestion would be to use SCAR and DISI in the CIOMS report and explain why both these terms are used together.

David liked the idea of using both and then one could use Drug-Induced **Serious** Skin Injury/**S**CAR (s = severe). In the introduction, one could describe "Drug-Induced-Skin-Injury" vs DISSI/SCAR. This would have to be explained very clearly at the outset.

Haur Yueh too liked the idea of using DISI (with a single “s”) as the umbrella term, but keeping SCAR is preferable as it’s a more familiar term. Introducing DISI and DISSI could be confusing to clinicians and other readers who won’t necessarily know what “skin injury” means. What is “serious”? What is “severe”?

Chapter 1

A table should be included to compare DISI to non-DISI or SCAR vs common non-SCAR (cADRs).

Referring to the statistics in the report, Alex asked how reliable they were. If they are not final, should they be included? More specifically, Alex mentioned the part on epidemiology e.g. prevalence and incidence. How stable are they? Should we include them in the report? E.g. 31% of 58 patients… Is probably from a scientific article, but does the report need to provide this level of detail? Are there any references for this? Yes. They will be provided. Melissa asked if the rationale for this question was to know if this is the standard understanding or is it because it wasn’t referenced? When you’re trying to create a case definition, when going back to assess for cases, that might be a point if it’s taken as a fact. It was the latter that it was taken as a fact. The CIOMS report is a guidance document and we should know if that figure is fact or if it’s from an article that was referred to at that point in time? Alex mentioned he asked himself the same questions in connection with the chapters he drafted. This kind of reference is useful for a paper, but might not have the same relevance for the CIOMS document.

Because SCAR is so uncommon, it might, nevertheless, be useful to include information like that in the report with references so that you know, what is the viable or trusted reference to go to because when one does searches, many things come up that just keep repeating citations. The value of this document is to have a gold standard for numbers like this because it's almost like a statement of fact, but Melissa felt it should be cited. In this way, the person reading it who wants to know how strong the study was can go back to that reference if needed.

Chapter 2

Neil raised a point about DRESS. A patient will have every feature of this, e.g. atypical lymphocytes, but won’t have eosinophilia so the diagnosis is “it can’t be DRESS”, which is an inappropriate conclusion. Therefore, Neil recommends using a lower case “e” i.e. DReSS, just to say this is a holding place for eosinophila, atypical lymphocytes and other changes, but it's not absolutely necessary or specific. would happen. So, lower case “e” will be used throughout the whole report.

Should there be a statement in the report that eosinophilia is not a requirement? The group agreed this would be advisable.

Pancytopenia is associated with the worst prognosis for DReSS. This is very important because if people don’t see eosinophilia, they don't recognize DReSS and don't treat it. So, we need to make sure that people understand that eosinophilia is not a requirement. And sometimes having other white blood cells abnormalities or red blood cell abnormalities are an important part of the disease. Is this point made sufficiently clear for the group?

Alex asked how specific section 2.5.2.1 is to skin reactions as opposed to good medical practice? It’s not specific, but it’s important because in many cases it’s not happening. Ensure that it’s very clear to physicians that this is part of the management. Often in adverse reaction cases, there are a lot of lawsuits because the communication was poor. It’s about communication and how to approach a family. It’s up to the group as to whether or not this is included in the report.

Should one tell the patients this is their allergy? Because from Melissa’s point of view, there is confusion. It’s not always clear that it is an allergy. Should the group include a discussion about the difference between delayed hypersensitivity vs immediate hypersensitivity? Melissa asked this to the clinicians, as “allergy” is the term patients would be more likely to understand vs “mechanism of action”.

The area where there are the most problem with SJS and that patients are unnecessarily afraid of the drugs. A clinician will not use terms such as “type three or four”, but rather “you’re sensitive to this drug”,

but there may be other drugs that are related to this as well. So, if a patient asks “Am I allergic to this drug”? One would have to answer “yes”, but Neil prefers not to refer to the term “allergy”. It’s up to clinicians as to how they do it, but if it’s very specific, patients should know that the reaction is caused by a class of drugs and there might be new drugs coming, but that is the situation today and that’s what clinicians need to be careful of. Neil wasn’t sure how much literature there is on how patients interpret the word “allergy”.

The content of this part doesn’t have to be that specific, but the principle should be specific. The principle of how to communicate with the patients and their family could be mentioned in this chapter. It's great to have this content in this chapter so that readers know that communication of a DISI case is important, and how we communicate with the patient and family.

To Priya, the heading is a bit confusing, because it says reporting the case to patient health care providers and regulatory agencies. Whereas the text is more about the interaction between these three parties, which may then result in the reporting. So maybe it could be reworded as ”Interactions between patient, family, healthcare provider and regulatory agencies for reporting”. Priya asked if that is the only place in the report where reporting is mentioned or is there another place? If so, how do we cross-reference? There is another place in the chapter on surveillance.

Could this chapter focus on the interaction and then state the section on poor reporting? The reference about the reporting could be placed somewhere else.

Regarding the CIOMS guidance, is it intended to help prevent legal action as it would be preferable to stay away from this and instead, provide generalized recommendations that one should display empathy and use language that the patient understands. The reference can be included later on with additional recommendations interactions as Priya suggested or provide a website. The report shouldn’t be defensive. The information provided should be expressed in a scientific manner.

The group agreed that simple terms should be used to inform the patient and the family that the patient has a reaction to a drug. The primary care physician can in turn, inform the patient on the medication they are allergic to. Generally, the paragraph does seem defensive, but it is very important.

Chia-Yu reminded the group that they are welcome to add comments to the report for those who are unable to share their views on this call. Catherine is also capturing the changes.

Sylvia recommended removing the phrase “following the DISI and decrease the likelihood of lawsuits” and anything that refers to this. The paragraph should remain general and emphasize the importance of good communication strategies and avoiding re-exposure. The section should be shortened.
The group agreed with this approach. Chia-Yu also mentioned that DISI should not only be reported to healthcare providers or the family, but to regulatory authorities as well. Priya suggested rewording the section and not necessarily shortening it. First, it’s not about reporting a DISI case, but a case of suspected DISI. Maybe the group needs to discuss this, but regulators accept suspected cases, not only those that are confirmed.

The good communication strategies will aid in the interactions with the patient and family, not following a DISI, but in identifying, diagnosing and potentially reporting a DISI. Also, all references to the law should be removed because otherwise, nobody would report these cases. Then the section could state that physicians could consider a couple of points about how to manage such interactions. The tone shouldn’t be too authoritative.

The first step could be to listen to the patient in a respectful and empathetic manner in order to identify what their experience is as that is part of the diagnostic process. The part about the apology should be removed and reworded to acknowledge the reality of the experience for the patient. If the doctor wants to apologize, that is up to them. What’s important is the acknowledgement of the patient experience. What is the “www.sorryworks.net” reference? Also, it’s not clear what the disclosure meeting is. What is disclosed? What is its purpose in terms of diagnosis and potential reporting?

This is part of good communication, but it’s more general. It doesn’t only apply to SCAR. It’s also for DILI and other conditions. Although a SCAR may look much more serious and scary than a DILI case.

Does the group have anything in terms of communications about serious adverse drug reactions in other documents? Lembit replied that he didn't believe there were any other materials. Maybe clinical guidelines could be referred to instead of including it in this section.

The group wasn't sure if there were any clinical guidelines on this, but the International Pharmacists Federation (FIP) produced guidance on adverse reaction risk communication, specifically for medicines used in psychiatric diseases although this mainly focuses on pharmacists. It would be extremely useful to find out if guidelines on communication for healthcare professionals exist. Maybe the group could investigate further and prepare some ideas to be discussed at the next meeting. Who should take this on? Filippa responded that she would be happy to provide some general principles about patient safety.

Chapter 3

Haur Yueh stated that the first challenge was to decide how granular to be. The chapter could be a lot more concise and at the same time, depending on how the group feels, we could expand on some of the sections. The second issue was to avoid overlaps. Have the sub-sections on allergological evaluation, in vitro patch tests and HLA screening been covered elsewhere in the report? If so, it would be a good idea to cross-reference them rather than including them in this chapter. It might be covered in the chapter on biomarkers and other places as well. Chia-Yu said he was comfortable with the content of this chapter.

Chapter 4

Sylvie provided an overview of the chapter. She would like to rework the definition and had some difficulties with skin safety biomarkers. And, in general, how does one define a biomarker? Is the group aligned with respect to the definition as it is stated in the report? Should "skin" be removed and use "safety biomarkers for SCAR? If "skin biomarkers" is used, it could be interpreted that the location of the biomarkers is in the skin. Whereas, most biomarkers are more general, such as the HLA. So, Sylvia prefers the term "safety biomarkers". So, "skin" was removed from the title.

Some changes will be added to the introduction based on Gerd's comments and based on what was said earlier, chapter 4 should align with chapter 3 because there was some language about safety biomarkers as well. Maybe references to biomarkers in chapter 3 could be moved to chapter 4.

Sylvia provided a synopsis of the different sections. She mentioned the Nature publication by Chung et al who were the first to write about HLA and SJS. Regarding the new genetic basis of drug hypersensitivity, she asked the group what their thoughts were and if it should be kept. Sylvia felt it should be kept as it mentions other pathways, not only the HLA pathway. The immune system is very complex and so, this should be kept. Then, the section on further research about the role of Tregs and poor signalling which is important as not all patients with an HLA expression is prone to get SJS and vice-versa. So, it would be a good idea to keep this paragraph about further research.

Point 4.3 "Current challenges (what are the challenges in developing and implementing safety biomarker use in clinical trials and clinical practice?)" was removed.

So, the section "Guidance on biomarker labelling language" was renumbered as 4.3. Tegretol was used as an example (the brand name should be removed and replaced with carbamazepine). It would be good to keep some text as an example because depending on the regulatory authority, e.g. FDA or Health Canada, there is a very strong label that Carbamazepine should not be used in certain indications. EMA and some other regulatory agencies are not that strong. If the group wishes, the section can be shortened. Or, there could be a reference to the label instead of copying/pasting it in the text. So, there are several options to shorten the section. The advantage of referring to the label is that if the label is updated, the text does not need to be updated.

Overall, what's important in this chapter is to demonstrate that HLA screening is widely-adopted, the research is ongoing, but that there are challenges and limitations as well. Sarah provided a nice questionnaire which we can make a reference to.

Regarding the labelling advice, Priya asked if it is used to identify patients who are at risk for SCAR or DISI and singling them out so as not to expose them under closer monitoring. Labelling advice is also covered in Chapter 7 on risk management and minimization measures. Would it make sense to move this to chapter 7? Yes. The group agreed to do this. But what should be kept in chapter 4 is the discussion about usefulness and limitations. If it is a discussion about utility, when to consider what and which risk minimization measures are appropriate, then this would have to apply to all risk minimization measures and thus, be included in chapter 7. If not, it would be more appropriate in chapter 4. Sylvia agreed and would support either option in terms of readability.

This could be reviewed by the editorial team. The challenge will be to manage the overlaps, e.g. the part about how to explain to the family relates to risk mitigation as well as prevention in the future. It might make sense to include it in the more clinical part, e.g. chapter 2 and in the final chapter, reference it back even if in a table that summarizes the advice. This could also be about advice before the report given that the risks are communicated to the patient prior to the treatment. Where would this idea fit into the report?

Melissa liked this idea, even for clinicians who already have that information in the labelling of the product. This is part of the patient counselling prior to prescribing. It's a very challenging topic and Melissa thanked Sylvia for tackling it. Does the group want to make a statement with a recommendation about its utility? It could be under point 4.5 Future outlook.

Alex mentioned that there are a lot of programs that perhaps don't move forward because of HLA typing and others that require HLA typing in order to move forward. Also on an individual patient level, we see a lot of causality being dismissed because the patient did or did not have the HLA. So, the group really needs to explain what these biomarkers are about and how they will be used.

It depends on the group because CIOMS working groups have made recommendations in the past. So, it's up to the group to decide.

The group agreed that it would make sense to include Alex's comment on development in this chapter. How does labelling effect the actual development of a new product and regarding the regulatory aspects, what are the criteria? Maybe citations for the different regulatory agencies could be included for reference and mention that these issues exist

Chapter 5

Violeta listed the different sections in this chapter and pointed out that there might be some overlap with other chapters, in particular for risk factors. The authors mentioned both DISI/SCAR, but it should be DISSI with two "s".

Where should the "risk factor" section be in the report? It would be nice to have them for each type of SCAR and have just a cross-reference to it here. If the risk factors are generic or more specific, that could be mentioned as well. The group should address this as it is not an editorial question. Also, regarding the order and the confounding factors that come before the causality assessment, is the term "confounding factors" used in the true epidemiological sense of confounding the exploration of a causal association as opposed to a loose way, as is often used in pharmacovigilance. An example is, in safety assessments when people have risk factors, one often hears, "Oh! They have a confounder", but the individual does not have a confounder, just patient factors or risk factors. Violeta confirmed that confounder was taken in the clinical sense and that it applies to studies.

To clarify, Alex asked Priya if "confounder", as a definition is a variable that has a relationship to both the predictor and the outcome. Is that the way it should be used? Yes, but this definition is only applicable when one investigates inference on a population level, not when one is looking at causality in an individual patient. As an example, if one takes SCAR as the outcome variable and HIV or seizure as the predictor, the confounder would be the drug that's given for seizure that is causing SCAR.
An example Priya mentioned is a patient who has a suspected adverse reaction, but also has a myocardial infarction and high blood pressure. Some would say that this was a confounded case. Whereas it's not the case that is confounded, the patient just had a risk factor.

The high blood pressure is a pre-existing condition, not a confounder. The language gets jargon-like and it is so common and should be avoided.

Regarding the information to be collected, is that based on the form Sarah provided or is it separate? Violeta responded that it was created separately.

Regarding the section on confounders, Priya suggested the section title could be changed to “Risk factors and confounding factors” and the following could be added “on an individual level, there may be additional risk factors and one has to be aware that in safety studies or clinical trials for safety studies that these risk factors could confound the study outcome if not addressed properly.”

To Violeta, this section is different from the risk factors mentioned previously. These are clinical manifestations that could easily be confounded by or could be attributed to a SCAR diagnosis, but it’s not necessarily about risk factors.

In that case, it might not be about confounding factors, but rather differential diagnosis or alternative etiologies/differential diagnoses. The heading should be changed to “Differential diagnosis and other etiologies”

Alex asked if these were specific to a life cycle phase or if they were much broader and applied across the board to SCARs. So, if we are talking about differential diagnosis, it must be general and not just pre-marketing. So, based on that, is the chapter structured in the right way? Should pre- and post-marketing be separate? Should biomarkers be separate from pre-marketing? Maybe the report should include a dedicated chapter on differential diagnosis? Or, merge differential diagnosis with the diagnosis itself or SCAR and then just have a brief chapter on specifics related to pre marketing and post-marketing?

Melissa recommended including the part about differential diagnosis in the clinical chapter. As to the question about separating out pre-marketing, she asked if there was enough content to highlight pre-marketing activities? The piece Melissa sees as related to pre-marketing is for adjudication when one seeks contributions from dermatologists, allergists, immunologists. Maybe the form Sarah produced could be referenced in this chapter as a standardized way to obtain the information for review.

What is unique to pre-marketing is to have a DMC and an adjudication committee. We can include some criteria to have a dermatologist as part of DMC or criteria to separate the DMC from adjudication. There is sufficient material to highlight what’s unique about pre-marketing. What some struggle with is, when is an adjudication required as opposed to having a dermatologist on the DMC and leaving it at that?

The issue is the level of information one has in clinical vs marketing. The level of detail for a case given that in pre-marketing one has protocols that are very well set up, and that one can build on with one’s experts might be more of a struggle in a post-marketing scenario. The section on adjudication is individualized, but the level of information may be better in a pre-marketing setting.

Based on the above, the storyline could be that one can collect much more information in pre-marketing than post marketing. This is the level of information that's needed for a thorough assessment of SCAR and these are the criteria one should use to involve SCAR experts in a programme and then call for different types of adjudication and review for SCAR. Perhaps “differential diagnosis” can be moved to the clinical diagnosis, but the principle of involving a DISI or SCAR expert in the pre-marketing risk management team is important. Also, given that in a controlled clinical trial, there is a greater ability to obtain more information to characterize the risk in the pre-marketing phase. So, if an event occurs that’s consistent with SCAR, that is when the information must be obtained. That’s when manufacturers provide questionnaires or query forms within the CRF and photographs document this as well. However, the report will not provide guidance on this. This needs to be made clear.

One additional comment from Violeta, because of the reason that Ariel just highlighted, namely that we are in a controlled space, where information is easier to collect, and the assessments might be easier, or we could instruct investigators to conduct a more thorough assessment.

So, because of all this, Violeta recommends keeping a reference to differential diagnosis in the chapter on premarketing. Even though the text fits better in the diagnosis chapter, Violeta would prefer to keep a part on differential diagnosis in chapter 5 to reinforce the needs with investigators to adopt a detailed assessment and ensure that there is a SCAR event.

One tends not to see SCAR in the pre-marketing space because it's such a small population and so uncommon. Maybe this is where it should be highlighted that this advice is how to characterize a case even if one is unlikely to need this. How much does one use those considerations in terms of planning the monitoring during development for a certain molecule with a similar structure and if it's in the same class and even if the group needs to comment on that in the report.

There is a reference to some information in terms of the design of the trial or using a drug that's within the drug class that's known to induce SCAR. Probably in the risk factor section. It's mentioned in the Investigator assessment section as well.

Regarding causality, the amount of information available in the pre-market is more important, but when it comes to different approaches to causality and different algorithms, because they're specific to SCAR, there wasn't anything that was specific to premarketing. So, again, does causality deserve having a dedicated chapter?

When looking specifically at rashes, in Neil's experience on DMCs, he didn't recall ever using causality tools. If there's a specific SCAR or DILI the manufacturer is concerned about, the manufacturer will create or adapt their own system just for that study. There'll be nuances based on e.g. something for children or for a certain disease. It's something that might be useful to DMCs and are often ignored completely in publications. One is not told who's on a DMC. It's very secretive. Maybe CIOMS could come up with guidelines for Data Monitoring Committees.

As a follow up to Neil's comment, Melissa asked if, based on the different kinds of causality assessments, there was enough overlap or commonality to be useful for the CIOMS report in the context of the pre market space specifically? Neil responded that there 's a lot of data that's unblinded so there is an opportunity to make a decision. If one looks at the data before it's unblinded, it is meaningless. One can't tell who did what. It's unlikely causality assessments are used until something is published. Even then, when the clinical trials are published, there's not even much there. It's usually that there are no new safety signals or if there's a specific concern, there may be a comment about it.

Anybody who's ever been involved with clinical trials will know that when you're doing a clinical trial, and then you see it published, how many times does one ask if that's really what was seen or said? There's a lot of massaging as things go from actual clinical trials and data monitoring committees, and then get into publication. So that's another aspect that is strange. There's a lot that could be done better. From the regulatory perspective, regulators will see all the data, but it gets translated to "Preferred Terms" so their job is to assess if it's a constellation that requires their attention or not and if they should request the case narrative. Also, should the case report form be separate from a summary statement? Is that useful to include here? Should it go under Causality?

In terms of the clues that will make one monitor DISI more closely in a clinical trial, was there any mention about non clinical evidence being included? Is that seen in animal models and if so, does it kill the drug? Is that a consideration to be included here? So, class of medication can be a clue and can any non-clinical evidence of cutaneous manifestations be a consideration as well? That's probably where we provide a setup or a part of the clinical protocol to evaluate cutaneous skin manifestations, and are included in the measures that are applied in the clinical trials. Was that a concern to look at non-clinical evidence? Is it common to see it in animals before?

For skin disease, animals are irrelevant. People sometimes panic because some mice got toxic epidermolysis in the early study, but it's not seen in humans or other models. The skin is pretty unique. Livers are similar and other organs too, but skin is unique in the animal world. The drugs might still "die on the vine", but it doesn't add much right now.

It's not clear how applicable it is whereas with DILI, renal disease or embryo (?) toxicity are seen in animals, but with skin, if it isn't, it does not need to be included in the report. If it manifests, then most likely the development will not be pursued. As a response to Ariel's comment, Alex stated that precedents and existing evidence are covered in the section on causality, but it's more general. The existing evidence can push the causality assessment one way or another. That's the extent of it, but if there's anything that needs to be done better, then we should do that.

There was a brief discussion on adjudication reports.

Causality is such a big part of SCAR and there's a lot of overlap. Melissa asked if its place is in premarketing or should it be a separate chapter? It's mentioned in chapter 2, but it's only a small part. Should it be expanded in the clinical chapters as well? Or have a dedicated chapter? It's so complex and so important.

Neil, who uses a Bayesian approach, mentioned that it isn't just a case of "we've seen this reaction and we've made a diagnosis. So it's got to be this drug". It may be that drug, but it might also be another drug or another exposure. It's not a single point diagnosis when you say "causality". The Bayesian approach should be taught in order to look at the statistics and the information in the literature to determine the baseline rate, but based on the timing, and other factors, I think this is the number one cause, number two potential cause and number three potential cause. But that basically, one doesn't know. People want to say "it's this one or that one" and it just becomes a guessing game. One can say that something is more or less likely, but it's not zero. Causality really deserves more attention and it helps people come to more scientifically-thoughtful associations, as well as potential signals. Maybe it only occurs on days, eight, nine and 10 or after exposure. There's a lot of information that comes out of the Bayesian approach.

Does the group agree that causality deserves its own chapter or should it remain in the premarketing chapter? One thinks about causality as individual cases because they are so uncommon. So, it would be hard to look at this in the pre-market space on a population level. The approach is about determining what evidence and causality assessment is crucial for the case? If it is a reaction, then one has to have the label. The focus is to know what is required to make sure it is true and that one is able to determine the causality of the case. Causality is very important because when one is looking for information and if one is struggling with case, that is what one would look at first in terms of guidance. Lesley opted for having it as a separate chapter, but it could be a stand-alone at the end of the report as that is the topic readers will look for first. Alex mentioned that the group has enough material on this topic to make it a stand-alone chapter. Melissa asked if anyone was opposed to making it a separate chapter. Should it go before or after the chapter on biomarkers?

Priya asked if causality assessment at individual level would be considered for clinical trials and patient care? Could the chapter on causality be about how to determine the causality of the different types of SCAR? This was stated in Chapter two. Rather, the scope of the new chapter on causality would be a "deeper dive" into what causality means and what is needed for causality assessment, how to determine the culprits based on causality assessments. There was not enough information about this in regard to clinical trials specifically. So, it's applicable to clinicians and all those involved in pre- and post-authorization. In that case, it belongs closer to the chapter on pharmacovigilance, e.g. after post-marketing, before risk management? As it's applicable to both, pre- and post-marketing.

Alex asked to finish reviewing the content and then as a second step, look at the table of contents to see if/which chapters/sections need to be moved around to a different place in the report, e.g. part on risk factors and confounders.

Priya was suggesting to insert the chapter on causality between chapters six and seven. Or between five and six? Chia-Yu agreed, that it would be ok between six and seven.

Priya thought the heading "Clinical care" should be more specific because risk minimization communication is clinical care as well. She asked the group for ideas on this. Alex offered that it was about management. Chapter three is about managing the different types of SCAR clinically and "risk minimization communication" is more generally about the concept. Also, strong cross references should be inserted between chapters three and eight

The new chapter should be titled “Causality assessment” rather than just “Causality”. And adding “in pharmacovigilance” so that it speaks to chapters 5 and 6. Or, adding “in pre-and post-authorization surveillance”. Chapter 2 title should be reworded “Diagnosis and identification”. Then is “Management”. Chapter 4 “New skin safety biomarkers” : should it be reworded as” The application of new safety skin biomarkers”? “New” should be removed as well. Are they really safety biomarkers? Potential safety biomarkers? Or, “Application of biomarkers for safety”? The biomarkers are not safety biomarkers per se, but they are used for patient safety. DISSI is mentioned in most headings, but not all. Is that a problem? Keep it in Chapters 2 and 3. It should not be included in 4, 5, 6, 7 or 8. Because the whole report is about DISSI, the group agreed to remove DISSI from the heading in Chapter two i.e. “Diagnosis and identification of cases”. Chapter 3: “Case management in clinical care”

For Chapter 7, the title should be “Causality assessment in pre-Marketing and post-Marketing surveillance”

Priya wondered about risk assessment. It is more than causality assessment. There's also risk quantification and the implications of the risk, but it does not appear in the draft report. Is it part of post marketing surveillance or risk minimization? There is a dedicated chapter on causality, but risk assessment is missing. Also, is post marketing surveillance the same as pharmacovigilance? Because if it’s only surveillance without the assessment, then pharmacovigilance is not fully covered in Chapter 6. Ariel shared that this was mentioned in the chapter on post-marketing although it also applies to pre-marketing. Priya asked if Chapter 7 could be titled “Causality and risk assessment”. It will mainly cover causality, but will also include information about risk assessment. Alex asked if causality belongs in the same chapter as risk assessment. Does the group have anything about risk assessment? There is some information, not a lot which is why it shouldn’t be a chapter on its own and was put with causality assessment as otherwise, risk assessment would be missing. The risk needs to be quantified before it is minimized.

Ariel stated it was covered in the introduction of the risk minimization chapter, but it’s just an introduction. The group suggested changing Chapter 8 to “Risk assessment and management”. So, assessment would be covered and additional pharmacovigilance activities, risk minimization and communication would go under management. The title of Chapter 7 would now be “Causality assessment”. The term “risk” should be removed. Ariel referred to the additional assessment in Chapter 6 and suggested it could be moved to Chapter 8 and if more material were added to Chapter eight, risk assessment would not only be featured in the introduction.

Chapter 6

This purpose of this chapter is to explain what postmarketing is about and its limitations. The chapter also covers the datasets/sources of data for postmarketing with their limitations; spontaneous reports, their limitations and how electronic health records partly address those limitations because we have more information. The limitations of electronic health records are described as well. Then, it describes the networks that combine electronic health records and to some extent, the data, spontaneous reports and expert assessments. There was insufficient information about SCAR or skin reactions so cases were described and referenced with examples taken from the literature on SCAR.

Melissa asked if there was a discussion about the use of published literature in this chapter. Alex said there was a section on literature, but as there wasn’t a lot of information about this, the section was removed, but maybe it could be reinserted. It’s used as a resource and also used to connect back to the clinicians “on the front line”. It’s useful to publish cases for regulatory agencies, e.g. the British Journal of Dermatology issued a letter encouraging anyone who was submitting a case of a new cutaneous AE to the Journal to also report it to their regulatory authority.

The idea being that regulators may see the case sooner than if it goes through the review process for the journal. Alex asked if Melissa could share a copy of this letter. Melissa said she would.
Priya mentioned that sometimes the scientific literature is presented as an additional data source when actually, it isn’t one really. Rather, it's a source of evidence, which is different from data.
Any study report or case report can be considered data and can be published. So, the literature works on a meta level between data and assessment. Is that something the group should clarify, namely the utility of the scientific literature in both publicizing case reports and encouraging healthcare

professionals to publish as much as the need for review articles. Is that worth mentioning? It isn't specifically about SCAR, but more generally about the role of scientific literature in safety surveillance. There is a reference to this in the chapter on adjudication. In step-by-step assessments, one looks at the data, pattern analyses and then the textbooks and literature. It's a step-by-step approach.

There are some references in the report to the Bradford Hill criteria and the criterion of consistency and plausibility. Existing knowledge is one of the criteria and that usually comes from the literature as well. So, maybe some cross-references could be included in the report in this regard if the group agrees.

It appears that most often, reports come from hospital-based pharmacies who are very good about reporting. Some have to be reported because of legal reasons in certain jurisdictions. In Canada, there's an issue that is named after a young lady who died from an adverse event. And there are rules in such cases. It's usually the pharmacy that reports those. The trouble with clinicians reporting these cases is that, as a result, they are constantly receiving requests by the manufacturer as well as by the government to provide an update on the case, which can be a deterrent to reporting a case again. Maybe this is an issue that can be solved, but today, it is very punishing. One has to think about who is reporting and what the consequences will be. There are, however, local jurisdictions. Canada is not the only jurisdiction that has rules for when one should report severe cutaneous events.

The group was pleased with the material it has for the new chapter on causality assessment and section 6.3 will be moved to Chapter 8. Priya added that the new structure could be kept after it is edited. Alex asked Catherine to move the section on Causality assessment on aggregate data to the new chapter on causality and insert it in the new outline of the report

Regarding reporting in jurisdictions where it is encouraged e.g. Sweden and Japan where people are covered if they suffer an adverse event. These are important stories. Much like genetics stories that result from screening. There are certain parts of the world where AE reporting is encouraged and is supported from the perspective of the patient. Maybe that could be included in the report, e.g. as a list of countries that have made strides to help with accurate reporting.

In the context of postmarketing, right now, the way this chapter is covered is mainly about sources of data, and what to do once the data is in the databases. Should we have a section to encourage reporting and give some guidance on reporting? Is that what the group would like to do? That is not provided at the moment.

Lembit quoted the example of the DILI working group who said that one doesn't necessarily have the information one needs in the individual case safety reports to make the proper assessment. So they proposed to create a reporting form that contained additional data fields for those who want to do targeted monitoring. An example of a report form was provided by Lesley and could be included in the report as well.

This might be something the CIOMS AI Working Group could take up. Referring to an example of from his experience, Neil mentioned a project he worked on to adapt airline technology (an industry that is also heavily regulated and used to managing safety and complexity) to create a dynamic feedback system for event reporting such that if an event is reported that has occurred before, but in other sites, one would know about it. The data would keep changing, which changes the ranking of the possible AEs, but with AI, the information can be updated continually e.g. this is the third report of what we had. Clinicians would enjoy being involved in this way as opposed to sending the information with no outcome. People can see they are making a change. To date, interactions between clinicians and regulatory officials have not very strong, but AI could change this.

Priya commented that there are several pages of references, but it's a short section. Alex replied that there will be overlap in the references throughout the report. However, if the sources are used, they should definitely be listed. Lembit stated that in general, references are combined in a single appendix at the end of the report, rather than at the end of each chapter. It also helps to avoid duplication.

Chapter 7/new 8

The chapter team group provides some background including the definition of a risk, what has been historically used to categorize risks, the severity of a risk, and how we translate that into certain regulatory documents, how we categorize the different types of risk, e.g. important risk and identified versus potential. This is very specific to regulatory and pharmaceutical professionals, but it's also useful to educate clinicians about how the risk gets translated into the label and other regulatory aspects of pharmaceutical development.

Even missing information is covered in a definition. Next is risk management and how one categorizes and defines risk, but what's lacking is the “meat” about assessment itself which will be a good addition to our chapter. Because the last part of chapter 6 will be moved to this chapter which will provide more context in the introduction so it will be more than an introduction, It will be more about risk assessment. And then we describe routine risk minimization measures, which is quite European, that's why Ariel asked Melissa if she could look at this section and see how it can be applied to the US as well.

In the section on additional risk minimization measures, there are references to certain labels. These might be too detailed and the group can remove those that are not needed, Regarding Tegretol, is it okay for the working group to provide an actual label? We don't want to point a finger at certain products that have SCAR as an adverse reaction. Melissa asked the same question: how does one cite examples such as these? Which labels should the group chose?

There was agreement in the group that label examples would be useful with a view to achieving long term consistency across labels, between products and potentially, globally as well. The group should draw on real world examples where the group believes the label is good. However, the product name may not need to be mentioned. Generic wording could be extracted and used instead. Can the section on clinical case management advice in Chapter 3 be cross-referenced to this chapter? Because if the group had a model for each of the five SCAR, maybe cross-references could be provided and that way, product names would not need to be stated. It would be in generic terms.

Maybe a model could be provided with the example, including the components of an event or the risk that will be included in the label, the onset, acuity, severity and characteristics. The language used in package leaflets for the lay public is not standardized. If definitions could be provided for SCAR medical conditions e.g. SJS, it would be very helpful.

The last section is on additional risk minimization where examples are provided, e.g. patient guides that were used, such as Abacavir. It’s fine as an example, but should it also be included as an appendix or a reference? Lembit replied that it could. Looking to the future, it would be useful to adopt a harmonized approach across different regulatory documents. As long as the examples are in the public domain, CIOMS can refer to them as long as they are not portrayed in an overly negative way or for a very serious case, remove the product name and leave the information about the AE. The problem is that if examples are provided for each of the five SCAR, people will remember these drugs and forget the others, which is very dangerous. That’s why the group thought it best to provide unidentifiable labels.

This is partly true, but this book is not meant for the layman and is rather for a specialized audience. So, there is less danger of this happening. Priya agreed, but highlighted that if the report is used as teaching tool, the five products will keep coming up which is what the group is worried about. But specialists will pick the name up even if it is anonymized. Lembit recommended thinking about how to proceed on this. One option could be to ask the product owners what they think and if they would agree to using the product as an example.

Next, Ariel referred to the educational patient guides and guides for HCPs and again, non-specific examples are provided. A lot has also been extracted from the EU GVP so Priya suggested cross-checking with other jurisdictions if the information is applicable and maybe also make the example more generic according to the terminology used in different jurisdictions. Melissa asked if a table would be useful to highlight the different terminologies and documents from different jurisdictions that reference how to perform these types of risk minimization. Lembit thought this was a good idea. Doesn’t such a table already exist in the CIOMS report (IX) on risk management? It might be outdated

as it was published in 2014. Ariel said Chapter 8 would look into adding a table also for the risk minimization measures earlier.

The conclusion mostly provides references to the chapters in which risk mitigation aspects are discussed. Examples of the SmPC are provided for specific products with SCAR so we can cut these down. Risk assessment still needs to be included in this chapter. Ariel asked if there were any other comments? Priya asked Lembit if examples could be displayed in a different colour as in previous reports. This would help readability. Lembit said the group can discuss this when we get to the layout stage. The report would also need instructions to help readers find the sections they are interested in quickly.

Next steps

A meeting will be held with chapter leads to review changes and check for duplication. Catherine will prepare a table of contents with the subheadings. The full group could meet in e.g. between August 15th and 30th If additional input is needed from colleagues in member organizations, this could be done over the summer before the full WG meets again.

Priya would like the chapter groups to see their chapters again before the full WG. So, they can review, delete or even transfer sections to other chapters. Chapter groups should receive the whole report, not only their own chapters.

A doodle will be sent out for a meeting with the chapter leads (June??) to integrate the changes discussed at the 5th WG.

A doodle will be sent out for the full WG meeting in mid-August-September.

The editorial committee will be convened after the 7th meeting.

End.